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Abstract

Analytic treatment interruption (ATI) studies utilizing broadly neutralizing antibody (bnAb) infusions are associated with delayed viral rebound if viruses found in the participants are sensitive to the bnAbs. Yet, viral sensitivity is typically evaluated only after the ATI has been conducted. For a future ATI that will enroll 35 participants from the RV254 Thai cohort, we screened HIV-1 sequences for sensitivity to the bnAbs that will be used in the ATI: GDM1400LS and VRC07-523LS.

Plasma samples were sequenced via single genome amplification or the Pacific Table 1: Characteristics of the study participants at diagnosis in acute HIV-1 infection Biosciences single molecule real-time platform using unique molecular identifiers. Envelope (*env*) sequences were cloned and pseudoviruses with these Env were tested for neutralization sensitivity to bnAbs using IC80<1ug/mL as a cutoff. Among 649 participants enrolled during acute HIV-1 infection who initiated antiretroviral treatment (ART) within days of diagnosis, 168 (98% male) met study eligibility criteria and 39,907 *env* sequences were obtained from 160 participants. Most participants had CRF01_AE env (85%). Sequence analysis showed minimal diversity (average mean pairwise diversity=0.004) with a single HIV-1 lineage in most participants (67%). The deep sequencing data showed that two thirds of the infections with multiple founder lineages had rare lineages that represented <3% of the viral population. For each participant, in silico predictions of bnAb sensitivity were used to select representative *env* sequences for neutralization assays. Neutralization data from 143 participants showed that 32 participants had viruses sensitive to both bnAbs and 67 had viruses sensitive to one bnAb (32 to PGDM1400LS and 35 to VRC07-523LS). Considering 1ug/mL<IC80<3ug/mL, 25 participants had viruses sensitive to at least one bnAb. We HIV-1 within-host diversity is low in acute infection also modeled the Instantaneous Inhibitory Potential (IIP) values; at week 20 post ATI, 86 single lineage participants had clones with IIP (PGDM1400 + VRC07)>3.5, allowing prioritization of participants for study enrolment.

We developed a strategy combining sequence analysis, in silico bnAb sensitivity predictions and neutralization assays to prioritize enrollment of participants with the most sensitive viruses to the bnAbs that will be used in an ATI. Our approach benefitted from the fact that participants initiated ART in acute infection and therefore had a typically homogeneous viral reservoir recapitulated by the limited number of distinct env sequences we sampled. While the benefits of this approach will only be ascertained after the ATI is conducted, these data provide the largest description of sensitivity to two potent bnAbs across CRF01_AE viruses.

Background

BnAb infusions delay viral rebound in participants with viruses sensitive to the administered bnAbs.¹ A new ATI that will enroll 35 participants from RV254 Thai cohort: Infusions of two bnAbs: PGDM1400LS (5 mg) and VRC07LS (40 mg). Enrollment based on bnAb sensitivity screening.

Methods

Sequencing: Samples collected during acute HIV-1 infection were sequenced via single genome amplification (SGA) or the Pacific Biosciences single molecule real-time platform using unique molecular identifiers (PacBio)².

In silico bnAn sensitivity: Weighted epitope distance fitting against CATNAP IC50 data were used to predict IC50 for each Env sequence¹.

In vitro bnAb sensitivity: Env clones were tested for neutralization sensitivity to bnAbs using IC80<1ug/mL as a cutoff (CROI poster 421, Smith et al.).

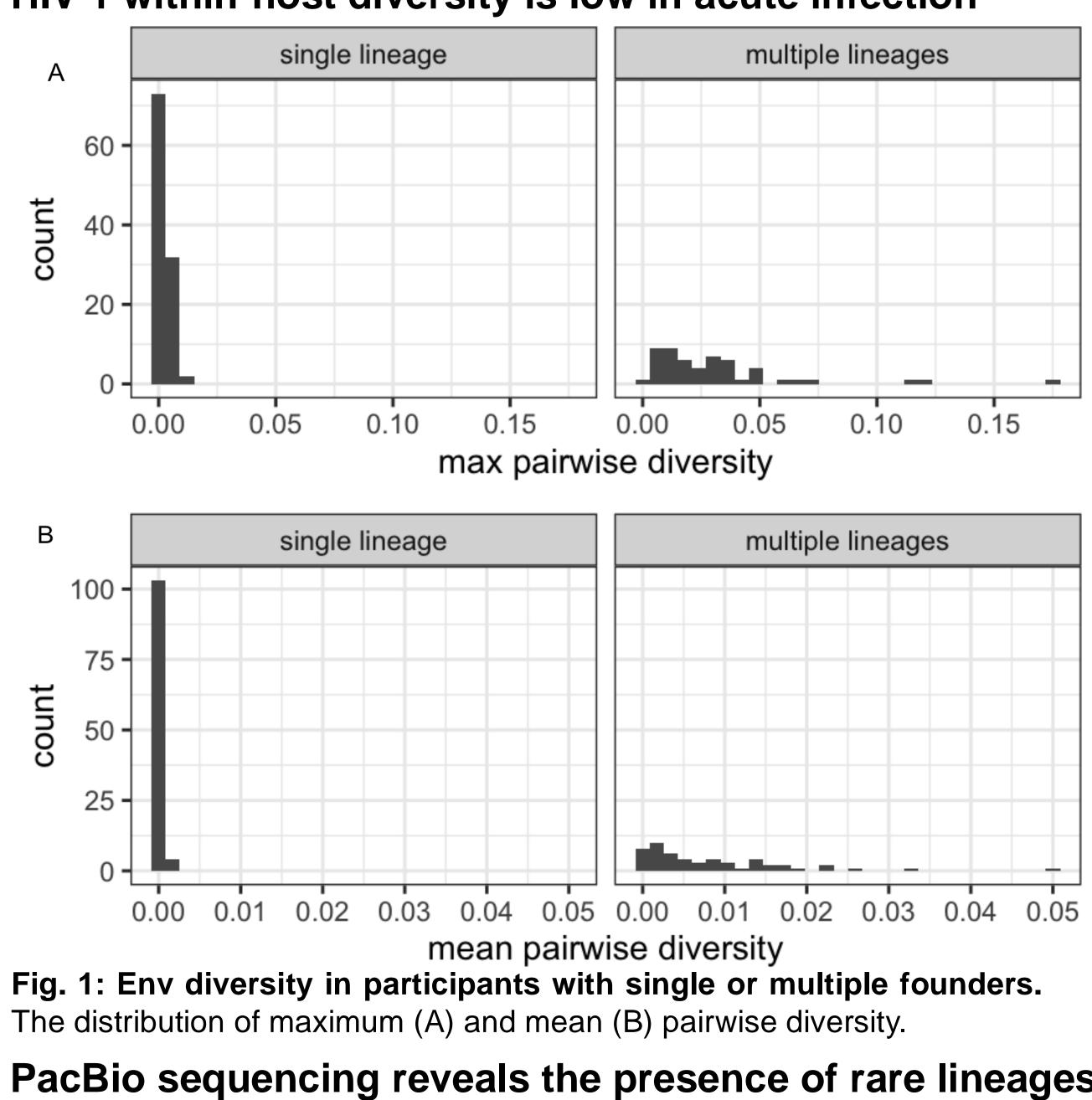
IIP: log-fold reduction in virus infectivity was calculated with Bliss-Hill model for combining the two bnAbs³.

Maximizing Benefits to Participants in Analytic Treatment Interruption with Antibody Infusions

In silico and in vitro neutralization measurements were used to prioritize enrollment of participants most likely to benefit from PGDM1400LS and VRC07-523LS infusions

Results

Fiebig	n	mean viral load (copies/mL)	mean CD4 count	Env subt	уре
1	22	63700	465	CRF01_AE	21
				В	1
				CRF01_AE	28
2	31	2612394	358	В	1
				CRF01_AE/B	2
				CRF01_AE	65
3	79	9656285	376	В	4
				CRF01_AE/B	10
				CRF01_AE	17
4	22	9199507	381	CRF01_AE/B	4
				G/CRF02_AG	1
5	6	4919017	484	CRF01_AE	6



PacBio sequencing reveals the presence of rare lineages Fig. 2: Rare lineages were detected in participants with multiple founders. Phylogenetic tree and highlighter plot from one participant with multiple founders.

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the Department of the Army or the Department of the Army or the Department of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of the Army or the Department of Defense. Research was conducted under an IACUC-approved animal use protocol in an AAALAC International - accredited facility with a Public Health Services Animal Welfare Assurance and in compliance with the Animal Welfare Act and other federal statutes and regulations relating to laboratory animals. The investigators have adhered to the policies for protection of human participants as prescribed in AR 70-25.

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In silico prediction of bnAb sensitivity was incorporated into the selection of representative sequences for neutralization assays

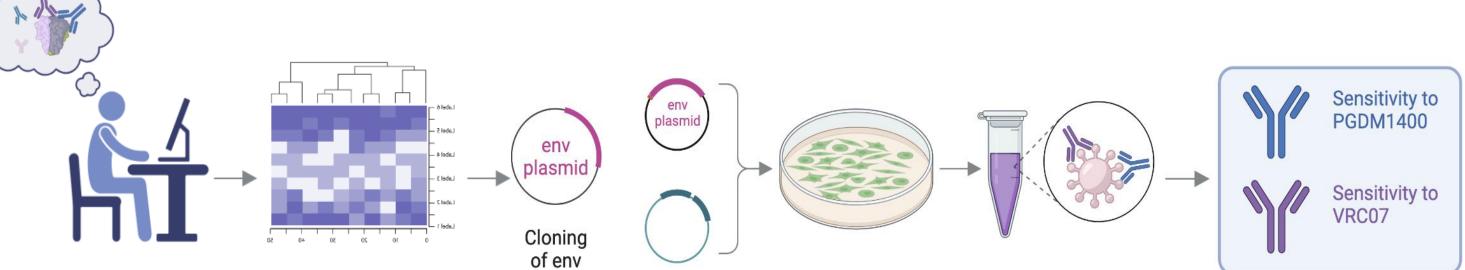
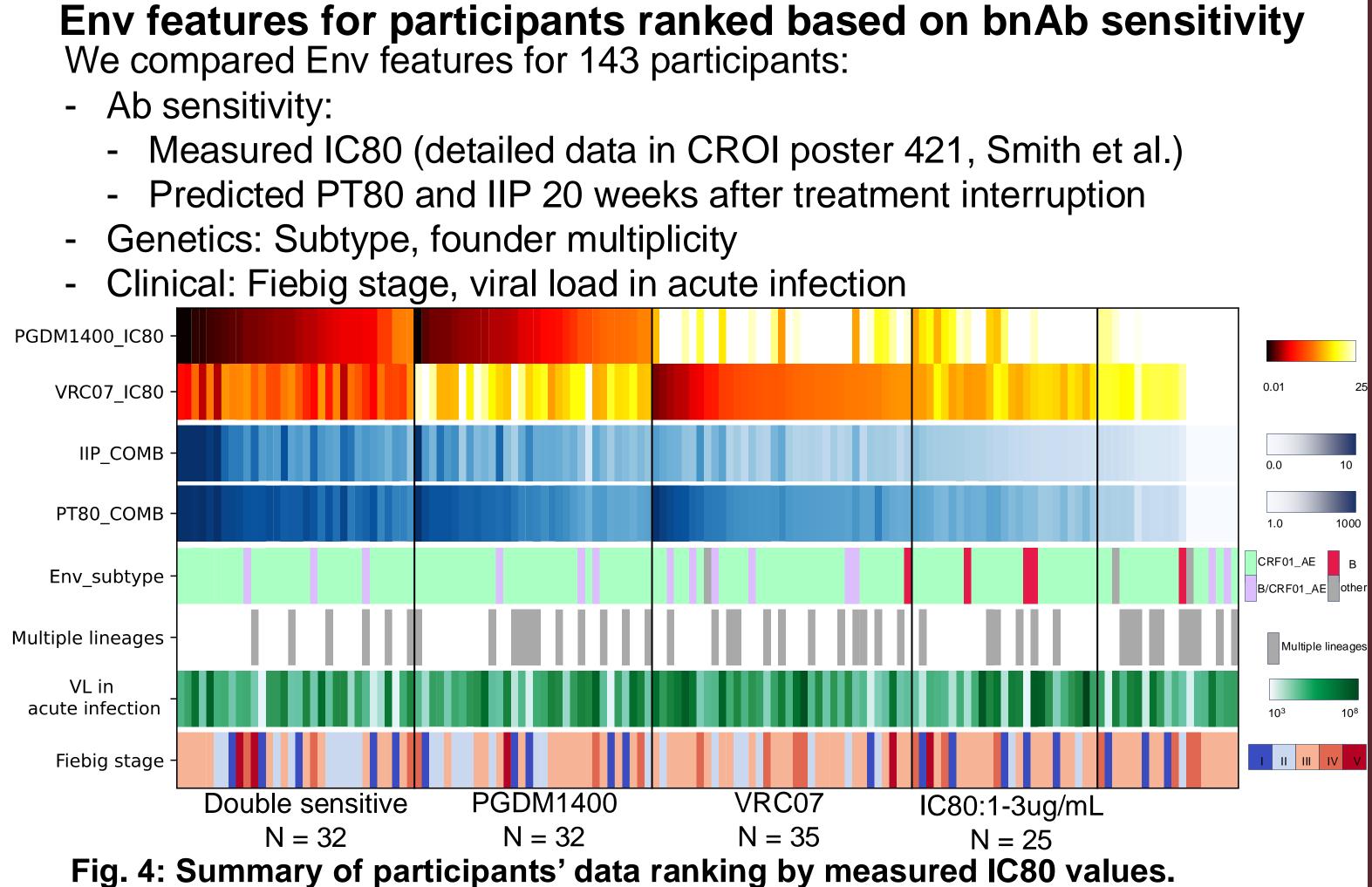


Fig. 3: Workflow to test sensitivity to bnAbs. Env sequences were selected for cloning based on the in silico predictions of bnAbs sensitivity and pseudoviruses with the env were tested for neutralization sensitivity.



Conclusion

founder lineage References Evolution, 10(1). veae019.

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- Viral sequences were obtained from 160 participants during HIV-1 acute infection using SGA or PacBio sequencing strategy

- HIV-1 within-host diversity is low in participants with single

- Rare lineages were present in 2/3 of the participants with multiple founder lineages

- Neutralization sensitivity was the main criterion for ranking participants' viruses: participants with viruses sensitive to both bnAbs were prioritized for enrollment

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