Maximizing Benefits to Participants in Analytic Treatment Interruption with Antibody Infusions

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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 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 also modeled the Instantaneous Inhibitory Potential (IIP) values; at week 20 post ATI, 86 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 sequence[1].

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 bnAbs[3].

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

Table 1: Characteristics of the study participants at diagnosis in acute HIV-1 infection

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

HIV-1 within-host diversity is low in acute infection

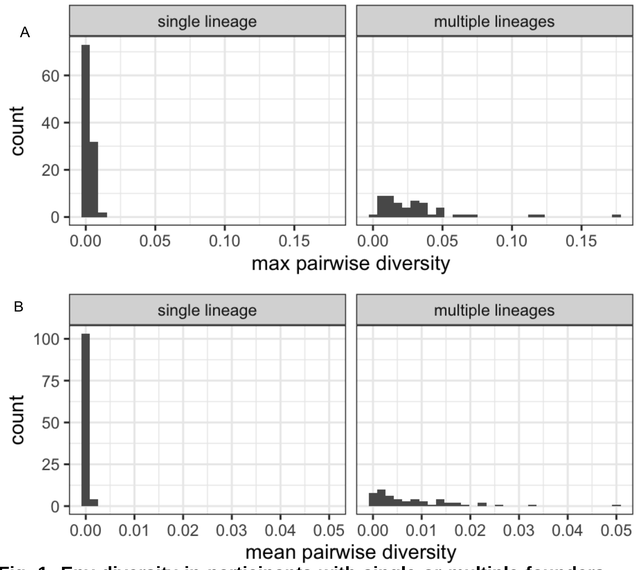

Fig. 1: Env diversity in participants with single or multiple founders. The distribution of maximum (A) and mean (B) pairwise diversity.

PacBio sequencing reveals the presence of rare lineages

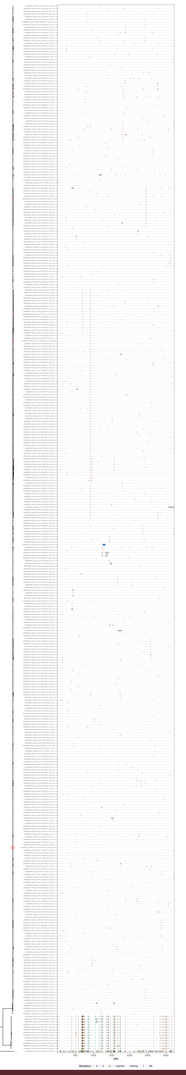

Fig. 2: Rare lineages were detected in participants with multiple founders. Phylogenetic tree and highlighter plot from one participant with multiple founders.

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

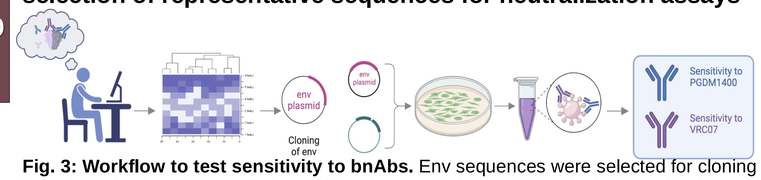

Fig. 3: Workflow to test sensitivity to bnAbs. Env sequences were selected for cloning based on the in silico predictions of bnAbs sensitivity and pseudoviruses with the env were tested for neutralization sensitivity.

Env features for participants ranked based on bnAb sensitivity

We compared Env features for 143 participants:

- Ab sensitivity:
  - Measured IC80 (detailed data in CROI poster 421, Smith et al.)
  - Predicted PT80 and IIP 20 weeks after treatment interruption
- Genetics: Subtype, founder multiplicity
- Clinical: Fiebig stage, viral load in acute infection

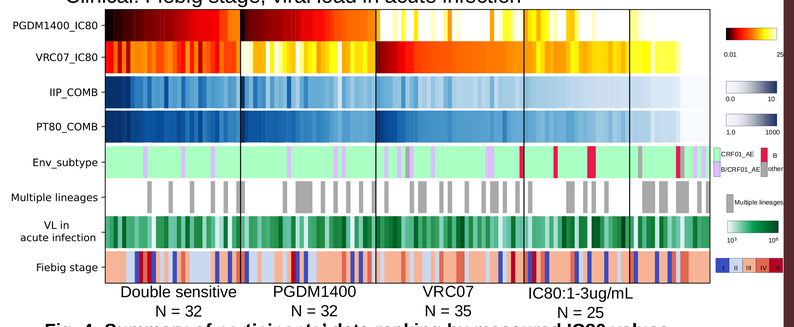

Fig. 4: Summary of participants' data ranking by measured IC80 values.

Conclusion

- 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 founder lineage
  - 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

References

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