Harnessing Proviruses to Define bNAb Sensitivity in Infants With In-Utero HIV-1 (IMPAACT P1115)

842

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BACKGROUND

Broadly neutralizing antibodies (bNAbs) are under study to contribute to ART-free remission. Determining HIV-1 subtype and regional differences in phenotypic susceptibility of contemporaneous transmitted variants are critical to optimize bNAb use. Phenotypic testing on plasma virus is standard to determine therapeutic efficacy but is labor intensive and yields low results in clinical trials (53-56%). In infants, low plasma volume and plasma viral loads also limit this approach.

We posit these barriers may be overcome with a proviral sequencing approach.

STUDY AIMS

1. Define bNAb susceptibility profiles for infants with in-utero HIV-1 using proviral genomes to generate infant-derived pseudoviruses.
2. Evaluate Bliss–Hill-predicted best dual and triple bNAb combinations in vitro.

METHODS

Study Population

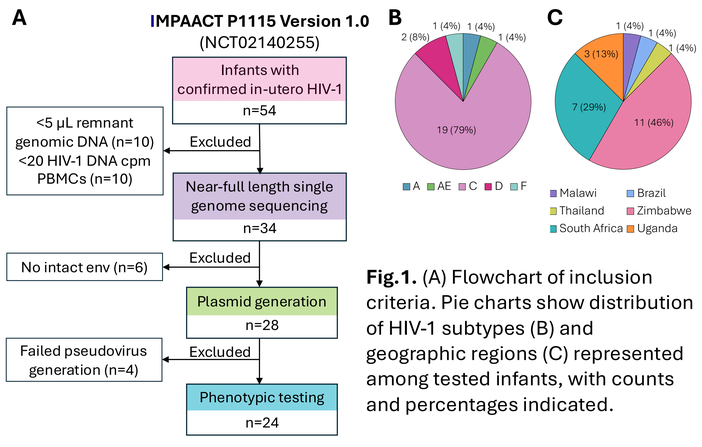

Fig.1. (A) Flowchart of inclusion criteria. Pie charts show distribution of HIV-1 subtypes (B) and geographic regions (C) represented among tested infants, with counts and percentages indicated.

Near Full-Length Single Genome Sequencing (nFLSGS)

A nested near full-length PCR was performed on genomic DNA at limiting dilution. Amplicons were sequenced with Illumina MiSeq and intactness was determined by HIVSeqinR.

TZM-bl Neutralization Assay

Representative env sequences were selected by closest identity to consensus. Env plasmids were generated by Twist Biosciences. Phenotypic testing was performed with the TZM-bl neutralization assay against a panel of 11 bNAbs:

CD4 binding site (CD4bs)		V1/V2 Apex	Glycan-V3	CD4 receptor (CD4r)
VRC01	N6LS	PGDM1400	10-1074	Ibalizumab
VRC07-523LS	1-18	CAP256V2LS	ePGT121.L15	**CD4bs+V1/V2 Apex**
3BNC117			PGT121.414LS	CAP256J3LS

Bliss-Hill Modeling

In vitro 50% or 80% inhibitory concentrations (IC50 and IC80) were analyzed using Los Alamos National Laboratories CombiNAber (hiv.lanl.gov) to predict bNAb combinations that achieve maximal neutralization.

Proviral sequencing and neutralization testing provided bNAb sensitivity profiles for 24 of 28 (86%) infants, supporting the potential for proviral genomes to guide bNAb therapy for *in-utero* HIV-1.

RESULTS

- 257 near full-length genomes (median 8.5; range 1-31) were detected in the 28 infants studied.
- Full-length env was derived from **105 intact** and **26 defective genomes.**
- Pseudovirus generation and subsequent phenotypic testing was successful in 24/28 (86%).
- One infant with divergent env had two pseudoviruses tested (Fig.2).

Env sequences were **homogenous** within infants (**median 99.9% shared identity**; range 96.7-100%)

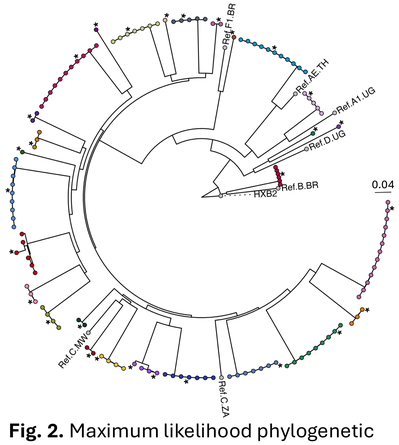

Fig. 2. Maximum likelihood phylogenetic tree constructed with IQTREE of 131 *env* sequences derived from HIV-1 proviral genomes showing participant-specific clustering. Selected env(s) is designated with an asterisk.

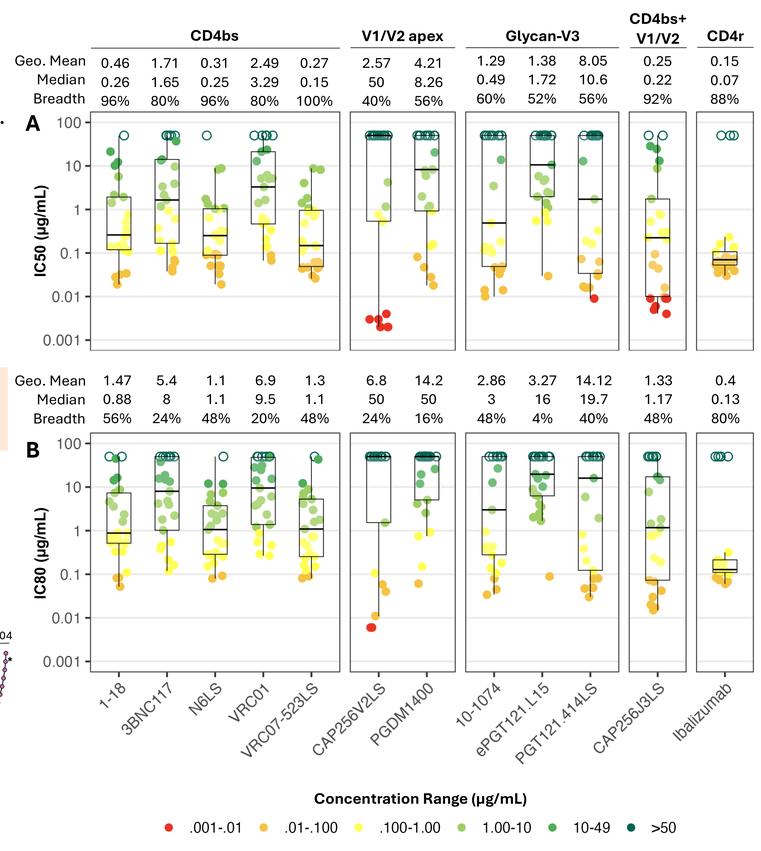

Fig. 3. Neutralization activity of both IC50 (A) and IC80 (B) titers of bNAbs against Env from infants with in-utero HIV-1. Each infant-derived pseudovirus (N=25) is represented by an individual point. Geometric mean, median and neutralization breadth at IC50 <50 µg/mL or IC80 ≤1 µg/mL is included for the corresponding antibody. CD4bs, CD4 binding site; CD4r, CD4 receptor.

PLAIN LANGUAGE SUMMARY

HIV-1 DNA can be used to predict how well antibody therapies will work. This approach could help pick the best antibody treatments for infants born with HIV-1.

ACKNOWLEDGEMENTS

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Bliss-Hill modeling identified **VRC07-523LS+PGT121.414LS** and **VRC07-523LS+PGDM1400+10-1074** as the most effective universal dual and triple bNAb combinations.

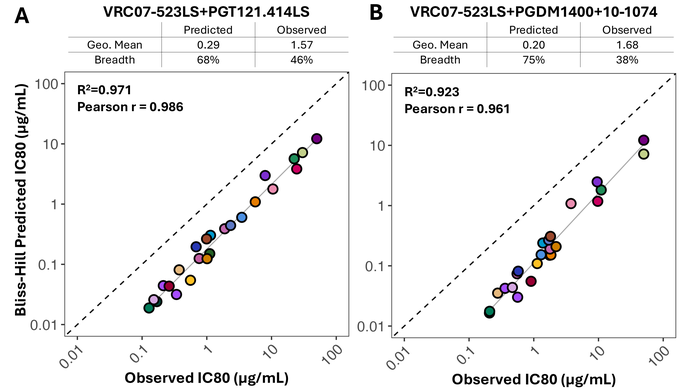

Fig.4. Bliss–Hill–predicted and observed in vitro IC80 values for the predicted best dual (A; VRC07-523LS+PGT121.414LS) and triple (B; VRC07-523LS+PGDM1400+10-1074) bNAb combinations. Geometric mean, median, and neutralization breadth at IC80 ≤1 µg/mL are indicated. Potency–breadth curves (C) compare predicted and observed IC80 values. VRC07-523LS is included as the single bNAb reference.

Fig.5. Targeted (T) vs universal (U) approach. Universal applies the best single or combination bNAb therapy to all infants. Targeted uses sensitivity profiles to select the best single or combination bNAb therapy per infant.

LIMITATIONS

- Only 28/34 (86%) infants had intact sequences or full-length env, which may be overcome with sufficient genomic DNA.
- Four infants failed pseudovirus generation.

CONCLUSIONS

- 100% of selected infants had at least 1 near full-length sequence amplified from proviral DNA.
- Bliss-Hill predicted IC80 values were left-shifted relative to observed, indicating that Bliss–Hill model overestimates potency and coverage compared to in vitro data.
- Targeted approach can achieve maximal neutralization breadth with two bNAbs .

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