An Efficient Envelope Genotypic Assay to Identify bNAb Susceptibility in Infants with HIV

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BACKGROUND

HIV-1 envelope (Env)-specific broadly neutralizing antibodies (bNAbs) have several potential clinical benefits over current antiretroviral treatment (ART) options. The bNAbs with modified Leucine-Serine (LS) Fc receptors permit infrequent subcutaneous dosing and may facilitate viral reservoir reduction and contribute to functional cure. However, data on HIV-1 Env evolution and bNAb susceptibility in perinatally infected infants are limited.

METHODS

Study population:

- Five infants (4 female) living with HIV-1 with intermittent viraemia
- Initiated 3TC, LPV/r & ABC within 90 days of diagnosis
- Investigated over 19.3 months (range: 16.9 - 21)

Table 1. Participant samples investigated and the respective viral loads in copies/mL

Participant	Visit 2 2 months	Visit 3 3 months	Visit 4 6 months	Visit 5 12 months	Visit 6 18 months	Visit 7 24 months
SA-TY-012	355 930	902 552	*1 344 319*	81 796	653 059	*333 199*
SA-TY-015	*293 787*	-	*200 345*	738	-	*115*
SA-TY-025	3 382	*391 854*	*19 376*	135 969	*200*	*4 143*
SA-TY-032	1 150	*754*	154	<100	LDL	*8 885*
SA-TY-034	1 049	*428 562*	*9 650*	*1 954*	*9 239*	*1 420*

Plasma sample investigated

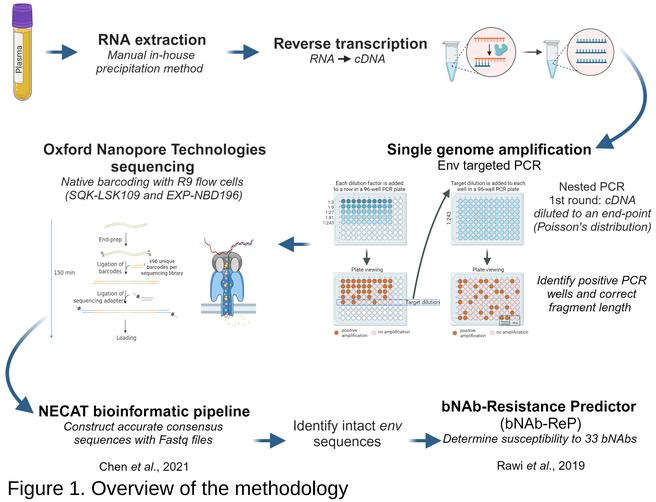


Figure 1. Overview of the methodology

Early intra-patient *env* evolution and diversification seems to have a limited impact on bNAb susceptibility, whereas predicted bNAb susceptibility varied across individuals due to a high level of inter-patient *env* diversity.

RESULTS

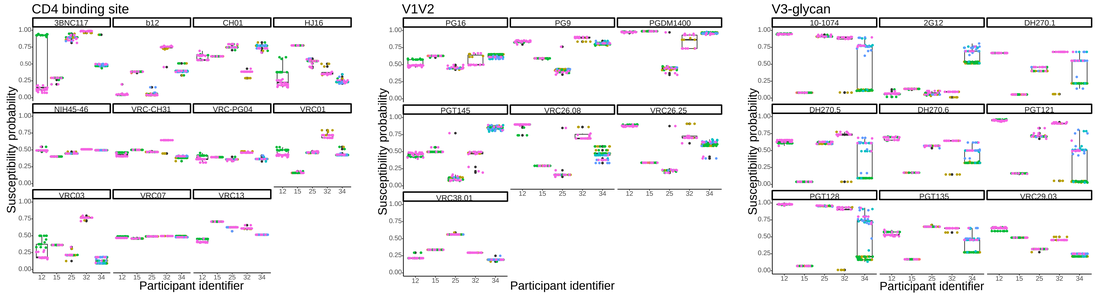
The intra-patient average pairwise distances (APD) ranged from 0.08% - 1.29% (median: 0.43%). Different evolutionary patterns were observed, and length variation emerged in 4/5 (80%) infants. Phylogenetic trees showed temporal structure in four cases with new variants emerging either from majority or minority populations or apparent ancestral or archived variants. All variants were identified as CCR5-tropic by three genotypic prediction models.

Table 2. Investigation of HIV-1 *env* of five infants and the highest predicted bNAb susceptibility

Participant	Duration of observation (months)	Env APD[#] (%)	Length variation (base pairs)
SA-TY-012	16.9	1.02	2 550 – 2 571
SA-TY-015	19.5	0.08	2 568
SA-TY-025	19.1	0.36	2 565 – 2 568
SA-TY-032	19.3	1.29	2 568 – 2 583
SA-TY-034	21	0.43	2 553 – 2 568

[#] APD – average pairwise distance

Overall, the predicted bNAb susceptibility showed a higher inter-patient than intra-patient variability.



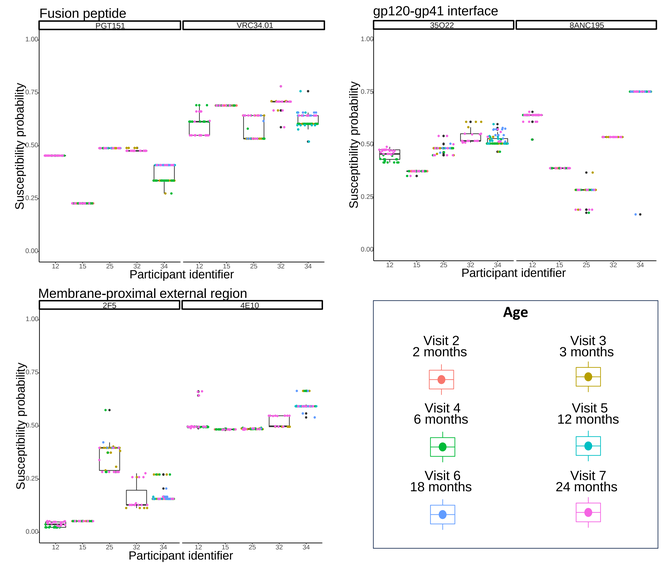


Figure 2. The bNAb-Rep predicted susceptibility results for each binding domain

CONCLUSIONS

We developed an efficient *env* genotypic assay, combining single-genome sequencing with ONT to accommodate *env* sequence length variation as phenotypic bNAb susceptibility testing is costly and has low reproducibility. Applying our workflow, the predicted susceptibility to bNAbs varied across individuals due to high levels of inter-patient *env* diversity. Early ART-treated infants often have viraemia due to adherence challenges. However, early intra-patient *env* evolution was limited and unlikely to impact bNAb susceptibility. Updated prediction algorithms require validation across HIV-1 subtypes.

ADDITIONAL KEY INFORMATION

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