PERFORMANCE OF A PHENOTYPE AND 2 GENOTYPE ALGORITHMS FOR bNAb SENSITIVITY PREDICTION

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BACKGROUND

The use of broadly neutralizing antibodies (bNAbs) in clinical HIV trials have increased in the past years. Treatment with bNAbs can prolong time to viral rebound significantly compared to control groups, in ATI settings. This effect of bNAbs on viral rebound is not seen for all participants, since not all participants harbor bNAb sensitive virus. It has therefore become clear that it is necessary to predict whether participants harbor bNAb sensitive virus, preferentially prior to inclusion in bNAb clinical trials. Here we compare two genotypic and one phenotypic assay of bNAb sensitivity prediction for the two bNAbs; 3BNC117 and 10-1074.

METHODS

Baseline plasma samples from the 59 ART-naïve participants included in the clinical study eCLEAR was sent to Monogram Biosciences for sensitivity prediction by using their PhenoSense® HIV Monoclonal Antibody Assay (figure 1A).

For the two genotype algorithms, RNA was extracted from baseline plasma and cDNA was synthesized using HIV specific primers. The cDNA was diluted, prior to performing nested PCR, to obtain <30% wells containing HIV envelope cDNA. The PCR products were sequenced on an Illumina MiniSeq (figure 1B). The sequences were analyzed using "bNAb-ReP" developed by VRC/NIH and by using "HIV screening analysis" developed at Rockefeller University.

bNAb sensitivity prediction methods does not agree for all HIV participants. In this study an agreement of 52% was observed for 3BNC117 and 79% for 10-1074 across three prediction assays.

RESULTS

Of the 59 participants, Monogram was able to obtain sensitivity predictions for 48 participants and it was possible to amplify and sequence HIV envelope from all 59 participants for the genotypic algorithms.

The three methods did not make the same sensitivity predictions for all participants. The "HIV screening analysis" predicted more participants to be sensitive for 3BNC117 than the two other methods, for 10-1074 the percentage of predicted sensitive and resistant participants was more similar (figure 2 a+b). When comparing the predictions for each participant across all three methods an agreement of 52% was observed for 3BNC117 and an agreement of 79% for 10-1074 (figure 2 c+d). It varied which methods stood out from the others (figure 2c + d).

The sensitivity prediction results was correlated with presumed time of infection (table 1) and with subtype (table 2), since we observed a high subtype diversity in the cohort. We found that all participants having subtype CRF01 (n=14) are resistant to 10-1074, regardless of the prediction method.

Time of infection	No. of participants (PhenoSense)	3BNC117 Sensitive			10-1074 Sensitive		
		PhenoSense	bNAb-ReP	HIV screening analysis	PhenoSense	bNAb-ReP	HIV screening analysis
<6 Months	28 (24)	67%	68%	89%	46%	61%	57%
>6 Months	28 (22)	45%	37%	86%	59%	44%	54%

Table 1: The participants were divided into two groups based on the presumed time of infection (+/- 6 months), the table displays the sensitivity predictions for the two groups. The numbers in the brackets is the number of participants with prediction results in the PhenoSense® Assay.

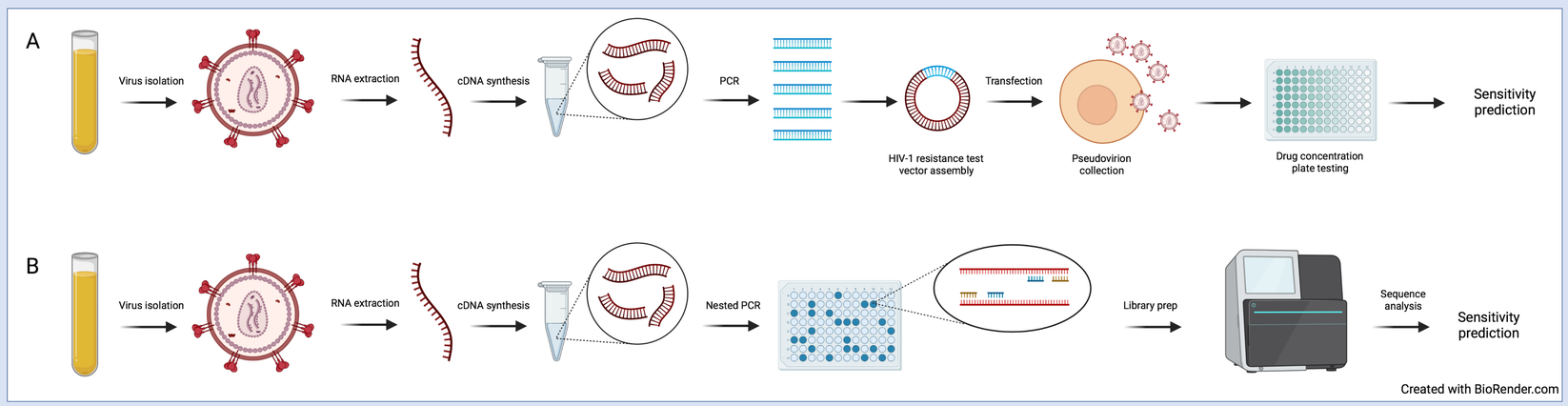

Figure 1: Illustration of the method in the PhenoSense® assay (A) and the method for envelope sequencing for the genotypic assays (B).
Figure 1a is adapted from https://monogrambio.labcorp.com/resources/phenotyping.

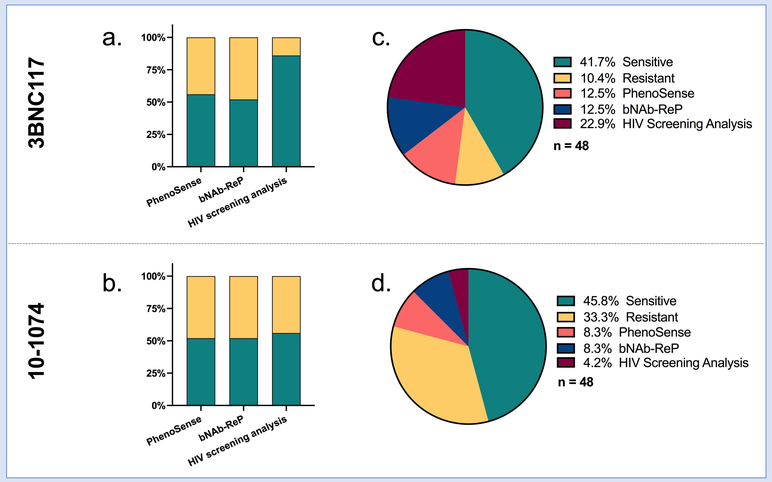

Figure 2: The graphs shows the percentage of participants predicted sensitive and resistant for each of the three methods for 3BNC117 (a) and 10-1074 (b). The pie charts (c + d) shows the percentage of agreement for sensitive and resistant participants and which method stands out in case of disagreement.

Subtype	No. of participants (PhenoSense)	3BNC117 Sensitive			10-1074 Sensitive		
		PhenoSense	bNAb-ReP	HIV screening analysis	PhenoSense	bNAb-ReP	HIV screening analysis
A	2 (1)	0%	50%	50%	0%	0%	50%
B	29 (25)	64%	57%	86%	68%	75%	69%
C	5 (3)	33%	20%	80%	67%	100%	100%
D	2 (1)	0%	50%	100%	0%	0%	50%
F	1 (1)	100%	0%	100%	100%	0%	100%
G	1 (1)	0%	0%	0%	100%	0%	100%
CRF01	14 (11)	45%	50%	93%	**0%**	**0%**	**0%**
CFR02	3 (3)	67%	100%	100%	67%	50%	67%
CRF other	2 (2)	100%	50%	100%	100%	100%	100%

Table 2: The table displays the sensitivity predictions for the different subtypes. The numbers in the brackets is the number of participants with prediction results in the PhenoSense® Assay.

CONCLUSIONS

We conclude that there is a substantially difference between the three prediction methods for 3BNC117. This difference is problematic since results obtained from clinical trials can be difficult to compare if different methods are used for sensitivity prediction. For 10-1074 the agreement on 79% is more acceptable.

We don't observe any correlation between subtype and sensitivity predictions for 3BNC117, but for 10-1074 we observed predicted resistance for all subtype CRF01, which can be important for inclusion of participants with CRF01 in bNAb clinical trials.

ADDITIONAL KEY INFORMATION

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Acknowledgements
Data-set-go.dk