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MUTATIONAL LANDSCAPE OF 10-1074 AND 3BNC117 SENSITIVITY IN A UK POPULATION WITH PRIMARY HIV INFECTION

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BACKGROUND

HIV envelope (Env) is the viral target for broadly neutralising antibodies (bNAbs). 10-1074 and 3BNC117, which target the V3 glycan and the CD4bs respectively, are two potent bNAbs which together can maintain viral suppression after antiretroviral treatment (ART) interruption. Due to its high diversity rate and the dense array of glycans that shield the underlying bNAb epitopes, HIV can escape neutralisation. Although there is no established bNAb sensitivity screening method, several algorithms have identified certain genetic signatures that may predict potential bNAb sensitivity in people living with HIV (PLWH). Here, we aim to assess the utility of bNAb sensitivity screening for clinical trials and to present the distribution of 10-1074 and 3BNC117 sensitivity landscape in a UK cohort.

METHODS

Samples from a total of 173 participants in the HEATHER trial diagnosed and treated during primary HIV infection (PHI), within an estimated 6 months of seroconversion were processed. All participants had been on ART for >1 year and had undetectable viral load at the time of sampling. An average of 20 proviral env sequences per sample were amplified using single genome amplification from 147 participants. Following sequencing, we inspected the amino acid residues that have been reported to confer resistance to 10-1074 (N332 glycosylation motif and ^{324}GDIR^{327}) and 3BNC117 (positions D279, N280 and ^{456}RDGG^{459}) epitopes.

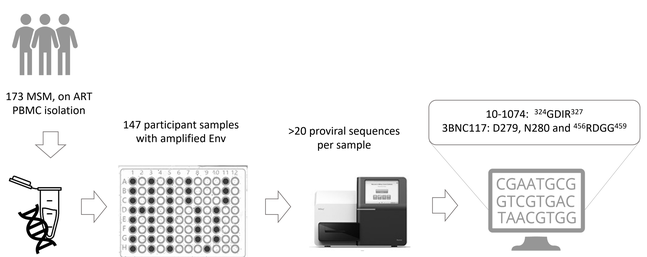

Figure 1: Visualization of the bNAb sensitivity process.

BNAb sensitivity prediction shows that **38.7%** of bNAb treatment-naïve PLWH with PHI in a UK cohort may have at least one sequence resistant to either or both **10-1074 and 3BNC117**. Developing an accurate bNAb sensitivity algorithm will be key for treatment selection and monitoring.

RESULTS

A total of 3122 proviral env sequences were sequenced and analysed (Table).

Participants			
Seroconversion to ART		59 days (range: 3-245 days)	
Env amplification Status (of all participants in cohort)			
Amplified Env		147 (84.9%)	
Clade (% of all participants with amplified Env)			
B clade		106 (72.1%)	
other clades		41 (27.9%)	
Distribution of resistant sequences per participant	**Any sequence resistant (% of all participants with amplified Env, n=147)**	**All sequences resistant (% of all resistant samples)**	**Mix of WT and resistant sequences (% of all resistant samples)**
10-1074	43 (29.2%)	35 (52.2%)	8 (11.9%)
3BNC117	19 (12.9%)	8 (11.9%)	11 (16.4%)
Both	5 (3.4%)	2 (2.9%)	3 (4.4%)

Table: Cohort demographics and sensitivity statistics

Predicted sensitivity per HIV clade was in line with the literature, even though there were only a few non-B clade samples. All CRF01-AE samples were found to be resistant to 10-1074 and >40% of A1 and CRF02-AG were predicted to be resistant to 10-1074 (Figure 2).

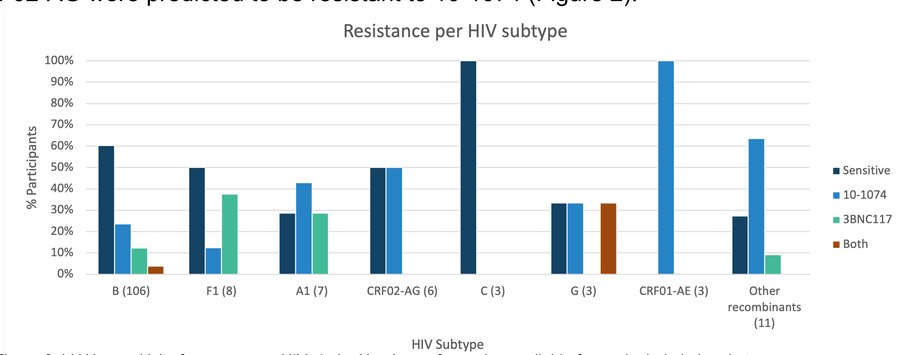

Figure 2: bNAb sensitivity frequency per HIV clade. Numbers of samples available for each clade in brackets.

Mutations affecting the N332 glycosylation motif Asn-X-Ser/Thr were the most common 10-1074 resistance-associated mutations (85%) (Figure 3a). The most frequently mutated 3BNC117 sites were 456 and 459 (47.8% and 34.7%, respectively) (Figure 3b). However, there was considerable variation between participants, including between those with mixed and full resistance.

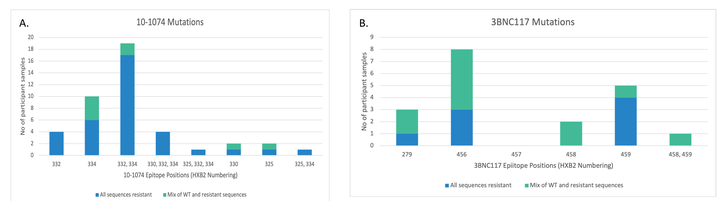

Figure 3: Frequency of mutations conferring resistance to A. 10-1074 and B. 3BNC117.

Maximum likelihood phylogenetic trees revealed patterns of both transmitted and in-host evolution, in participants where pre-ART HIV DNA and/or RNA samples were available (Figure 4).

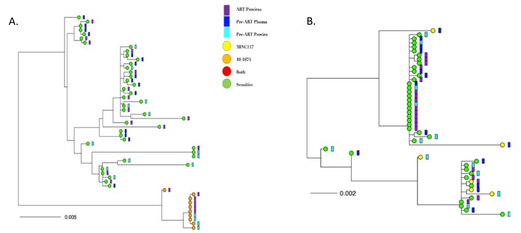

Figure 4: Examples phylogenetic trees showing A. transmitted resistance to 10-1074 and B. resistance to 3BNC117 evolved after transmission.

CONCLUSIONS

Our findings show that ~40% of individuals treated during PHI has potential pre-existing resistance to 10-1074 and 3BNC117 based on current in silico approaches. Although it is unclear how well these algorithms predict clinical response to bNAbs in real world settings, the suggestion from these data is that screening may be key to guide effective treatment.

ADDITIONAL KEY INFORMATION

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