TEROPAVIMAB AND ZINLIRVIMAB SENSITIVITY IN PEOPLE LIVING WITH MDR HIV-1: PRESTIGIO REGISTRY DATA

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BACKGROUND AND AIMS

Teropavimab (TAB) and zinlirvimab (ZAB) are bNAbs that target nonoverlapping HIV-1 envelope spike sites and have been engineered to have long half-lives, potentially allowing for twice-yearly dosing. [1,2]

In a phase 1b proof-of-concept study in PWH with virologic suppression who discontinued oral ART and initiated a regimen of SC lenacapavir + weight-based IV infusions of TAB + ZAB, 18/20 (90%) participants maintained virologic suppression at week 26 [3].

Here, we characterized sensitivity to TAB and ZAB in people living with 4-class drug-resistant HIV (4DR-PWH).

STUDY DESIGN AND METHODS

This was a multicenter, observational study using plasma or PBMCs collected from 50 4DR-PWH (25 with HIV-1 RNA > 1000 copies/mL matched by age, sex, nadir CD4+ and years on ART to 25 virologically suppressed [HIV-1 RNA < 50 copies/mL] PWH) enrolled in the PRESTIGIO Registry (NCT04098315; **https://registroprestigio.org**) with a documented 4DR (NRTI, NNRTI, PI and INSTI).

Phenotypic sensitivity to bNAbs was determined using the PhenoSense Monoclonal Antibody assay (Monogram), with susceptibility defined as IC90 ≤2 mcg/mL.

HIV-1 env was genotyped from PhenoSense test vectors by next-generation sequencing.

Sequences were analyzed for presence of multi-position HIV-1 Env amino acid signatures associated with in-vitro phenotypic susceptibility to teropavimab and zinlirvimab[4]. Briefly, in vitro neutralization data combined with virus sequence information were used to identify HIV Env amino acid positions important for susceptibility (IC50 <1 µg/mL). Only base-pair positions with variability <2% in viral quasi-species were considered part of a signature.

Descriptive statistics are used to present results. Spearman's rank test used for associations between phenotypic susceptibility and clinical variables.

RESULTS

Characteristics of included individuals with analyzed samples (n=46; 4 assay failures) were indicative of extensive treatment history (Table 1).

Of 46/50 (92%) participants with PhenoSense mAb assay results, 35 (76%) were phenotypically sensitive to TAB, 23 (50%) to ZAB, and 19 (41%) to both bNAbs; 7 (15%) had phenotypic resistance to both bNAbs (Table 2). The IC_{90} values for TAB and ZAB in the PWH included in the study are shown in detail in Figure 1. Of 22 viremic participants, 19 (86%) were phenotypically sensitive to TAB, 10 (45%) to ZAB, 9 (41%) to both bNAbs, and 2 (9%) to neither. Of 24 participants with virologic suppression, 67% were phenotypically sensitive to TAB, 54% to ZAB, 42% to both bNAbs, and 5 (21%) to neither. The proportion of participants with sensitivity to both bNAbs was similar (p=0.99) in viremic participants (9/22 [41%]) compared to those with virologic suppression (10/24 [42%]).

More complex signatures predicted phenotypic susceptibility to teropavimab (Figure 2; Panel A) and zinlirvimab (Figure 2; Panel B) with greater specificity.

Nonsignificant correlations between phenotypic sensitivity to bNAbs and age, years of ART, CD4+ cell count, HIV-RNA, type of ART regimen at the sample collection, viral tropism and HIV subtype. There were marginal correlations between phenotypic sensitivity to TAB and years since HIV diagnosis (Spearman r= 0.287, p=0.053) and phenotypic sensitivity to ZAB and CD8+cell count (Spearman r= -0.317, p=0.049).

Table 1: Demograpic, virological and therapeutic characteristics of PWH at the time of sample collection according to HIV-RNA viral load (Panel A and B)

Panel A

Variable	Category	Overall (n=46)	HIV-RNA ≥1000 cp/mL (n=22)	HIV-RNA <50 cp/mL (n=24)	p-value*
Age (years)		54.5 (48.1 - 58.1)	53.7 (32.0 - 58.1)	54.9 (49.4 - 59.1)	0.461
Sex at birth					1.000
	Female	9 (19.6%)	4 (18.2%)	5 (20.8%)	
	Male	37 (80.4%)	18 (81.8%)	19 (79.2%)	
HIV-1 tropism					0.724
	CCR5	16 (37.2%)	8 (40%)	8 (34.8%)	
	CXCR4	27 (62.8%)	12 (60%)	15 (65.2%)	
HIV-1 subtype					0.508
	B	31 (91.2%)	18 (94.7%)	13 (86.7%)	
	CRF02_AG	1 (2.9%)	0 (0%)	1 (6.7%)	
	F	2 (5.9%)	1 (5.3%)	1 (6.7%)	
Years since HIV infection		25.8 (22.9 - 31.7)	25.5 (22.3 - 31.4)	26.6 (23.0 - 31.8)	0.717
Years of ART		23.2 (20.8 - 26.77)	23.3 (20.8 - 26.9)	23.2 (20.7 - 25.4)	0.652
Nadir CD4+ (cells/mcL)		36 (8 - 83)	43 (5 - 91)	33 (14.5 - 77.5)	0.982
CD4(cells/mcL)					<0.0001
	<200	13 (28.3%)	11 (50%)	2 (8.3%)	
	≥200 – <350	9 (19.6%)	9 (40.9%)	0 (0%)	
	≥350 – <500	7 (15.2%)	2 (9.1%)	5 (20.8%)	
	≥500	17 (37%)	0 (0%)	17 (70.8%)	
CD4/CD8 ratio		0.45 (0.22 - 0.81)	0.25 (0.13 - 0.36)	0.81 (0.47 - 0.96)	<0.0001

Panel B

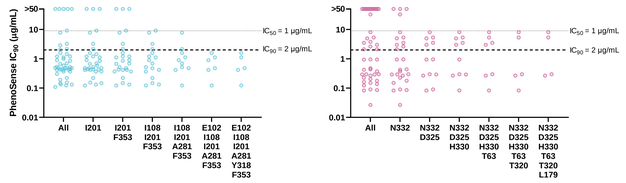
Variable	Category	Overall (n=46)	HIV-RNA≥1000 cp/mL (n=22)	HIV-RNA<50 cp/mL (n=24)	p-value
NRTI-including regimens					0.080
	No	19 (41.3%)	6 (27.3%)	13 (54.2%)	
	Yes	27 (58.7%)	16 (72.7%)	11 (45.8%)	
NNRTI-including regimens					1.000
	No	31 (67.4%)	15 (68.2%)	16 (66.7%)	
	Yes	15 (32.6%)	7 (31.8%)	8 (33.3%)	
PI-including regimens					0.139
	No	9 (19.6%)	2 (9.1%)	7 (29.2%)	
	Yes	37 (80.4%)	20 (90.9%)	17 (70.8%)	
INSTI-including regimens					0.128
	No	8 (17.4%)	6 (27.3%)	2 (8.3%)	
	Yes	38 (82.6%)	16 (72.7%)	22 (91.7%)	
FI-incuding regimens					0.197
	No	33 (71.7%)	18 (81.8%)	15 (62.5%)	
	Yes	13 (28.3%)	4 (18.2%)	9 (37.5%)	
Type of ART regimen at sample collection					0.159
	≤3 ART drugs	25 (54.3%)	9 (40.9%)	16 (66.7%)	
	4-5 ART drugs	20 (43.5%)	12 (54.5%)	8 (33.3%)	
	6-7 ART drugs	1 (2.2%)	1 (4.5%)	0 (0%)	
Number of previous therapeutic lines		9.5 (5 - 20)	10 (4 - 27)	9 (5.5 - 16.5)	0.590
Number of major NRTI mutations		6.5 (4 - 9)	7 (5 - 10)	6 (4 - 8)	0.237
Number of major NNRTI mutations		3 (2 - 5)	3.5 (2 - 5)	2.5 (2 - 3.5)	0.248
Number of major PI mutations		7 (4 - 10)	7 (4 - 8)	6.5 (4.5 - 10.5)	0.842
Number of major INSTI mutations		2.5 (2 - 4.5)	4 (2 - 5.5)	2 (1.5 - 3)	0.006

FI: fusion inhibitors; ART: antiretroviral treatments; *: Wilcoxon rank-sum test for continuous variable; chi-square or Fisher exact test for categorical variables, as appropriate

Table 2: Phenotypic susceptibility to TAB and ZAB according to viral load at the time of sample collection

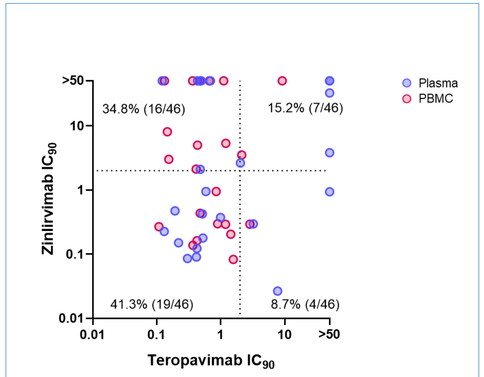
Phenotypic sensitivity	Category	Overall (n=46)	HIV-RNA≥1000 (n=22)	HIV-RNA<50 (n=24)	p-value
Phenotypic sensitivity to TAB					0.118
	No	11 (23.9%)	3 (13.6%)	8 (33.3%)	
	Yes	35 (76.1%)	19 (86.4%)	16 (66.7%)	
Phenotypic sensitivity to ZAB					0.555
	No	23 (50%)	12 (54.5%)	11 (45.8%)	
	Yes	23 (50%)	10 (45.5%)	13 (54.2%)	
Overall Phenotypic sensitivity to BnAbs					0.483
	None	7 (15.2%)	2 (9.1%)	5 (20.8%)	
	TAB or ZAB	20 (43.5%)	11 (50%)	9 (37.5%)	
	TAB and ZAB	19 (41.3%)	9 (40.9%)	10 (41.7%)	

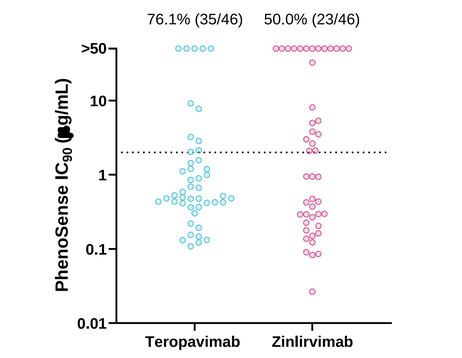
Figure 2: Prediction of Phenotypic Susceptibility by Genotypic Signatures



RNA viruses and DNA proviruses from individual participants were plotted based on presence of HIV-1 envelope signatures for TAB (Panel A) and ZAB (Panel B) sensitivity. "All" indicates all participants independent of presence of HIV-1 envelope signatures. Dashed line represents IC90 value = 2 µg/mL. Dotted line indicating IC50 = 1 µg/mL included for comparison to other studies[4]

Figure 1: Distribution of TAB and ZAB IC_{90} values among PWH included in the study





CONCLUSIONS

- A significant number of the analyzed 4DR-PWH were found to have virus susceptible to TAB and ZAB.
- Demographics and clinical characteristics of analyzed population did not appear to be correlated with susceptibility to TAB and ZAB.
- Confirmation of these findings in a larger sample may elucidate if heavily treatment experienced PWH with multidrug-resistant HIV could be considered candidate for future trials investigating bNAbs-containing regimens to achieve or maintain virologic suppression

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