Development of Individualized Antibody Treatment Regimens for Patients With Multidrug-Resistant HIV

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Background and Rationale

- People living with HIV (PLWH) with multidrug-resistant (MDR) viruses have limited therapeutic options and present challenges regarding clinical management.
- Recent studies have shown that passive transfer of combination broadly neutralizing antibodies (bNAbs) against HIV and anti-domain 1 CD4 antibody UB-421 can sustain virologic suppression in PLWH in the absence of antiretroviral therapy (ART).
- Yet studies addressing the therapeutic potential of these antibodies and/or detailed characterization of immunologic and virologic parameters in PLWH with MDR HIV are lacking. We conducted the present ex vivo study to address this issue.

Materials and Methods

Study population: We conducted an extensive analysis of eleven treatment-experienced PLWH with MDR HIV. Blood from study participants was collected in accordance with a protocol approved by the National Institutes of Health. All study participants provided written informed consent.

HIV reservoir quantification: The frequency of cells carrying intact HIV proviruses was determined by Intact Proviral DNA Assay (IPDA).

Immunologic parameters: Immunologic phenotyping was done using flow cytometry.

HIV neutralization/suppression: Near-clonal replication-competent HIV isolates were derived from CD8$^+$ T cells-depleted peripheral blood mononuclear cells (PBMCs) of the MDR participants. Each viral isolate was incubated with 10μg/ml of bNAbs and anti-CD4 antibodies for 90 minutes followed by incubation with TZM-bl cells for 48 h. Cells were subsequently lysed and substrate (Promega) was added to measure the luciferase activity (Tecan).

Table 1

Clinical Characteristics of Study Participants

Study participant	Age	Sex	Race or ethnic group	Plasma Viremia (copies of HIV RNA/ml)	CD4$^+$ T cell count (cells/μl)	% CD4$^+$ T cells	CD8$^+$ T cell count (cells/μl)	% CD8$^+$ T cells
1	24	F	AA	84,626	16	2	599	73
2	54	M	Caucasian	39,950	23	1	1,896	84
3	50	M	AA	143,379	222	20	610	55
4	42	M	AA	11,464	4	1	197	46
5	44	M	AA	80,156	42	4	593	57
6	26	F	AA	49,585	69	7	550	56
7	52	M	Hispanic	43,873	48	2	1,071	45
8	50	F	AA	99,051	13	1	403	32
9	61	F	AA	33,669	42	5	535	63
10	29	M	AA	73,265	16	2	512	64
11	52	M	Caucasian	5,053	149	13	655	57

Table 2

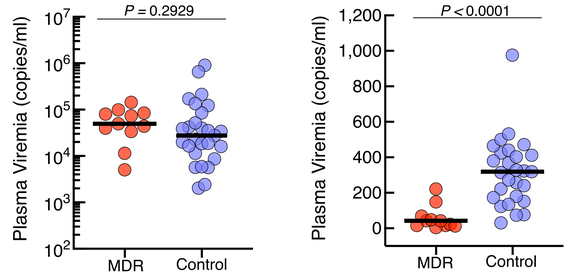
HIV Genotypic Resistance Testing in Study Participants

Drug Class	Participant 1		Participant 2		Participant 3		Participant 4		Participant 5		Participant 6		Participant 7		Participant 8		Participant 9		Participant 10		Participant 11	
Nucleoside Reverse Transcriptase Inhibitors	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile	Score	Profile
Lamivudine (3TC)	25	L	95	R	95	R	55	I	65	R	75	R	80	R	75	R	80	R	70	R	80	R
Abacavir (ABC)	75	R	145	R	100	R	155	R	85	R	125	R	100	R	95	R	100	R	90	R	105	R
Zidovudine (AZT)	100	R	115	R	105	R	140	R	60	R	95	R	140	R	130	R	130	R	45	I	135	R
Stavudine (D4T)	110	R	115	R	105	R	175	R	70	R	95	R	170	R	115	R	130	R	70	R	120	R
Didanosine (DDI)	105	R	155	R	105	R	170	R	125	R	135	R	145	R	85	R	100	R	105	R	90	R
Emtricitabine (FTC)	25	L	95	R	95	R	55	I	65	R	75	R	80	R	75	R	80	R	70	R	80	R
Tenofovir DF (TDF)	40	I	75	R	75	R	135	R	15	L	55	I	70	R	50	I	70	R	35	I	55	I
Non-Nucleoside Reverse transcriptase Inhibitors																						
Efavirenz (EFV)	75	R	130	R	115	R	90	R	10	P	115	R	135	R	0	S	75	R	130	R	70	R
Etravirine (ETR)	55	I	115	R	90	R	75	R	10	P	40	I	50	I	0	S	80	R	40	I	70	R
Nevirapine (NVP)	120	R	205	R	190	R	120	R	10	P	135	R	150	R	0	S	120	R	130	R	70	R
Rilpivirine (RPV)	55	I	120	R	135	R	120	R	10	P	75	R	90	R	0	S	90	R	75	R	105	R
Protease Inhibitors																						
Atazanavir (ATV/r)	25	L	150	R	160	R	125	R	105	R	90	R	155	R	185	R	160	R	45	I	130	R
Darunavir (DRV/r)	0	S	90	R	85	R	95	R	15	L	30	I	70	R	105	R	100	R	70	R	80	R
Fosamprenavir (FPV/r)	20	L	225	R	255	R	235	R	90	R	100	R	230	R	305	R	265	R	175	R	225	R
Indinavir (IDV/r)	30	I	200	R	190	R	170	R	110	R	90	R	170	R	240	R	205	R	85	R	150	R
Lopinavir (LPV/r)	15	L	140	R	130	R	145	R	60	R	55	I	120	R	155	R	135	R	85	R	115	R
Nelfinavir (NFV)	75	R	200	R	270	R	190	R	150	R	115	R	245	R	315	R	275	R	125	R	245	R
Saquinavir (SQV/r)	40	I	125	R	160	R	130	R	105	R	75	R	155	R	190	R	170	R	30	I	105	R
Tipranavir (TPV/r)	0	S	115	R	60	R	65	R	35	I	95	R	60	R	75	R	70	R	70	R	110	R
Integrase Inhibitors																						
Dolutegravir (DTG)	0	S	10	P	45	I	100	R	90	R	0	S	80	R	0	S	0	S	0	S	45	I
Elvitegravir (EVG)	0	S	75	R	90	R	115	R	105	R	0	S	130	R	30	I	0	S	0	S	90	R
Raltegravir (RAL)	0	S	75	R	90	R	120	R	105	R	0	S	130	R	15	L	0	S	0	S	90	R

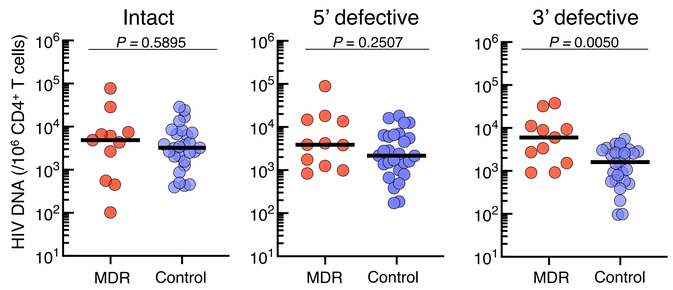
S, susceptible; P, potentially low-level resistance; L, low-level resistance; I, intermediate resistance; R, high-level resistance

Results

Comparison of Plasma Viremia and CD4$^+$ T-cell Counts

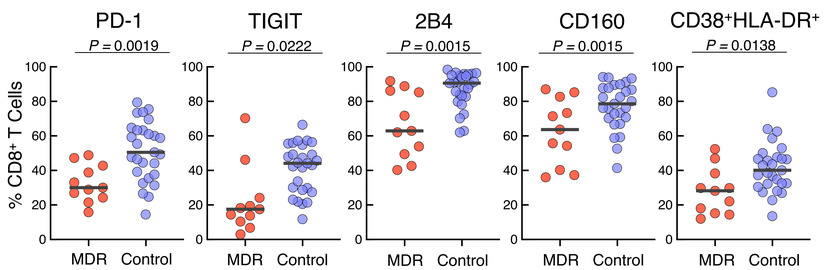


Levels of Intact and Defective HIV Proviral DNA



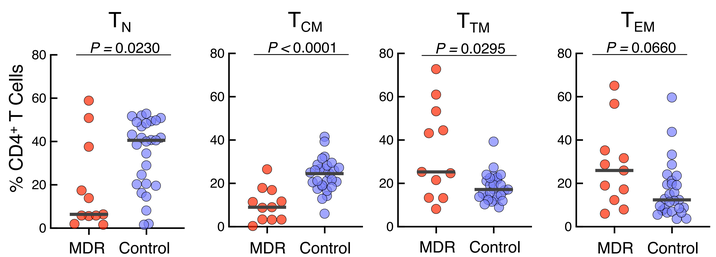
- The level of CD4$^+$ T cell-associated intact and 5'-defective HIV proviral DNA was comparable between the groups. However, the size of the reservoir carrying 3'-defective HIV DNA was higher in MDR group.

Immune Exhaustion and Activation Markers on CD8$^+$ T cells



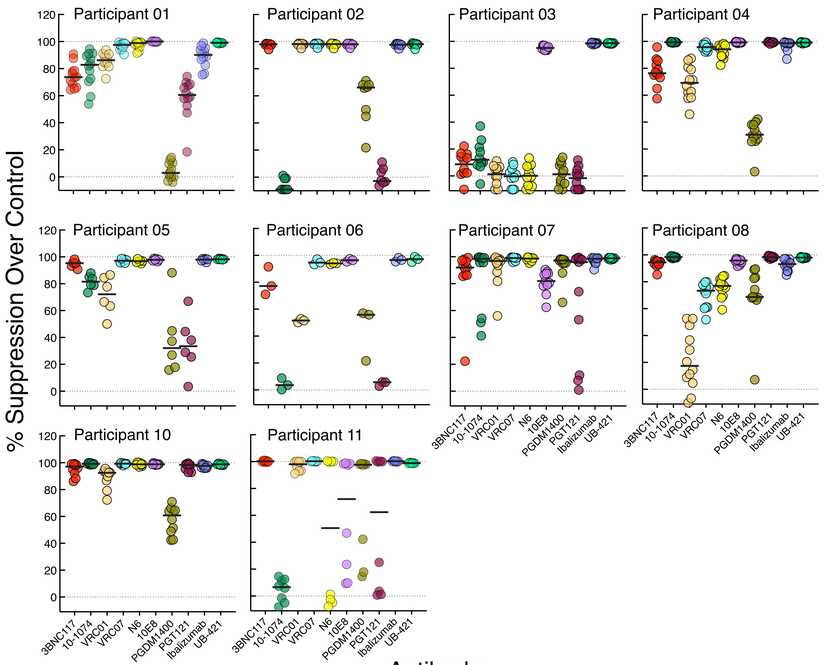
- Expression levels of activation and exhaustion markers PD-1, TIGIT, 2B4, CD160 and CD38$^+$/HLA-DR$^+$ were significantly lower in the CD8$^+$ T cells of the MDR HIV group compared to the control group.

Comparison of the Levels of CD4$^+$ T cell Subsets



- The levels of naïve and central memory CD4$^+$ T cells were significantly lower in the MDR group. In contrast, the level of transitional memory CD4$^+$ T cells was significantly higher in the MDR group.

Neutralization/Suppression Capacity of bNAbs and Anti-CD4 Antibodies against Replication-competent Viral Isolates derived from Study Participants with MDR HIV



- The infectious viral isolates from each study participant with MDR HIV were resistant to at least 2 bNAbs (average 4 bNAbs per participant). However, with the exception of Participant 03, the infectious viral isolates from all study participants were sensitive to at least one of the CD4-binding site (3BNC117, VRC01, VRC07, and N6) and one of the non-CD4 binding site Abs (10-1074, 10E8, and PGT121)
- Notably, none of the 93 infectious viral isolates obtained from the study participants were resistant to UB-421

Study Limitations

- Major limitation of this study is the small sample size; necessary to confirm our findings in a larger cohort of PLWH with MDR HIV and to conduct clinical trials of HIV-specific bNAbs and/or UB-421 in the presence of optimized background regimens.
- It remains a challenge to perform extensive pre-screening of autologous HIV to determine sensitivity profiles against the antibodies being considered for treatment.

Conclusions

- We demonstrate that the infectious viral isolates derived from the majority of study participants could potentially be neutralized by a combination(s) of two bNAbs that bind to two non-competing regions on the HIV envelope protein.
- To our knowledge, this is the first study to examine the immunologic and virologic parameters associated with MDR virus.
- Our data suggest that the therapeutic options for heavily treatment-experienced PLWH with MDR viruses could be potentially expanded to include HIV-specific bNAbs and UB-421, an avenue that has until now not been explored.

References

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