Patients Infected with Multi-class Resistant HIV-1 and with Viral Suppression Treated with No More than One Active Drug: Comparison of Historical Resistance Reports and Drug Resistance in Proviral DNA

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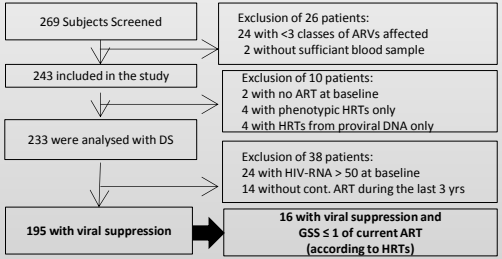
BACKGROUND

- Archived drug resistance-associated mutations (DRMs) may compromise ART for life-time and necessitate complex therapies for decades.
- However, there are anecdotal reports on patients (pts) with long-term control of HIV despite extensive resistance to current ART, suggesting that DRMs may be dispered in different clones.[1]
- Deep sequencing (DS) assays represent an accurate and reproducible approach to analyze HIV-1 mutant spectra in proviral DNA, even at variant frequencies well below those routinely detectable by conventional population sequencing-based assays.[2,3]
- We were interested in the mutational patterns in proviral DNA in pts who had achieved viral suppression (VS) despite history of multidrug-resistant variants and despite a low genotypic susceptibility score (GSS) of current ART regimen.

METHODS

- LOWER was a nation-wide, cross-sectional study of patients with major DRMs in ≥3 ARV classes (of NRTIs, NNRTIs, PIs, INSTIs) in Germany.
- In patients who had achieved viral suppression (VS) at the time of inclusion, mutational patterns in proviral DNA (after APOBEC filtering) were compared with cumulative DRMs available from historical resistance tests (HRTs). GSS was assessed using Stanford-HIVdb v8.6.1.
- This subanalysis focusses on patients with VS whose ART consisted of ≤1 active agent based on HRTs.

Figure 1. Patient disposition/selection in the LOWER study



RESULTS

- Of 195 pts with VS, HRTs indicated in 16 (8%) that ART had a GSS ≤1.
- In 9 pts with a GSS of 1, fully active drugs were INSTIs (n=5), boosted PIs (n=2), and entry inhibitors (n=2). Among the 7 pts with a GSS <1, 3 were found to have a GSS=0. Median time of VS in the 16 pts was 9.7 years.
- Even with a low DS cut-off of <2%, many DRMs were not re-detected by DS and mean GSS increased from 0.69 (range 0-1) to 1.66 (0-3).
- In 11/16 pts, proviral drug resistance yielded a GSS increase of ≥0.5 for current ART, compared to HRTs. Only 1 patient had a GSS of < 1 both in HRTs and in the proviral DNA.

Table 1. Characteristics of all patients with VS in LOWER.

	Patients with VS and with GSS >1	Selected Patients with VS and with GSS ≤ 1
n	179	16
Male gender	89.4 %	93.8 %
Median age, yrs (range)	55 (21-80)	58 (48-77)
Caucasian Origin, subtype B	100.0 % (88.1%)	90.0 % (100.0%
Median yrs since first HIV+ (range)	25.0 (6.7-34.3)	24.4 (19.7-31.6)
Current CD4 cells/µl, Median (range)	600 (39-2293)	503 (324-1160)
Nadir CD4 cells/µl, Median (range)	67 (0-510)	111 (9-335)
Prior AIDS-defining illness, %	53.4 %	37.5 %
Initiation of ART prior 2000, %	86.7 %	100 %
Median duration/years of VS (range)	8.5 (0-18.6)	9.6 (0-18.4)

Table 2. Active drugs in the 16 pts with a GSS ≤ 1 of current ART, based on HRTs. Drugs with GSS=0.5 are depicted in brackets.

Subject	Yrs of VS	Current ART	GSS by HRT	Active ARVs by HRT	GSS by DS	Active ARVs by DS from proviral DNA
68	4,4	TAF+FTC+DTG bid	1	DTG	1,5	DTG+(TAF)
82	14,8	TDF+FTC+ATV/r	0,5	(ATV)	3	TDF+FTC+ATV
88	10,0	3TC+RAL+DRV/r bid	1	RAL	2	RAL+DRV
96	12,0	TDF+FTC+FPV/r	0,5	(TDF)	1,5	(TDF)+FPV
118	0,0	ABC+3TC+DRV/r	1	DRV	3	ABC+3TC+DRV
126	11,7	TAF+FTC+EVG/c	1	EVG	1	EVG
137	1,5	ATV/r+MVC	1	MVC	2	ATV+MVC
141	18,4	ABC+3TC+LPV/r	1	LPV	1	LPV
174	0,5	TAF+FTC+LPV/SQV/r	0	-	3	FTC+LPV+SQV
183	1,3	ATV/r mono	0	-	1	ATV
187	9,4	LPV/r mono	0	-	0	-
198	0,5	ETV+DRV/r bid	0,5	(DRV)	1	DRV
204	15,8	LPV/r+RAL	1	RAL	1	RAL
210	7,1	DRV/r bid+ETV+T20	1	T-20	2,5	DRV+(ETV)+T20
219	9,9	ABC+3TC+ETV+DRV/r bid	0,5	(ETV)	2	ETV+DRV
224	12,9	DTG mono	1	DTG	1	DTG

Table 3. Resistance testings in the 7 patients with VS and less than 1 active agent based on historical resistance testings. Active drugs and GSS using using a Sanger-like cut-off (15%) and DS from proviral DNA

Subject	Current ART	Cumulative historical resistance tests (HRs)	RT from proviral DNA (Sanger, 15 %)	RT from proviral DNA with DS
82		K65R, V75I, M184V/ K103N, P225H/ M46I, L90M	None	Y188C
	TDF	High-level	Active	Active
	FTC	High-level	Active	Active
	ATV/r	Intermediate	Active	Active
96		M41L, M184V, L210W, T215Y/ K103N/ I54V, V82A, L90M	M41L, M184V, T215Y	M41L, M184V, L210W, T215Y/ K103N/ L90M
	TDF	Intermediate	Intermediate	Intermediate
	FTC	High-level	High-level	High-level
	FPV/r	High-level	Active	Low-level
174		M41L, D67N, V75I, M184V, L210W, T215Y/ Y188L/ M46I, L76V, I84V, L90M	M41L, A62V, V75I, L210W, T215Y	M41L, A62V, V75I, L210W, T215Y
	TDF	High-level	High-level	High-level
	FTC	High-level	Low-level	Low-level
	SQV	High-level (active?)*	Active	Active
	LPV/r	High-level	Active	Active
183		M41L, K65R, D67N, K70R, L74V, M184V, T215Y, K219Q/ Y181C/ M46I, I84V, L90M	M41L, D67N, D210W, T215Y/QS8E	M41L, D67N, K70R, L74V, M184V, D210W, T215Y, K219Q/Y181C/QS8E
	ATV/r mono	High-level	Active	Active
187		M41L, D67N, M184V, L210W, T215Y/ M46I, V82A, I84V	M41L, D67N, M184V, L210W, T215Y/ M46I, V82A, I84V	M41L, D67N, K70E, M184V, L210W, T215Y/ M46I, V82A, I84V
	LPV/r mono	High-level	High-level	High-level
198		M41L, A62V, K65R, D67N, T69N, K70R, L74V, V75I, F77L, Y115F, M184V, L210W, T215Y/ L100I, K101H, K103N, V108I, Y181C, Y188HL/ M46I, G48V, I50V, V82A, I84V, L90M	M41L, D67N, T69N, M184V, L210W, T215Y/ K103N, E138A, Y181C, H221Y, M230I/ M46I, G48V, V82A	M41L, D67N, T69N, M184V, L210W, T215Y/ K103N, E138A, Y181C, Y188HL, H221Y, M230I/ M46I, G48V, I50V, V82A, I84V, L90M
	ETV	High-level	High-level	High-level
	DRV/r	Intermediate	Active	Intermediate
219		M41L,M184V, L210W, T215Y, K219Q/ Y181C/ V32I, M46I, I54V, Q58E, L76V, N88S, L90M	L210W, T215Y	M41L,M184V, L210W, T215Y/ M46I, Q58E, N88S, L90M
	ABC	High-level	Low-level	High-level
	3TC	High-level	Active	High-level
	ETV	Intermediate	Active	Active
	DRV/r	High-level	Active	Active

*Hypersusceptibility possible, based on a cohort study[4]

CONCLUSIONS

- Long-lasting viral suppression can be observed in selected patients with multi-class resistance, even when historical resistance reports suggest only one active agent (or even less) in the current ART regimen.
- In most of these patients, predicted GSS was higher using DS from proviral DNA, compared to cumulative historical testings.
- This indicates that at least some DRMs could have been cleared from the latent reservoir over time or lost their impact.

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