Frequent Detection of DRMs by Deep Sequencing in Patients with Documented Extensive Resistance and Long-lasting Viral Suppression: The Proviral DNA Archive Remains Stable for Decades

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BACKGROUND

- Deep sequencing (DS) assays may represent a reproducible approach to analyse HIV-1 mutant spectra, even at variant frequencies well below those routinely detectable by population (Sanger) sequencing.
- DS data from viral reservoirs (i.e. peripheral blood mononuclear cells) in patients (pts) with documented multiple viral drug resistance mutations (DRMs) and with long-standing viral suppression is scarce.

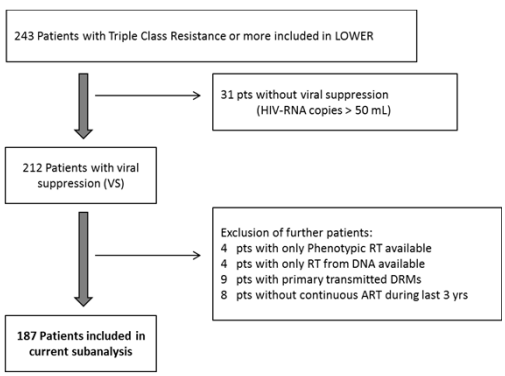
METHODS

- From April to November 2017, this nation-wide study has enrolled pts with extended resistance in 13 large HIV centres in Germany (LOWER Study, registered: DRKS00012396)
- For inclusion, signed informed consent and documented evidence of major drug DRMs to ≥3 ART classes of NRTIs, NNRTIs, PIs or INSTIs were mandated.
- In pts with viral suppression (< 50 HIV RNA copies/mL, VS), DS was performed from proviral DNA.
- The number of individually detected mutations by DS (after APOBEC filtering) was compared with all reported historical DRMs.
- We stratified pts according to the time of viral suppression (< 5, 5-10, > 10 years).

PATIENTS

- Of a total of 243 pts who have been included in the LOWER study, 187 pts (168 males, 19 females) with viral suppression (VS) and continuous ART during the last 3 years were selected for this subanalysis (see **Figure 1**).

Figure 1. Patient disposition/selection (RT= resistance testing)



RESULTS

Table 1. Characteristics of the 187 selected pts with VS (Demographics, HIV infection, ART)

	Selected Pts with VS (n=187)
Demographics	
Male gender	89.8 %
Median age, yrs (range)	55.4 (31.7-80.1)
Caucasian Origin	92.4 %
Subtype B	90.0 %
HIV History	
Median yrs since first HIV+ (range)	25.2 (6.8 – 34.3)
Current CD4 cells/µl, Median (range)	597 (39-2293)
Current CD4 < 200 cells/µl, %	1.6 %
Nadir CD4 cells/µl, Median (range)	69 (0-510)
Nadir CD4 < 200 cells/µl, %	83.0 %
Prior AIDS-defining illness, %	53.2 %
ART History	
Median yrs since first HAART (range)	20.7 (5.5 – 23.2)
Initiation of ART prior 2000, %	84.6 %
Initiation of ART 2000-2007, %	13.1 %
Initiation of ART after 2007, %	2.3 %
History of mono/dual NRTI regimens	78.6 %

Table 2. Characteristics and historical DRMs from genotypic resistance tests (GRTs) stratified by time of VS

	< 5 yrs of VS	5-10 yrs of VS	>10 yrs of VS
n	51	74	62
Male gender	86.3 %	91.9 %	90.3 %
Median age, yrs	53.9	56.2	58.0
Current (Nadir) CD4 cells/µl, Median	652 (72)	577 (50)	622 (76)
Viral suppression (VS)			
Median time of VS, yrs	2.8	8.2	12.3
Sustained VS/Blips/Others (during the last 3 yrs)	20/16/15	63/8/3	51/10/1
Median time first TCR → first VS, yrs	9.0	6.2	2.0
Historical GRTs			
GRTs per patient, mean	4.8	4.8	3.5
Total DRMs per patient, mean (n)	9.3 (473)	10.8 (797)	9.8 (609)
NRTI DRMs per patient, mean (n)	4.8 (244)	5.3 (392)	5.3 (329)
NNRTI DRMs per patient, mean (n)	1.9 (95)	1.9 (139)	1.9 (115)
PI DRMs per patient, mean (n)	2.3 (117)	3.5 (256)	2.6 (164)
INSTI DRMs per patient, mean (n)	0.3 (17)	0.1 (10)	0.0 (1)

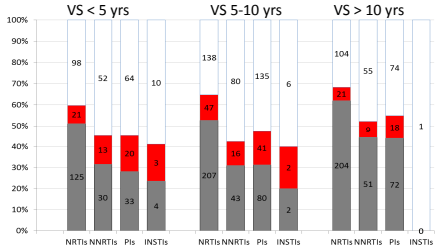


Figure 2.
DRMs in different classes: Redetection rates (%) by DS, stratified by the time of viral suppression (VS).
Grey: „Sanger-like" cut-off 15 %, red: 2-15 %

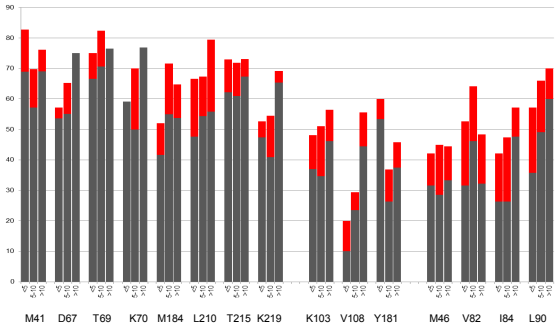


Figure 3.
DRMs at specific codons with >20 % prevalence in historical GRTs: Redetection rates (%) by DS, stratified by years of viral suppression.
Grey: „Sanger-like" cut-off 15 %, red: 2-15 %

CONCLUSIONS

- In this large cohort study of HIV+ pts with documented extensive resistance, DS of proviral DNA using a cut-off of 2 % detected (a little more than) the majority of DRMs that had emerged at previous virologic failures.
- Even in pts with continuous viral suppression (VS) of more than 10 years, detection rates of different DRMs (using different cut-offs) were not lower than in pts with shorter periods of VS.
- DS sensitivity appears to be not affected by the duration of VS. During the first decade of VS, the "resistance archive" in proviral DNA remains relatively stable.

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