Evaluation of HIV-DNA resistance evolution in highly treatment-experienced and multi-resistant individuals under virological control: a longitudinal study from the PRESTIGIO Registry

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Background

Highly treatment-experienced (HTE) people with HIV (PWH) harbouring a multi-drug resistant (MDR) virus are a fragile population at high risk of disease progression and virological failure. Despite this, due to the proper tailoring of optimized regimens, HTE individuals may reach and maintain virological suppression. In this context, few data are available about evolution of the viral reservoir and archived resistance during virological suppression in HTE MDR PWH.

Aim

This study aimed to clarify whether resistance detected in HIV-DNA might evolve in virologically suppressed HTE individuals with multidrug resistance.

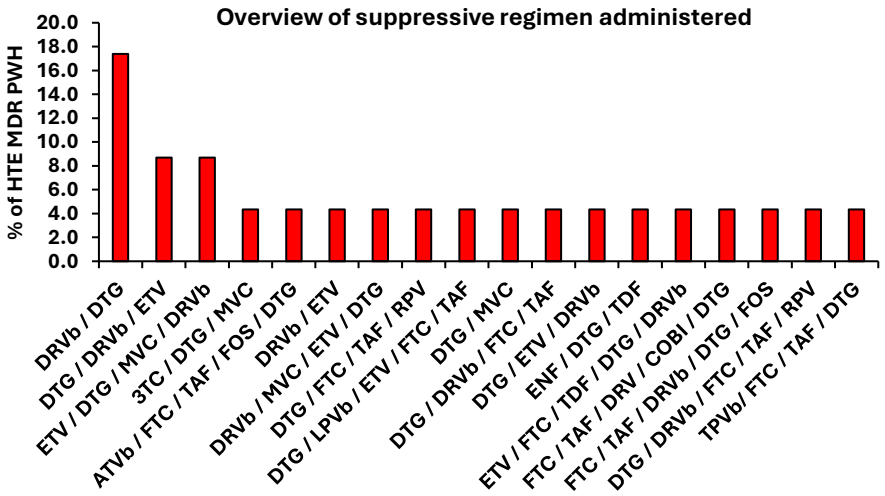
Methods

Virologically suppressed (HIV-RNA <50 copies/mL) HTE MDR individuals from the PRESTIGIO registry (https://registroprestigio.org/project) with two available longitudinal PBMC samples spanning at least 9-12 months (T0-T1) were Included. HIV-DNA quantification through droplet digital PCR and evaluation of HIV-DNA resistance through next generation sequencing (NGS, Illumina-MiSeq) set at 5% were performed at T0 and T1. Major resistance mutations (MRM) were evaluated according to HIVdb ver. 9.6 (https://hivdb.stanford.edu). To evaluate differences over time within the same individual, Wilcoxon test and McNemar test for paired samples were used for continuous and categorical variables, respectively.

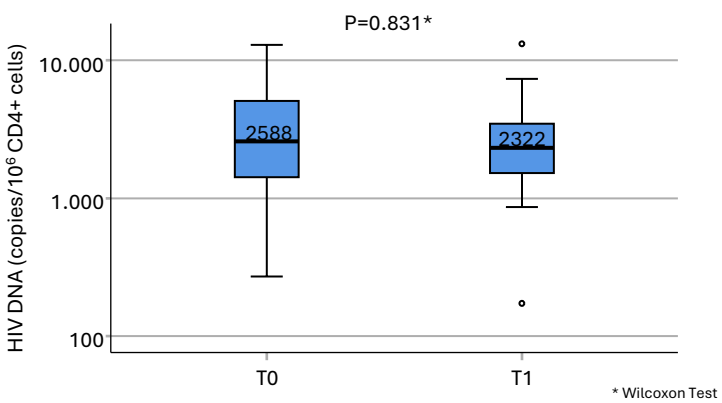
Participants' characteristics at T0

Characteristics	Overall (n=23)
Age, years, median (IQR)	55 (53-59)
Male, n (%)	17 (73.9)
Duration of ART, years, median (IQR)	22 (21-25)
Duration of last therapy, months, median (IQR)	37 (19-44)
CD4+ T-cells, cells/mm^3, median (IQR)	647 (453-975)
CD8+ T-cells, cells/mm^3, median (IQR)	1041 (752-1358)
CD4+/CD8+ ratio, median (IQR)	0.6 (0.4-1.0)
Total HIV-1 DNA, copies/million CD4+ T-cells, median (IQR)	2588 (929-5122)
Duration of virological suppression, years, median (IQR)	3 (3-5)
Time between T0-T1, months, median (IQR)	12.8 (11.8-13.6)

Suppressive salvage regimens mostly contained dolutegravir (95.7%) and/or darunavir (69.6%) and more than half (60.9%) were NRTI sparing



HIV-DNA levels did not significantly change from T0 to T1



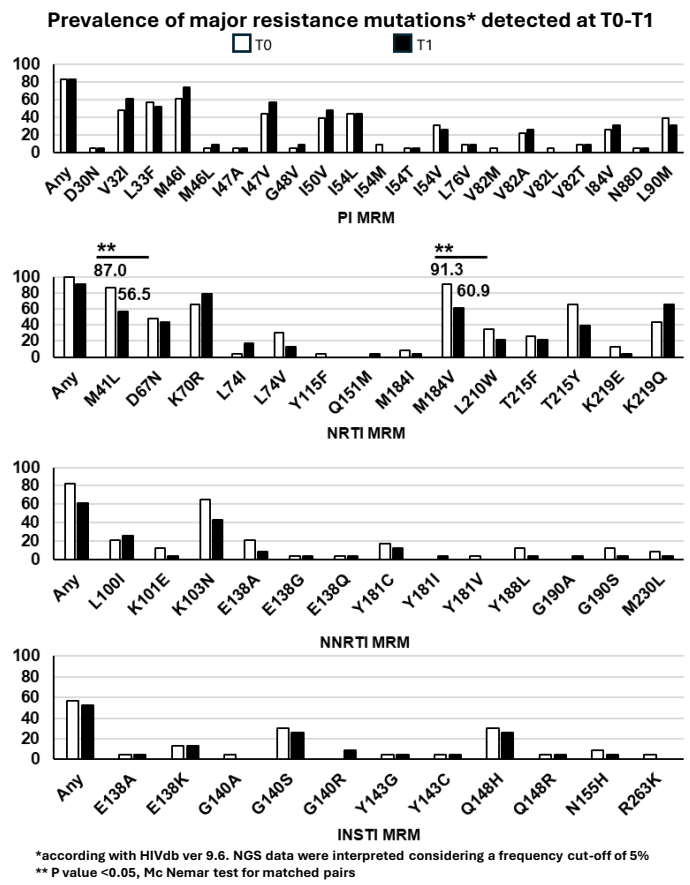
* Wilcoxon Test

In HIV-DNA, the prevalence of ≥ 3-class resistance was 87.0% at T0 and 78.2% at T1 (P=0.607). The number of any MRM and class-specific MRM did not significantly change over time

Number of MRM detected with NGS-GRT set at 5%, median (IQR)			
	T0	T1	P Value*
Any MRM	12 (10-16)	13 (8-14)	0.384
PI	6 (2-7)	6 (2-6)	0.617
NRTI	6 (4-6)	4 (2-7)	0.170
NNRTI	2 (1-3)	1 (0-2)	0.153
INI	1 (0-1)	1 (0-1)	0.822

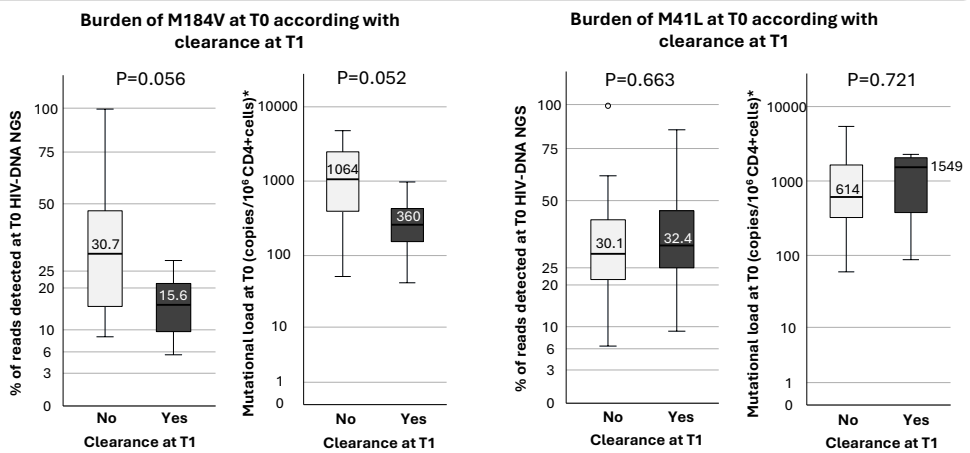
*Wilcoxon test for matched pairs

The prevalence of several RTI resistance mutations decreased over time, however a significant decrease was observed only for M41L and M184V



*according with HIVdb ver 9.6. NGS data were interpreted considering a frequency cut-off of 5%
** P value <0.05, Mc Nemar test for matched pairs

Individuals who lost M184V had a lower mutational load at T0 compared to those who had the mutation persistently detectable. M184V was more likely to be cleared in individuals with mutational load <1000 vs. ≥1000 copies/10^6 CD4+ cells at T0 (7 out of 13, 53.8% vs. 0 out of 8, 0%; P=0.018). This phenomenon was not observed for M41L



*Mutational load was calculated by multiplying the mutation frequency in PBMC DNA for the HIV-DNA levels detected in the same sample

Conclusions

Within 1 year of observation in stably suppressed HTE MDR PWH, there was minimal evolution of MRM. M184V and M41L declined over time and for M184V this decline was associated with low mutational load at the first time point evaluated. Therefore, assessing the M184V burden might help to identify individuals more prone to lose it.

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