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Factors associated with maintenance of high CD4 counts in heavily treatment experienced multidrug resistance PWH: data from PRESTIGIO Registry

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PURPOSE

Advances in antiretroviral treatment have allowed the majority of heavily treatment-experienced (HTE) people with HIV (PWH) with multi-drug resistance (MDR) to achieve and sustain an improved viro-immunological status over time. Nevertheless, this population often continues to face substantial therapeutic challenges due to the limited availability of fully active drugs and the frequent presence of extensive resistance patterns. Interestingly, despite these unfavourable conditions, a subgroup of HTE-MDR PWH is able to maintain persistently high CD4 counts, even in the absence of complete virological suppression.

The present study aims to investigate and characterize the viro-immunological and therapeutic factors associated with this peculiar condition.

METHODS

HTE MDR PWH from the PRESTIGIO registry (https://registroprestigio.org/), with at least one CD4 count and viremia measurement per year during 2021–2024, were included.

Sustained high CD4 count (hCD4) was defined as maintaining >500 cells/mm³ throughout the study period, and this definition was used to stratify the HTE-MDR population. Specifically, individuals with >75% of CD4 measurements >500 CD4 cell/mm³ were considered in hCD4 status and were compared with those while or >75% of measurement <500 CD4 cell/mm³.

Virological failure (VF) was defined as 2 consecutive viremia measurements >50 copies/mL or a single >1000 copies/mL . VF occurrence and the maximum value of viremia detected per each VF episode were assessed throughout the study period.

Cumulative resistance and drug susceptibility were evaluated through HIVdb v9.8; all mutations detected in genotypic resistance tests (GRT) available before 2021 were cumulated, and resistance was assessed based on the presence of major resistance mutations and genotypic susceptibility.

Associations of viro-immunological and therapeutic factors with hCD4 were tested using Chi-squared or Fisher's exact test, as appropriate for dichotomous variables, and Mann–Whitney test for continuous variables.

CONCLUSIONS

In the latest years, HTE PWH enrolled in the PRESTIGIO registry who achieved a high CD4 recovery maintain good immunological control despite MDR.

VF episodes with high viremia levels, full resistance to INSTI and lower CD4 nadir are associated with a lower likelihood of maintaining high CD4.

Further studies are needed to ascertain the role of INSTI resistance accumulation on immunological conditions

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RESULTS

Table 1. Characteristics of HTE MDR PWH according to the number of CD4 cell count over 2021-2024.

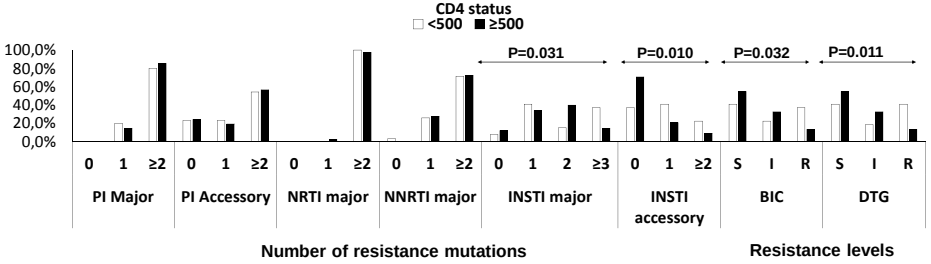
		CD4 cell count (cells/mm³) maintained over 2021-2024		
Variables at last observation	**Overall (n=118)**	**CD4 <500 (n=35)**	**CD4 ≥500 (n=83)**	**p-value**
Age, years, median (IQR)	60 (57-64)	61 (56-65)	60 (57-64)	0.802
Male gender, n (%)	78 (66.1)	26 (74.3)	52 (62.7)	0.314
Time from HIV diagnosis, years, median (IQR)	32.7 (28.4-36.0)	32.2 (28.4-36.6)	32.8 (28.3-35.7)	0.846
Time on cART, years, median (IQR)	28.3 (26.4-31.3)	29.3 (26.7-32.8)	28.1 (26.3-30.7)	0.217
Time from MDR onset, years, median (IQR)	**9.9 (7.8-13.5)**	**8.8 (6.2-11.6)**	**10.7 (8.7-13.7)**	**0.013**
Nadir CD4+, cells/mm³, median (IQR)	**118 (24-212)**	**64 (9-141)**	**149 (37-255)**	**0.007**
Viremia <50 copies/mL	100 (84.8)	30 (85.7)	70 (84.3)	1.000
Vf recorded in the last 4 years, n (%)	43 (36.4)	16 (45.7)	27 (32.5)	0.250
Peak of viremia at VF, median (IQR), copies/mL	**148 (76-4780)**	**5215 (772-62,532)**	**107 (71-259)**	**0.003**
X4 tropism during infection history, n (%)	94 (68.1)	16 (61.5)	48 (70.6)	0.400
Number of drugs currently received, median (IQR)	3 (2-4)	3 (2-5)	3 (2-4)	0.187
Number of drugs currently received, n (%)				0.317
Dual	37 (31.4)	11 (31.4)	26 (31.3)	
Triple	34 (28.8)	7 (20.0)	27 (32.5)	
More than three drugs	47 (39.8)	17 (48.6)	30 (38.1)	
Ever exposure to recently approved drugs, n (%)				
Doravirine	**30 (25.4)**	**15 (42.9)**	**15 (18.1)**	**0.005**
Fostemsavir	**26 (22.0)**	**14 (40.0)**	**12 (14.5)**	**0.002**
Ibalizumab	**7 (5.9)**	**6 (17.1)**	**1 (1.2)**	**0.003**
Lenacapavir	7 (5.9)	4 (11.4)	3 (3.6)	0.194
Islatravir	1 (0.8)	1 (0.8)	0 (0.0)	0.297

During the last 4 years, among 118 individuals included, 83 (70.3%) maintained hCD4; at last observation, viremia was undetectable in most individuals (84.8%) regardless of hCD4 status (Table1).

More recent MDR onset, lower nadir CD4 counts and exposure to novel drugs (doravirine, fostemsavir, ibalizumab, lenacapavir, islatravir) were associated with a lower likelihood of hCD4 status. VF occurred in 36% of participants but did not correlate with hCD4 status, however viremia at VF was higher in those not achieving hCD4.

Duration of treatment/infection and coreceptor tropism were not associated with hCD4 status (Table 1).

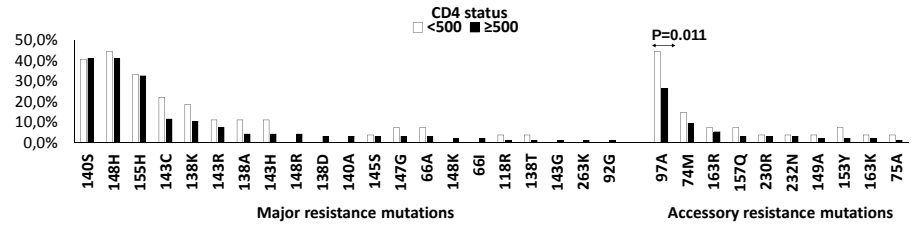
Figure 1A. Prevalence of cumulative PI/NRTI/NNRTI/INSTI resistance according to CD4 status maintained over 2021-2024.



Cumulative resistance to PI/NRTI/NNRTI were not associated with hCD4 status (Figure1A). Consequently, no difference was observed considering genotypic susceptibility (data not shown).

By contrast, the proportion of individuals with hCD4 significantly decreased when ≥2 major or ≥1 accessory INSTI resistance mutations were detected in cumulative GRT. The lowest proportion of subjects achieving hCD4 status was observed among those harboured full resistance to bictegravir or dolutegravir.

Figure 1B. Prevalence of cumulative INSTI resistance mutations according to CD4 status maintained over 2021-2024.



Among INSTI resistance associated mutations only the accessory T97A showed a significantly lower prevalence in HTE-MDR PWH with hCD4.

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