Viro-Immunologic Success Against the Odds: 7-Year Outcome in People With 4-Class Drug-Resistant HIV

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BACKGROUND

- Heavily treatment-experienced (HTE) people with HIV (PWH) are at increased risk of suboptimal virological suppression and impaired immune recovery [1-3].
- Our aim was to longitudinally assess virological and immunological outcomes in individuals with 4-class drug resistance (4DR).

METHODS

- Repeated cross-sectional analyses were conducted within the PRESTIGIO Registry, an ongoing multicenter cohort that prospectively collects data and provides multidisciplinary evaluation of adults on antiretroviral therapy (ART) with documented resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs).
- Data were analyzed at three predefined timepoints:
  - January 1, 2019 (1 year after registry initiation);
  - January 1, 2022 (4 years);
  - January 1, 2025 (7 years).
- For each timepoint, the last available measurement within the preceding 12 months was used.
- Because PRESTIGIO is an open cohort, individuals could contribute data at one or more timepoints.
- Temporal trends were assessed using logistic regression with generalized estimating equations, assuming a linear trend and accounting for within-patient correlation.
- Continuous variables are presented as median (interquartile range) and categorical variables as frequency (percentage).

RESULTS

- Overall, 255 4DR-PWH contributed ≥1 visit at the three snapshots.
- At the last available visit, 184/255 (72.2%) were assigned male at birth, the median age was 60.3 (56.0-63.9) years, and the median ART duration was 28.5 (IQR=26.0-31.6) years.

Virological suppression (<50 copies/mL) increased from **72.2%** in 2019 to **85.3%** in 2025 (p<0.0001) (Figure 1).

Immunological recovery improved:
CD4⁺ >500 cells/µL: from **57.3%** to **67.0%** (p=0.013) (Figure 2);
CD4⁺/CD8⁺ >1: from **19.9%** to **32.5%** (p<0.001) (Figure 3).

Figure 1. Viremia in the PRESTIGIO Registry in 2019, 2022, and 2025

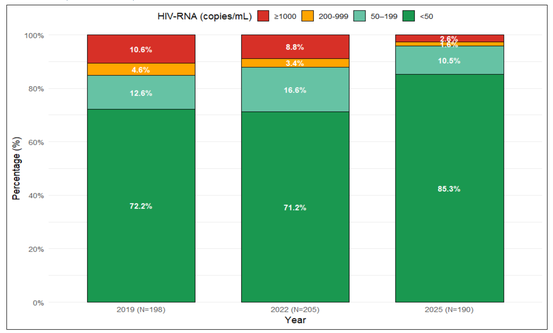


Figure 2. CD4⁺ count in the PRESTIGIO Registry in 2019, 2022, and 2025

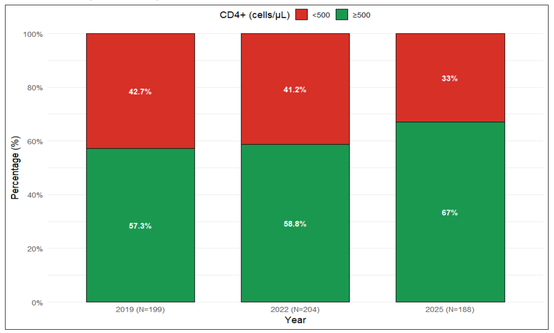


Figure 3. CD4⁺/CD8⁺ in the PRESTIGIO Registry in 2019, 2022, and 2025

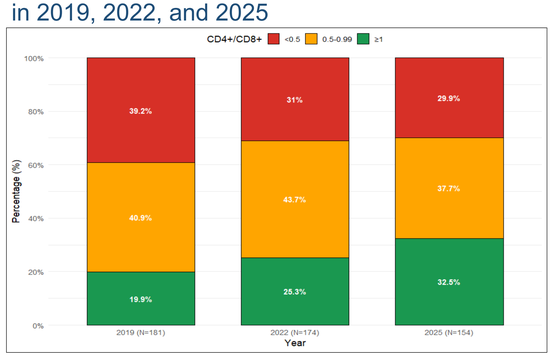


Table 1. Antiretroviral regimen composition in the PRESTIGIO Registry in 2019, 2022, and 2025

Regimen composition	2019 (n=210)	2022 (n=217)	2025 (n=217)	p
Use of NRTIs	50.5%	52.5%	53.9%	0.682
Use of NNRTIs	28.1%	33.6%	31.8%	0.290
Use of boosted PIs	82.9%	77.9%	69.6%	**<0.001**
Use of 1st-gen. INSTIs	8.6%	3.2%	1.8%	**0.001**
Use of 2nd-gen. INSTIs	81.0%	85.3%	84.8%	0.317
Use of entry inhibitors	25.2%	23.0%	34.1%	**0.005**
Fostemsavir	*4.8%*	*5.1%*	*18.9%*	***<0.001***
Use of lenacapavir	0%	3.7%	6.5%	**<0.001**
≥4-drug regimens	36.7%	40.1%	41.0%	0.224

- Regimen composition changed over time: use of boosted PIs and 1st-generation INSTIs significantly decreased, while entry inhibitors (mainly fostemsavir) and lenacapavir increased (Table 1).
- Results were consistent in individuals contributing data at all three timepoints.
- Among the 38 individuals who ended follow-up before 2025, last-visit outcomes were:
  - 65.8% virologically suppressed;
  - 41.7% CD4⁺ >500 cells/mL;
  - 5.4% CD4⁺/CD8⁺ >1.

CONCLUSIONS

- In this cohort with extensive drug resistance, virological suppression and immune recovery improved over seven years, coinciding with multidisciplinary care and wider access to novel agents.
- Although challenges persist in managing HTE populations, viro-immunological success can be achieved.

REFERENCES

1. Hsu RK, et al. BMC Infect Dis, 2023.
2. Clemente T, et al. Int J Antimicrob Agents, 2024.
3. Pelchen-Matthews A, et al. J Acquir Immune Defic Syndr, 2021.

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PLAIN LANGUAGE SUMMARY

Even people with HIV who have developed resistance to many drugs can regain viral control and immune strength. In a national cohort, outcomes steadily improved over seven years alongside the introduction of newer HIV medicines and specialized care.