From Widespread Use to Salvage Therapy: Seventeen Years of Protease Inhibitor Resistance Dynamics

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BACKGROUND

The use of protease inhibitors (PIs) has played a central role in antiretroviral (ARV) therapy, but has also driven the emergence of specific resistance mutation patterns. Over time, the PI class of drugs has evolved from the first generation of drugs, such as indinavir (IDV), saquinavir (SQV), nelfinavir (NFV) and amprenavir (APV), to more robust and better-tolerated agents, such as lopinavir/ritonavir (LPV/r), atazanavir (ATV/r) and darunavir (DRV/r).

This study aimed to assess changes in resistance levels and mutation profiles to PIs in relation to the evolving use of different PIs over a 18-year period among people living with HIV (PLWH) who experienced virological failure.

METHODS

In parallel, we analyzed the use of the different PIs in ARV-treated PLWH at an academic center (Pitié Salpêtrière hospital) and the HIV PI (ATV/r, LPV/r, and DRV/r) resistance profiles in RNA (2008-2025; analyzed using the latest ANRS-MIE algorithm v35).
All PLWH who were on ARV therapy and had received PI therapy for at least 3 months were included in this study.
The study focused on HIV PI resistance profiles in cases of virological failure, defined as 2 consecutive HIV viral load >50 copies/mL.
The prevalence of ANRS-MIE PI mutations was evaluated. Mutations with a prevalence of at least 2.0% over a period of one year or more are plotted.

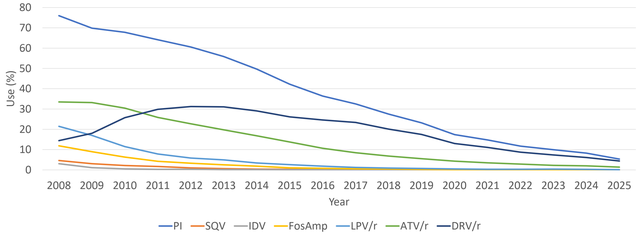


Figure 1: The prevalence of PI use during the study period (2008-2025)

The decline in PI resistance in most PLWH experiencing virological failure indicates that PIs remain active in the majority of cases and highlighting the potential for developing new compounds.

RESULTS

- There was a decrease in PI use during the studied period (2008-2025) (Figure 1 and Table 1).
- There was a decrease in PI resistance (Figure 2 and Table 1).
- DRV/r BID had the lowest level of PI resistance (Figure 2).
- M46I and L90M were the most prevalent mutations (Figure 3).

	Use	Resistance
ARVs	↗ 3 108 to 4 585 PLWH	
PIs	↘ 76.0% to 5.3%	↘ 29.3% to 3.8%
ATV/r	↘ 33.5% to 1.4%	↘ 25.8% to 5.8%
LPV/r	↘ 21.5% to 0.1%	↘ 26.8% to 2.8%
DRV/r	↘ 14.4% to 4.4%	DRV/r BID ↘ 12.7% to 0.9% DRV/r QD ↘ 18.0% to 3.4%

Table 1: Summary of the prevalence of use and resistance (2008-2025). ARVs: number of PLWH treated by antiretrovirals.

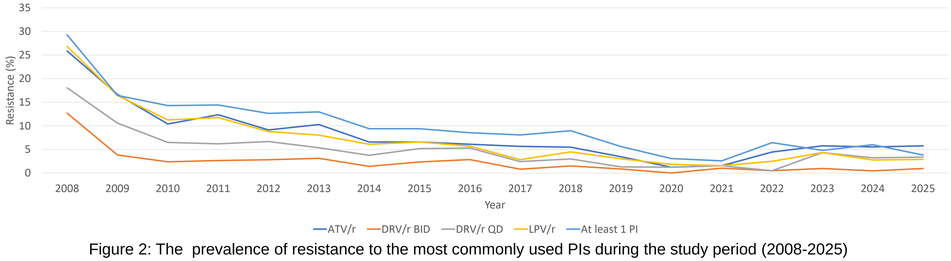


Figure 2: The prevalence of resistance to the most commonly used PIs during the study period (2008-2025)

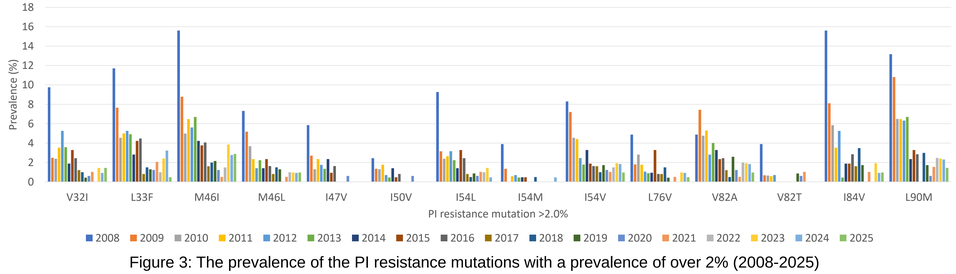


Figure 3: The prevalence of the PI resistance mutations with a prevalence of over 2% (2008-2025)

CONCLUSIONS

- Over 18 years, the use of PIs markedly declined in favor of integrase inhibitors, accompanied by a progressive decrease in PI resistance.
- PIs, particularly DRV/r BID, remain important salvage therapy options, warranting continued surveillance of resistance.
- Although current HIV PIs such as DRV/r are highly effective, there are still unmet needs due to lifelong therapy, the emergence of resistance in heavily treated PLWH, metabolic toxicity, and drug–drug interactions, particularly in aging PLWH.
- The next-generation PIs should ideally combine a very high genetic barrier to resistance with activity against multi-mutant variants, while eliminating the need for pharmacokinetic boosting. Their clinical value would be further enhance by improved metabolic and cardiovascular safety, optimal tissue penetration into viral reservoirs, and compatibility with simplified or long-acting regimens. Therefore, developing safer, booster-free, resistance-resilient protease inhibitors remains a relevant and strategically important objective in modern HIV therapeutics.

ADDITIONAL KEY INFORMATION

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PLAIN LANGUAGE SUMMARY

Our study shows that the use of HIV drugs called protease inhibitors has decreased over time, as resistance to these drugs. DRV/r remains particularly effective.