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ORIGINAL RESEARCH

The Role of Protease Inhibitors in HIV Treatment: Who Still Needs Them in 2025?

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ABSTRACT

***Introduction*:** Protease inhibitors (PIs) remain an effective antiretroviral therapy (ART) option for people with human immunodeficiency virus (HIV) (PWH), particularly in complex clinical and virological scenarios. However, they are associated with greater metabolic toxicity and drug–drug interactions (DDI) compared with newer ART classes. This study aimed to characterize PWH currently receiving PI-based ART and to explore the reasons for maintaining these regimens.

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Methods: We conducted a cross-sectional, observational study of all PWH on PI-based ART as of 30 June 2024 at the HIV Unit of Hospital Clínic de Barcelona. Demographic, clinical, laboratory, ART history, and genotypic resistance data were extracted from the institutional database and compared with the rest of the cohort.
Results: Among 6261 PWH on ART, 724 (11.6%) were receiving a regimen including a PI; their use progressively declined over the last two decades ($p<0.001$). The most frequent reasons for PI prescription were prior virological failure (36%) and toxicity to previous ART (41%). Compared with other PWH, those on PIs were older (median 54 versus 48 years, $p<0.001$), more frequently female patients (19% versus 13%, $p<0.001$), and had higher rates of heterosexual (33% versus 21%, $p<0.001$) and injection-drug-use transmission (15% versus 7%, $p<0.001$). Virological suppression was significantly lower among PWH on PIs (88% versus 96%, $p<0.001$). Genotypic resistance testing prior to PI prescription was available for 435 PWH; 74% had at least one major resistance substitution, and 70.4% had substitutions affecting two or more antiretroviral classes. In total, 299 PWH had experienced either virological failure or toxicity to non-nucleoside reverse transcriptase inhibitor (NNRTI)- or integrase strand transfer inhibitor (InSTI)-based regimens prior to initiating a PI-based regimen. Among them, 42 had documented failure of or toxicity to both drug classes.
Conclusions: Although their use has declined, a substantial number of PWH remain on regimens including a PI. These PWH typically have long-standing infections, prior ART failures, and documented resistance substitutions, supporting the continued use of PIs when other therapeutic options are limited.

Keywords: Protease inhibitors; HIV; Antiretroviral therapy; Virological suppression; Drug resistance; Treatment-experienced patients; Real-world cohort

Key Summary Points

Although protease inhibitors (PIs) are no longer preferred first-line therapies, a relevant number of people with HIV (PWH) remain on PI-based regimens. Their clinical profile, reasons for continuing these treatments, and potential for regimen simplification had not been systematically described in recent years.

As antiretroviral therapy (ART) continues to evolve toward simplified, better-tolerated options, understanding the characteristics of those who still require PIs is essential for tailoring care in an aging HIV population with complex treatment histories.

This study aimed to describe the demographic, clinical, and resistance profiles of PWH currently on PI-based regimens in a large real-world cohort and to identify the factors supporting the ongoing use of these treatments in 2024.

Among 6261 people with HIV (PWH) on ART, 11.6% were on PI-based regimens. Most had long-standing infection, prior ART failures, and high levels of drug resistance. Virological suppression was lower in the PI group (88% versus 96%), and 70.4% had resistance mutations affecting two or more antiretroviral classes.

While some PWH continue to require PI-based ART owing to multidrug resistance or past intolerance, a subgroup of them may be eligible for simplified alternatives. These findings highlight the need for individualized treatment strategies and periodic reassessment of PI use.

INTRODUCTION

Human immunodeficiency virus (HIV) protease inhibitors (PIs) have been available since 1995 when, in combination with nucleoside reverse transcriptase inhibitors (NRTIs), they significantly improved the management and

prognosis of HIV infection. With multiple, more convenient antiretroviral options having been developed over the years, PI use has decreased, limited by adverse effects, particularly dyslipidemia, cardiovascular events, and gastrointestinal intolerance, as well as significant drug–drug interactions (DDI). The last developed PIs, such as atazanavir and especially darunavir [1], offered improved safety profiles and simpler once-daily dosing. However, they still require pharmacokinetic enhancement with ritonavir or cobicistat, which continue to be associated with relevant metabolic toxicity and DDI.

With the introduction of integrase strand transfer inhibitors (INSTIs), a new era of antiretroviral treatment (ART) began, offering improved safety profiles, high genetic barrier, particularly with second-generation INSTIs such as dolutegravir [2] and bictegravir [3], and fewer DDI. In addition, new non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as rilpivirine and doravirine, have been developed. Although they exhibit lower potency compared with INSTIs, they have shown excellent safety and tolerability profiles, ensuring adequate virological control when appropriately prescribed.

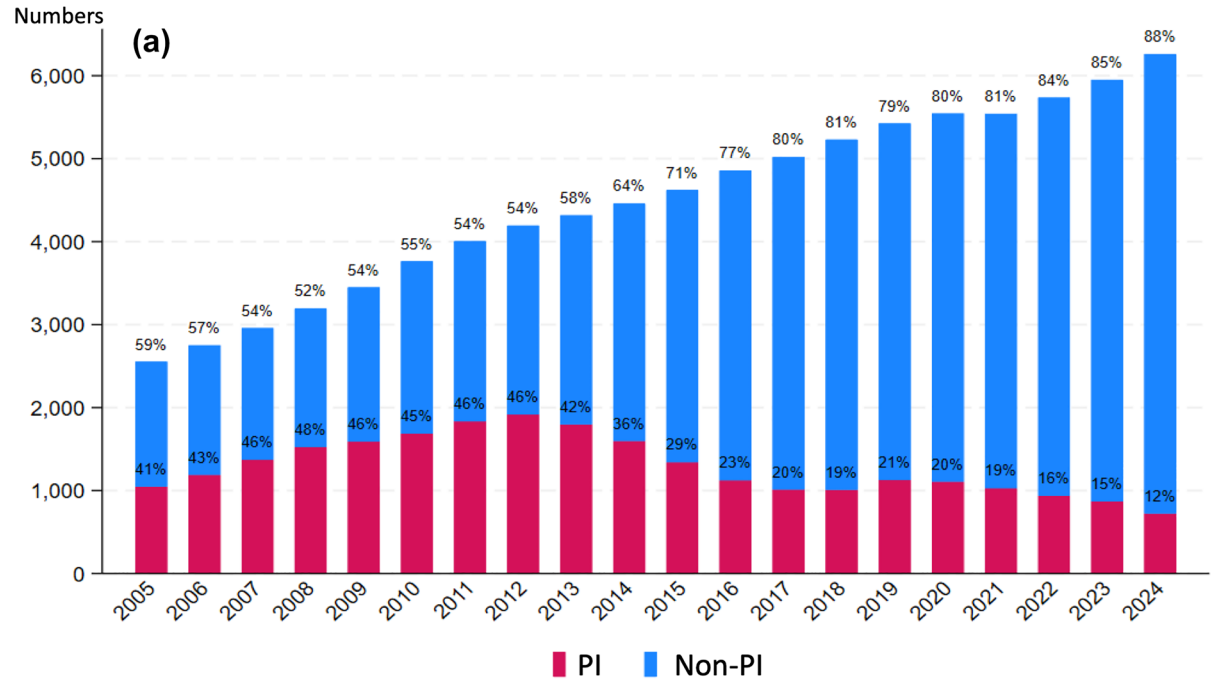
With the progressing ageing of PWH worldwide [4], and the consequent increase in comorbidities and polypharmacy, most international guidelines have recommended in recent years, whenever possible, the switch to ART combinations not including pharmacokinetic enhancers [5, 6]. Thus, PIs have progressively become an alternative rather than a preferred option. Indeed, currently, any person receiving a PI without a clear indication (e.g., intolerance or failure with other antiretroviral families) may benefit from switching to more convenient alternatives. However, PIs (particularly darunavir) are still necessary for situations with resistance to other combinations or when newer drugs have not been tolerated. While the 2018 European and US guidelines still considered boosted PIs as first-line options in certain contexts, in current European AIDS Clinical Society (EACS) and Department of Health and Human Services (DHHS) recommendations (2023–2024), they are part of alternative initial regimens [5, 6]. Nevertheless, PIs retain important advantages in specific clinical scenarios. Their high genetic barrier to resistance makes them particularly useful for individuals with prior virological failure, suboptimal adherence, or transmitted resistance. They are also considered when rapid ART initiation is required before genotypic resistance testing is available, although INSTIs are preferred also in this scenario. As a result, PIs continue to be prescribed in selected PWH profiles where treatment simplification or INSTI use may not be feasible. Real-world cohort studies, including RESPOND, have shown that people on PIs tend to have longer treatment histories and lower baseline CD4 counts, compared with those on INSTIs [6]. Similarly, data from NA-ACCORD and a San Francisco-based cohort highlight that PWH with socioeconomic vulnerabilities or late HIV diagnosis are more likely to remain on PI-based regimens [7, 8].

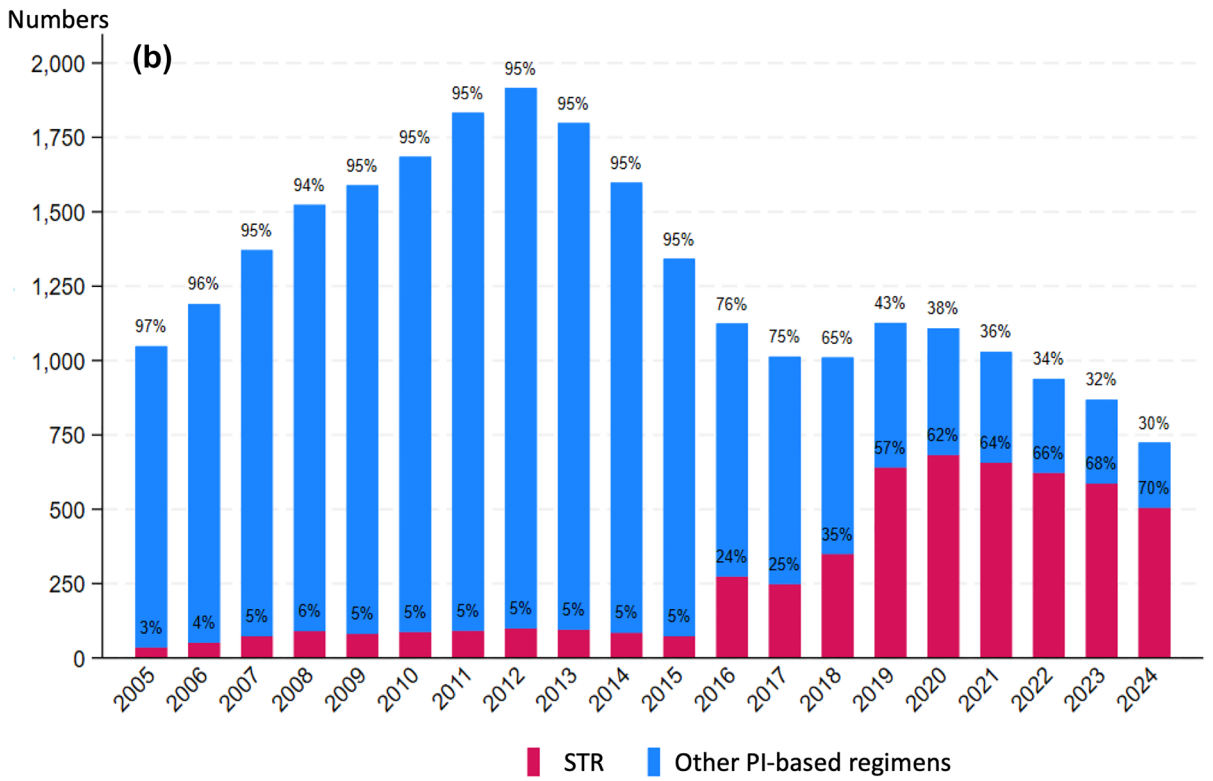
The aim of this study was to characterize the current profile of PWH receiving ART regimens including a PI in 2024 within a large, single-center real-world cohort. We sought to assess the demographic, clinical, and resistance-related features of this population; evaluate the current treatment compositions; and explore the reasons for maintaining these regimens despite the availability of more recent therapeutic alternatives. In addition, we explored whether a subset of this population might benefit from regimen simplification.

METHODS

We conducted a single-center retrospective, observational cross-sectional study within the cohort of PWH who were actively followed up in the HIV Unit of the Hospital Clinic of Barcelona. We selected all PWH on an ART that included any PI as of 30 June 2024 and compared them with the rest of the cohort not receiving regimens including PIs.

We analyzed the demographic characteristics and relevant medical history (hypertension, diabetes, renal function, and dyslipidemia), along with HIV-related data (year of diagnosis, number of previous treatments, documented


Numbers
(a)
6,000
5,000
4,000
3,000
2,000
1,000
0
59% 57% 54% 52% 54% 55% 54% 54% 58% 64% 71% 77% 80% 81% 79% 80% 81% 84% 85% 88%
41% 43% 46% 48% 46% 45% 46% 46% 42% 36% 29% 23% 20% 19% 21% 20% 19% 16% 15% 12%
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024
PI
Non-PI


Numbers
(b)
2,000
1,750
1,500
1,250
1,000
750
500
250
0
97% 96% 95% 94% 95% 95% 95% 95% 95% 95% 95% 76% 75% 65% 43% 38% 36% 34% 32% 30%
3% 4% 5% 6% 5% 5% 5% 5% 5% 5% 5% 24% 25% 35% 57% 62% 64% 66% 68% 70%
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024
STR
Other PI-based regimens

◂**Fig. 1** **A** Evolution of PI-based ART as a proportion of total ART prescriptions (2005–2024). Annual comparison of the number of PWH receiving regimens including and not including a PI. Data refer to 30 June of each year. **B** Temporal trends in the use of PI-based ART regimens (2005–2024). Proportion of PWH on regimens including a PI over time, classified as STR or non-STR. Data refer to 30 June of each year

resistance substitutions, and suppression rates). These data were retrieved from the electronic medical record system of the HIV unit, together with the analytical results of their most recent control prior to the database closure corresponding to the cross-sectional time point (30 June 2024). Finally, we estimated the percentage of PWH on PIs who could potentially benefit from a switch to a different, more convenient ART combination.

Qualitative variables were described using frequency and percentage, and quantitative variables were described using median and interquartile range (IQR). To compare variables between groups, chi-squared test or Fisher's exact test was used for qualitative variables, and Wilcoxon rank sum test for quantitative variables. To compare the difference of number of PWH on single-tablet regimen (STR) or IP treatment between two years, Poisson regression with cluster-robust standard errors at patient level was performed. The tests were two-tailed, and the significance level was set at 5%. Mutation analysis was performed according to the Major HIV-1 Drug Resistance Mutations list from the Stanford University HIV Drug Resistance Database (last updated 28 March 2024).

Statistical analyses were performed using StataCorp (2023) Stata, version 18, statistical software (College Station, TX: StataCorp LLC).

The study was conducted in accordance with local legislation (Real Decreto no. 957/2020, 3 November), which regulates all observational drug studies in humans. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (HCB/2023/0296). Given the retrospective nature of the study, its potential utility for society, and in accordance with the relevant legislation (Articles 6.1.e and 9.2j of the General Data Protection Regulation [GDPR], as well as Additional Disposition 17.2.d of LOPD-GDD 3/2018), the Ethics Committee of the Hospital Clinic of Barcelona waived the requirement for written informed consent.

RESULTS

Demographics and Clinical Characteristics

Out of a total of 6261 PWH actively followed in our HIV unit and on active ART, 724 (11.6%) were receiving an ART regimen that included a PI (darunavir=715, atazanavir=5, lopinavir=4) as of 30 June 2024. PI regimens included a PI plus two NRTIs in 412 cases (57%), 403 of them as STR, PI plus INSTIs in 125 cases (17%), PI plus NNRTI in 33 (4.5%), PI monotherapy in 104 (14.5%) and PI with other combinations in 50 (7%). The flow chart of ART use in our cohort is shown in Supplemental Fig. 1.

Temporal trends of PI use in our center are shown in Fig. 1. Although the total number of PWH on ART has steadily increased, the proportion receiving PI-based therapy has declined from 41% in 2005 to 12% in 2024 ($p<0.001$) (Fig. 1A). Figure 1B shows a progressive increase in STR prescriptions among PI users from 3% in 2005 to 70% in 2024 ($p<0.001$).

The median time on ART for the study population was 14.46 years (IQR 6.42–26.36), while the median duration of the current PI-based regimen was 8.64 years (IQR 4.34–16.83). STR was used by 70% (507/724), 403 of whom were receiving darunavir/emtricitabine/tenofovir alafenamide (D/C/F/TAF) and 104 were on PI monotherapy. Most PWH (85%) had received prior ART, and 56% had been exposed to six or more different ART regimens. Notably, 65.5% (474/724) of PWH had previously been on a non-PI-based regimen before switching to their current therapy.

Table 1 presents the baseline demographic and clinical characteristics. Compared with the rest of the cohort, PWH receiving a PI were older (median age 54 versus 48 years, $p<0.001$), more frequently female patients (19% versus 13%, $p<0.001$), and less likely to identify themselves as men who have sex with men (MSM) (62% versus 73%, $p<0.001$).

In contrast, the proportion of heterosexual individuals was significantly higher in the PI group (33% versus 21%, $p<0.001$). A higher percentage had acquired HIV through injection-drug use (15% versus 7%, $p<0.001$), and they had been diagnosed for longer periods of time (median 20 versus 14 years, $p<0.001$). Virological suppression was lower among those on PI-based regimens, with 88% having an undetectable viral load compared with 96% in the non-PI group ($p<0.001$). Suppression rates remained below 90% across all PI-based regimen combinations, except for those on monotherapy (102/104, 98%) and other less common regimens (47/50, 94%). The chronological trends of virological suppression in people with different PI-containing regimens is shown in Supplemental Fig. 2. CD4 counts were slightly lower (678 versus 710 cells/μL, $p<0.001$), but the CD4/CD8 ratio was similar. Coinfections with hepatitis B and C were more common among PWH receiving PIs (5% versus 2% for hepatitis B surface antigen [HBsAg], and 21% versus 16% for hepatitis C antibody [HCV Ab], both $p<0.001$). PWH on PI-based regimens had higher levels of total cholesterol (196 versus 181 mg/dL), LDL cholesterol (117 versus 109 mg/dL), and triglycerides (124.5 versus 105 mg/dL, $p<0.001$ for all comparisons).

The most common reasons for ART switching to the current regimen that included PI were toxicity (130 individuals, 41%) and virologic failure (114 individuals, 36%) to the immediately preceding ART regimen (Table 2**).** In addition, a total of 147 PWH had experienced toxicity to NNRTI-based regimens and 51 to INSTI-based regimens at some point during their follow-up. Virological failure had occurred in 26 patients on NNRTI-based therapies and in 75 on INSTI-based regimens. Overall, 42 patients had documented either toxicity or virological failure to both drug classes. Finally, four individuals initiated a PI-based regimen after long-acting cabotegravir–rilpivirine failed.

Comorbidities and HIV-Related Complications

Table 3 presents comorbidities and HIV-related events among PWH receiving PI-based regimens compared with those on other ART. A significantly higher proportion of individuals on PI-based ART had a history of opportunistic infections (21.5% versus 11%, $p<0.001$). Similarly, neoplasia was more common among those on PIs (8% versus 4%, $p<0.001$). In contrast, common comorbidities such as diabetes and hypertension showed minor differences or similar frequencies between groups.

ART History and Virological Control Among PWH on PI-Based Regimens

Comparison between PWH virologically suppressed and non-suppressed on PI-containing regimens is presented in Table 4. Individuals with detectable viral load ($n=84$) had shorter time on ART (median 10.9 versus 14.9 years) and shorter time on PI-based regimen (5.3 versus 9.3 years). Genotypic resistance testing was performed in 435 PWH (60%) before the PI-based regimen, and major resistance mutations were identified in 215 individuals for NRTI, 177 for NNRTI, and 46 for INSTI. Details of the most frequent resistance mutation patterns are also presented in Table 4. PI-based combinations (stratified by virological response) are shown in Supplementary Fig. 2.

DISCUSSION

PIs have progressively become an alternative rather than a preferred option for HIV treatment in recent years, mainly owing to their long-term tolerability profile and pharmacokinetic requirements. Our study shows that, as of mid-2024, 11.6% of PWH at our center remain on ART including PI, reflecting a progressive decline in their use over the past two decades. Compared with the rest of the cohort, PWH receiving PIs were older, more frequently female patients, less often MSM, and had higher rates of heterosexual or injection-drug-use transmission. They had been living with HIV for longer, were more likely to have experienced prior virological failure, and had accumulated multiple ART regimens—nearly half had received more than five.

Table 1 Population characteristics of PWH receiving and not receiving a regimen including a PI at cross-sectional time point (30 June 2024)

Demographic characteristics	Other ART (*n* = 5537)	PI-containing ART (*n* = 724)	Total (*n* = 6261)	*p*-value
Age (years)	48 (38–57)	54 (43–61)	49 (39–58)	< 0.001
Sex at birth				
Male	4836 (87%)	583 (81%)	5419 (87%)	< 0.001
Female	699 (13%)	141 (19%)	840 (13%)	
Weight (kg, IQR, *n*)	74 (66–82) [4998]	72.4 (64.2–81) [621]	74 (66–82) [5619]	0.017
Height (cm, IQR, *n*)	174 (169–179) [4419]	172 (168–178) [510]	174 (169–179) [4929]	< 0.001
Gender identity				
Men	4596 (83%)	551 (76%)	5147 (82%)	< 0.001
Women	696 (13%)	141 (19%)	837 (13%)	
Trans men	2 (0%)	1 (0%)	3 (0%)	
Trans women	230 (4%)	31 (4%)	261 (4%)	
Non-binary	13 (0%)	0 (0%)	13 (0%)	
Transmission mode				
Sexual	5014 (92%)	587 (82%)	5601 (91%)	< 0.001
Parenteral—IDU	386 (7%)	109 (15%)	495 (8%)	
Parenteral—Transfusion	22 (0%)	3 (0%)	25 (0%)	
Vertical	34 (1%)	14 (2%)	48 (1%)	
Years from diagnosis (IQR, *n*)	14 (8–22) [5513]	20 (12–30) [723]	14 (8–23) [6236]	< 0.001
Undetectable VL (copies/mL)	5291 (96%)	640 (88%)	5931 (95%)	< 0.001
CD4 (× 10^6/mL)	710 (532–913) [5535]	678.5 (472–884) [724]	707 (525–909) [6259]	< 0.001
CD4/CD8 rate	0.9 (0.7–1.3) [5525]	0.9 (0.5–1.2) [721]	0.9 (0.7–1.3) [6246]	< 0.001
Coinfections				
HBsAg	118 (2%)	34 (5%)	152 (2%)	< 0.001
HCV Ab	872 (16%)	152 (21%)	1024 (16%)	< 0.001
Laboratory findings				
Creatinine (mg/dL)	0.99 (0.88–1.12) [5537]	0.95 (0.83–1.08) [724]	0.99 (0.87–1.12) [6261]	< 0.001
eGFR (mL/min/1.73 m^2)	87 (75–90) [5537]	89 (75–90) [724]	88 (75–90) [6261]	0.357
Total cholesterol (mg/dL)	181 (156–207) [5537]	196 (168–221) [724]	182 (157–208) [6261]	< 0.001
HDL-cholesterol (mg/dL)	46 (39–55) [5537]	47 (39–56) [724]	46 (39–55) [6261]	0.187
LDL-cholesterol (mg/dL)	109 (88–131) [5503]	117 (92–142) [720]	109 (88–132) [6223]	< 0.001

Table 1 continued

Demographic characteristics	Other ART ($n = 5537$)	PI-containing ART ($n = 724$)	Total ($n = 6261$)	p-value
Triglycerides (mg/dL)	105 (76–150) [5537]	124.5 (87–176) [724]	107 (77–153) [6261]	< 0.001
Glucose (mg/dL)	91 (83–99) [5536]	92 (84.5–101) [724]	91 (84–99) [6260]	0.014
ASAT/GOT (U/L)	24 (20–30) [5537]	23 (19–28) [724]	23 (19–29) [6261]	< 0.001
ALAT/GPT (U/L)	24 (18–33) [5537]	22 (16–30) [724]	24 (18–33) [6261]	< 0.001
Proteinuria (mg/L)	130 (80–197) [5532]	134.5 (81–218) [722]	131 (80–199) [6254]	0.064
Urinary protein/creatinine rate (mg/g)	97 (72–139) [5533]	111 (79–163) [722]	99 (73–141) [6255]	< 0.001

Table 2 Reasons for switching from the immediately preceding ART regimen to the current PI-based regimen

Reason for switching to PI	Total ($n = 314$)
Toxicity (n, %)	130 (41%)
Virologic failure	114 (36%)
Other reasons	70 (23%)

Virological suppression was significantly lower among PWH on PIs (88% versus 96%). This may also be reflecting the tendency of clinicians to prescribe high-genetic-barrier ART regimens to those PWH perceived as at risk of poor adherence. Indeed, in PWH on PI-based regimens with detectable viral load (VL), if no resistance is detected, adherence is often reinforced without changes to the regimen. This contrasts with cases where poor adherence is identified in individuals receiving a low-genetic-barrier anchor drug (e.g., rilpivirine or raltegravir), which often leads to a rapid change in the ART regimen. However, surprisingly, the highest suppression rate (98%) was observed in those receiving PI monotherapy. Contrary to those on triple ART PI-containing regimen, PI monotherapy may be biased by the careful selection of subset of PWH perceived as highly adherent. In addition, 25% of PWH were receiving a PI in combination with a non-NRTI drug class, likely reflecting NRTI resistance and the need for salvage regimens. Among those with genotypic resistance data, 74% had at least one major mutation, and 70.4% had mutations affecting multiple drug classes. These findings are consistent with RESPOND and other cohort data [9, 10] that confirm that PIs remain critical in managing individuals with extensive ART histories or multidrug resistance. Our study also highlights that a significant proportion of PWH on PIs require them, since they have experienced failure and/or toxicity to regimens including both INSTI and NNRTIs in the past. However, a substantial proportion might also be suitable to switch to a newer more convenient ART, such as second INSTI-based or doravine (DOR)-based regimens, all of which do not contain a pharmacokinetic (PK) enhancer, particularly considering that only a small percentage (42 individuals, 6%) had documented both virological failure and toxicity to NNRTI- and INSTI-based regimens simultaneously. Nonetheless, an important factor not reflected in our study is the group of individuals who, despite medical advice, choose not to change their current regimen, which may probably be the situation of most PWH on darunavir/cobicistat (DRV/c) monotherapy, a strategy not recommended in current clinical guidelines. Also, some PWH may not have genotypic testing performed before PI initiation but may have failed in other centers before or may have incomplete clinical data.

Emerging factors may also influence future trends in PI use. Although pre-exposure prophylaxis (PrEP) has significantly reduced HIV transmission, there have been reports of resistance substitutions in individuals who acquire HIV while taking it [11, 12]. This is particularly relevant in cases involving long-acting cabotegravir, where selected mutations can compromise

Table 3 Comorbidities and history of opportunistic infection (OI) among PWH on PIs and without PI ART

Comorbidities	ART including PI	ART without PI	*p*-value
Diabetes	20/616 (3%)	183/5003 (3.5%)	< 0.001
Hypertension	24/289 (8.5%)	214/2558 (8.5%)	0.006
PWH with history of OI	154/724 (21.5%)	630/5537 (11%)	< 0.001
Type of OI[a]			
M. tuberculosis	54/243 (22%)	199/874 (23%)	
Pneumocystis jirovecii	47/243 (19.5%)	181/874 (20.5%)	
Candida spp.	42/243 (17%)	148/874 (17%)	
CMV	18/243 (7.5%)	45/874 (5%)	
Toxoplasma	16/243 (6.5%)	40/874 (4.5%)	
Others	66/243 (27%)	261/874 (30%)	
PWH with neoplasia	57/724 (8%)	235/5302 (4%)	< 0.001
Type of neoplasia[b]			
Kaposi sarcoma	32/68 (47%)	136/255 (53.3%)	
Hematologic	13/68 (19.1%)	46/255 (18%)	
Cervix	7/68 (10.2%)	19/255 (7.4%)	
Anorectal	4/68 (5.9%)	8/255 (3.1%)	
Others	12/68 (17.6%)	46/255 (18%)	

[a]Number and percentage refer to the total of 243 opportunistic infections (OIs) identified in 154 PWH receiving ART including a protease inhibitor (PI) and 874 OIs in 630 individuals receiving ART without a PI

[b]Refers to 68 neoplasms diagnosed in 57 PWH receiving ART including a PI. For the ART-without-PI group, 255 neoplasms were diagnosed in 255 individuals

the entire INSTI class [13]. Furthermore, PWH failing long-acting cabotegravir plus rilpivirine often develop resistance to both drug families, potentially requiring PI-based regimens [14–16]. While these cases remain relatively uncommon, they highlight a clinical scenario in which PI use may persist or slightly increase in coming years. In our study, 4 PWH started a PI-based regimen following cabotegravir plus rilpivirine long-acting failure.

In the near future, a further decline in PI use is expected, driven by both the availability of better-tolerated and simplified regimens and the emergence of novel long-acting or combination therapies. Investigational strategies such as those combining lenacapavir plus bictegravir, or islatravir plus lenacapavir, or other new drug classes, may offer alternatives for PWH with multidrug resistance, currently the key population for whom PIs are indicated. Currently, lenacapavir is approved for individuals with multidrug-resistant HIV strains, a context in which PIs are generally also required. At present, it cannot be used as a substitute for PIs. Globally, since 2019, World Health Organization (WHO) guidelines have recommended transitioning PWH from lopinavir/ritonavir to dolutegravir when possible [17]. However, when resistance to companion NRTI drugs is significant, studies such as NADIA show that resistance emerges with second-generation InSTIs (e.g., dolutegravir) but not with boosted darunavir [18]. Therefore,

Table 4 Comparison between PWH virologically suppressed and non-suppressed on PI-containing regimens, at cross-sectional time point (30 June 2024)

ARV regimen	Unsuppressed VL on ART (VL > 50 copies/mL)	Suppressed VL on ART (< 50 copies/mL)	Total
Current PI-based ARV regimen	84 (11.5%)	640 (88.5%)	724
PI + 2NRTI	60 (14.5%)	352 (85.5%)	412
PI + INSTI	14 (11%)	111 (89%)	125
PI + NNRTI	5 (15%)	28 (85%)	33
PI monotherapy	2 (2%)	102 (98%)	104
PI + other combinations	3 (6%)	47 (94%)	50
Single-tablet regimen	62 (12%)	445 (88%)	507
Previous no-PI based regimen	59 (12.5%)	415 (87.5%)	474
ART timeline			
Years on ART	10.87 (5.74–19.01)	14.92 (6.46–26.88)	14.46 (6.42–26.36)
Years on PI-based regimen	5.26 (1.40–12.70)	9.34 (4.65–17.15)	8.64 (4.34–16.83)
Years on present PI-based regimen	2.46 (0.74–4.90)	5.18 (2.76–6.16)	4.98 (2.43–6.07)
Number of previous ART			Total
First regimen	12 (11%)	99 (89%)	111
2–5	36 (14%)	226 (86%)	262
6–10	29 (11.5%)	222 (88.5%)	251
> 10	13 (8.5%)	141 (91.5%)	154
Genotyping before starting PI	60 (14%)	375 (86%)	435
Major mutations detected before starting PI[+]			
NRTI[*]	29 (13.5%)	186 (86.5%)	215
NNRTI	28 (16%)	149 (84%)	177
INSTI[**]	8 (17.5%)	38 (82.5%)	46

[+]Major HIV-1 Drug Resistance Mutations list from the Stanford University HIV Drug Resistance Database (last updated 28 March 2024)

[*]M184V/I was found in 167 PWH, K65R in 31, Q151M in 3, and any thymidine analogue mutation (TAM) in 120 individuals, of whom 72 had three or more TAMs

[**]T66 was detected in 3 PWH, E92 in 3, G118 in 1, E138 in 30, Y143 in 4, Q148 in 16, and N155 in 19

PIs remain necessary in selected cases owing to their higher genetic barrier. National cohort data from the Netherlands and the UK show that PI use among ART initiators has dropped below 10% in 2020, being reserved primarily for PWH with resistance or contraindications [19].

Our study has several strengths. It includes real-world data from a large cohort with detailed clinical, virological, and genotypic resistance data. All individuals were actively followed in a high-resource HIV unit, ensuring consistency in clinical management and data collection. In addition, the extended observational window (2005–2024) allowed us to analyze long-term trends and contextualize current PI use within a historical treatment landscape. However, the study also has limitations. As a single-center retrospective analysis, findings may not be generalizable to other settings with different ART access or prescribing practices. Resistance testing was not available for the entire population, and reasons for ART modifications were not systematically recorded. Moreover, the cross-sectional nature of the analysis precludes evaluation of treatment durability, longitudinal virological outcomes, or causality. Finally, the retrospective nature of the data could lead to challenges related to incomplete or missing data, in addition to the inability to distinguish whether toxicity or resistance to a specific antiretroviral agent was interpreted as intolerance or resistance to the entire drug class. In practice, not all within-class agents share the same resistance profile or tolerability, but such distinctions are rarely documented in routine clinical databases. Consequently, some PWH might have been switched to PI-based regimens when alternative drugs from the same class could have been considered, potentially leading to an overestimation of the true clinical need for PIs.

CONCLUSIONS

Although the proportion of PWH receiving PI-based ART has decreased substantially in recent years, a relevant subset of individuals still requires these regimens in 2024–2025. PIs continue to play a critical role in managing PWH with extensive treatment histories, resistance to multiple drug classes, or barriers to using INSTIs. However, some of these cases might also benefit from switching to newer combinations. Only a small proportion of individuals on IP-based regimen had previously experienced failure or toxicity to both NNRTI and INSTI-based regimens. Future strategies should aim to further simplify ART and expand access to innovative drugs, while ensuring individualized and tailored care for PWH who nowadays continue to benefit from PI-based therapy.

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Declarations

Conflict of Interest. Abiu Sempere has received personal compensation from presentations from Gilead, ViiV and J&J outside of the submitted work. Juan Ambrosioni has received research funding from ViiV and Gilead; has participated in Advisory Boards for ViiV, Gilead, MSD, and J&J; has received personal compensation for presentations from ViiV, Gilead, MSD, and J&J; and has participated in Data Safety

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Ethical Approval. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona (approval no. HCB/2023/0296). Given the retrospective nature of the study, its potential utility for society, and in accordance with the relevant legislation (Articles 6.1.e and 9.2j of the General Data Protection Regulation [GDPR], as well as Additional Disposition 17.2.d of LOPD-GDD 3/2018), the Ethics Committee of the Hospital Clinic of Barcelona waived the requirement for written informed consent.

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