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Heavily treatment-experienced persons living with HIV currently in care in Italy: characteristics, risk factors, and therapeutic options—the ICONA Foundation cohort study

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ABSTRACT

Objectives: Heavily treatment-experienced (HTE) people living with HIV (PLWH) pose unique challenges due to limited antiretroviral treatment (ART) options. Our study aimed to investigate the prevalence and features of HTE individuals followed up in the Italian Cohort Naïve Antiretrovirals (ICONA) cohort as of December 31, 2021.

Methods: HTE were defined based on meeting specific conditions concerning their current ART and their ART history up to December 31, 2021. Descriptive statistics were performed by HTE status. Regression analyses explored factors associated with becoming HTE based on pre-ART patients' characteristics. Cluster dendrogram analysis provided insights into subgroups with inadequate responses based on clusters of differentiation (CD4) counts and viral load (VL) trajectories.

Results: Among the 8758 PLWH actively followed in our cohort, 163 individuals (1.9%), mainly female, younger, Italian, and infected through heterosexual contact, met the HTE criteria. A lower CD4 count at ART initiation (odds ratio [OR] 1.60 per 100 cells/mmc lower CD4, 95% confidence interval [CI] 1.06-2.41, $P = 0.03$) and hepatitis C virus antibody positivity (OR 1.90, 95% CI 1.16-3.11, $P = 0.01$) were associated with higher HTE risk. Thirty PLWH exhibited ongoing immune-virological failure (18% of the HTE subgroup and 0.003% of the total population). Thirty PLWH exhibited ongoing immune-virological failure (i.e., with a current CD4 count <200 cells/mmc or VL>200 copies/mL). A cluster analysis identified 13 (43%) with a current CD4 count <200 cells/mmc. Also, notably, 19/30 (63%) had major acquired resistance-associated mutations to at least one antiretroviral drug class.

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Conclusions: HTE is rare in our cohort and tends to co-exist with major resistance mutations. A focused investigation into treatment history and immuno-virological response is warranted, particularly given the availability of new antiretroviral drugs.

Introduction

Since the mid-1990s, improved combination antiretroviral therapy (cART) has transformed HIV into a lifelong condition [1,2]. While cART is effective, its prolonged use may reduce the efficacy of antiretrovirals (ARVs), leading to the need for personalized regimens [3–5]. Heavily treatment-experienced (HTE) patients are a subset of people living with HIV (PLWH) with limited ARV options due to past exposure, incomplete adherence, and acquired resistance mutations [6,7], resulting in a higher risk of unfavorable outcomes [8].

Recently, the availability of new classes of ARV drugs with entirely different mechanisms of action [9–11] has further boosted the identification and characterization of HTE. Nevertheless, despite many studies targeting this issue [12–14], many open questions about this research topic still need to be answered.

The quantification and characterization of this population face challenges due to variations in research contexts and the absence of a standardized definition for HTE. While genotypic resistance tests (GRTs) are important for accurate identification, their limited availability in clinical records and HIV cohort studies complicates the process [12,15–17]. In cases without GRT results, recent studies suggest that the history of ARV prescriptions and the composition of the current ARV regimen (including drugs indicative of HTE status), become crucial for identifying patients with limited treatment options [7,13].

Additionally, as people living with HIV age, co-morbidities, drug-drug interactions (DDIs), and concerns about safety, tolerability, and toxicity may further complicate ongoing ARV treatment, especially for those with already limited virologically potent options [18].

Finally, most previous analyses were epidemiological studies conducted on all PLWHs who entered the HTE status, not explicitly focusing on the estimate of the pool of patients in a particular country or region of the world who are currently still alive and in almost immediate need of starting new antiretrovirals.

On the contrary, one of the primary objectives of our analysis was to estimate the population of PLWH who, as of the end of the year 2021, was still alive and actively engaged in follow-up at one Italian Cohort Naïve Antiretrovirals (ICONA) Foundation Study cohort participating sites and who could retrospectively be classified as HTE based on their current and previous ART history.

Furthermore, within this cohort, we aimed to differentiate between individuals who were currently clinically stable, characterized by suppressed HIV-RNA levels and favorable CD4 counts, and those who were experiencing immune suppression or viral rebound, necessitating immediate consideration for the adoption of newly available drug classes, including entry and fusion inhibitors.

For both of these groups, our objectives included identifying factors that were measured when initiating ART, which could have influenced their long-term risk of becoming HTE. Additionally, we sought a comprehensive description of the HIV-resistance history and the trajectories of HIV laboratory parameters for individuals within the subgroup with current evidence of poor immune-virological assessment.

Methods

Patient selection and data collection

This cross-sectional study includes all PLWH enrolled in the ICONA Foundation Study cohort and under active clinical follow-up as of the end of 2021 (i.e., with at least one visit/laboratory test/therapy data recorded during 2021).

The ICONA Foundation StudyCohort is a multicenter prospective, observational cohort study including sociodemographic and clinical information of over 20,000 PLWH enrolled in 62 Italian Infectious Diseases centers since 1997 [19]. PLWH could be enrolled in ICONA at the moment of ART initiation and after providing written informed consent, following the ethical standards of the committee on human experimentation and the Helsinki Declaration (1983 revision). Each center has submitted and obtained its own independent Ethics Committee approval when participating in the ICONA Foundation Study.

Within this selected subset of participants and over their entire history from the date of entering the cohort and up to December 31, 2021, we distinguished between those who ever satisfied the criteria for classification as HTE vs those who, to the same date, have never met the same criteria.

Specifically, we defined participants as HTE based on their current ART and ART previous history if, after entering the cohort and up to December 31, 2021, they had met ≥2 of the following conditions: (i) had received a regimen which was deemed to be indicative of the (≥ three drugs, including ≥1 of the following: dolutegravir (DTG) *bis in die* or darunavir (DRV) *bis in die* or enfuvirtide (T20); etravirine (ETV) + DTG *bis in die* or maraviroc (MVC) or boosted DRV *bis in die* or T20/ ENF); (ii) had started a regimen with ≥3 of the main historical classes of ARV drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), protease inhibitors (PIs) or integrase strand transfer inhibitors (INSTIs); (iii) had started a regimen with ≥4 anchor agent switches with the subsequent line regimen, including one of the following:

- DTG or DRV *bis in die*or T20;
- ETV + DTG *bis in die* or boosted DRV *bis in die* or MVC or T20;
- ≥2 core agents + any other ARV;

(iv) had experienced ≥three documented virologic failures (defined as a single viral load (VL) >200 copies/ml or ≥ two consecutive VL >50 copies/ml within 90 days from each other followed by a treatment switch).

Among HTE PLWH, we identified a subgroup at high risk of clinical progression based on their current immune-virological status registered at their last follow-up visit. Specifically, this subgroup included all HTE with a detectable VL (>50 cp/ml) and/or a CD4 count <200/μl at their last follow-up visit in 2021.

The sociodemographic, clinical, and immune-virological characteristics of the participants collected before ART initiation were retrieved from the shared electronic database.

Only for the subset of HTE PLWH with current evidence of immune-virological failure, the clinical centers having any of these

patients in charge were asked to recall and provide additional detailed information (history of Virological Failure, the cumulative GRT, the current ARV regimen), along with reporting all HIV-RNA VL and CD4 counts collected since the moment of entering the HTE definition.

Statistical analyses

The study determined the prevalence of HTE patients at the follow-up conclusion. Frequency was calculated by dividing the number of qualifying patients by the total actively followed on December 31, 2021.

Descriptive statistics included means (± SD), medians, and interquartile range (IQR) for continuous variables, and absolute numbers with relative frequencies for categorical data. Chi-square tests and non-parametric Mann-Whitney tests compared HTE and non-HTE populations, focusing on those with immune-virological failure.

Logistic regression models identified factors influencing the risk of transitioning to HTE status by follow-up end, among the following exposures of interest, measured at ART initiation: (i) mode of HIV transmission (especially the PWID); (ii) AIDS diagnosis; (iii) hepatitis C virus antibody (HCVAb+) status; (iv) year of starting ART; (v) CD4 count nadir; (vi) whether the participants had started treatment with a two-drug, NNRTI-based therapy (2DR) before commencing combined ART (cART) with ≥3 drugs.

We examined primary exposures, adjusting for potential confounders, and reported unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) in tables. Results from models partially adjusted for sex and age are included. The same analysis was repeated using the risk of transitioning to HTE with immune-virological failure as the outcome. We repeated this analysis on the larger dataset of individuals who satisfied ≥1 of the conditions described in the previous paragraph.

Within this subgroup, unsupervised learning analysis via cluster dendrograms identified distinct patient subgroups based on immunological and virological profiles. The analysis focused on CD4 and VL trajectories, highlighting individuals entering HTE with consistently low CD4 T-cell counts (<200 cell/MMC), high viral loads (>200 copies/ml), or both—indicating a higher risk of AIDS/death and a greater need for treatment modification.

Based on cumulative GRTs, the virtual genotypic susceptibility score (GSS) was calculated using the Sanford University algorithm for 29 participants with evidence of immune-virological failure and resistance data available.

In particular, we estimated the number of INSTIs (among cabotegravir [CAB], bictegravir [BIC], DTG, raltegravir [RAL], and elvitegravir [EVG]) predicted to be still active at the end of 2021.

All Statistics were performed using SAS version 9.4 (Cary, North Carolina, USA) and R for the dendrogram analysis. A P <0.05 was considered as statistically significant.

Results

As of December 31, 2021, 8758 PLWH were under active clinical follow-up in the ICONA cohort. Since the time of entering the cohort, 767(8.8%) of them satisfied ≥1 of the individual HTE-defining conditions: 42 patients met (ii) (a regimen indicative of HTE), 551 met (ii) (use of ≥3 among NRTIs, NNRTIs, PIs, or INSTIs), 187 participants met (iii) (≥ four anchor agent switches with the 4th or subsequent line regimen indicative of HTE), and the remaining 186 met (iv) (≥ three virological failures within 90 days followed by ART switch).

One hundred sixty-three participants who satisfied ≥2 of these criteria were classified as HTE adults living with HIV-1 infection, with an overall prevalence of 163/8758 (1.9%), as graphically reported in the Venn diagram in Figure 1.

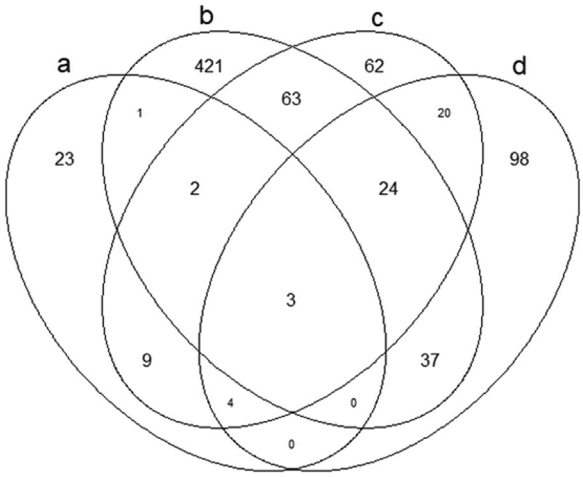

Figure 1. Venn diagram of the four definitions used to identify HTE subjects: (a) current regimen indicative of HTE; (b) at least three core ARV classes prior to current regimen; (c) individuals who had at least four anchor drug switches at any previous time; (d) ≥ three virological failures followed by a treatment switch.
ARV: antiretrovirals; HTE: heavily treatment-experienced.

The main characteristics of the study population collected at the moment of ART initiation, stratified according to HTE status by most recent follow-up, are summarized in Table 1. At univariable logistic regression, modality of HIV transmission (especially injective drug use vs other modes of transmission), CD4 cells count below 200/mmc, past or current HCV co-infection, history of AIDS diagnosis, and prior use of NNRTI as first-line ARV treatment were associated with a higher risk of entering the HTE status. After controlling only for age and sex in all models, the results were similar. After further adjustment for key potential confounders (such as HCV status and HIV-RNA at ART initiation and mode of transmission), baseline lower CD4 count and positivity to HCV Ab were the only two factors that remained significantly associated with a higher risk of becoming HTE (OR 1.60 × 100 cells/MMC CD4 lower, 95% CI 1.06-2.41, $P = 0.026$ and OR 1.90, 95% CI 1.16-3.11, $P = 0.01$, respectively, Table 2).

At multivariable regression analysis (Table 3), factors associated with the risk of transitioning to HTE with current immune-virological failure were similar to those of becoming HTE and included HCV-positive status, CD4 count nadir, and ART initiation with 2DR. Of interest, the association with AIDS was no longer significant after adjustment, and the OR appeared to go in the opposite direction. Setting aside the consideration of statistical significance, which may not have been obtained due to the limited number of events, we observed that the magnitude of the association increased after fitting the multivariable model. Specifically, individuals with a baseline HCV-positive status (OR = 2.61, 95% CI 0.85-8.00) and those who initiated ART with two-drug regimens (OR = 1.56, 95% CI 0.61-3.99) had a notably higher likelihood of developing current immune-virological failure, although without reaching statistical significance. Duration of ART was also associated with the risk of outcome, participants who initiated ART more recently were at reduced risk of becoming HTE for a given age and sex (Tables 2 and 3). Results of a sensitivity analysis conducted on the larger dataset of 767 participants who satisfied ≥1 conditions described in the methods carried similar results, with the only difference that having started suboptimal ART before cART was now significantly associated with the risk of becoming THE after controlling for sex, age, and year of ART initiation in this analysis (Table 4 in Supplementary Material).

Table 1
Main characteristics of patients by HTE status collected at the moment of ART initiation.

Characteristics at ART initiation	HTE status by the most recent follow-up			
	HTE[a] (N = 767)	Not HTE (N = 7991)	*P*-value[b]	Total (N = 8758)
Gender, n(%)			<.001	
Female	222 (28.9%)	1505 (18.8%)		1727 (19.7%)
Age, years			<.001	
Median (IQR)	38 (32, 45)	40 (32, 48)		40 (32, 48)
Mode of HIV Transmission, n(%)			<.001	
PWID	149 (19.4%)	625 (7.8%)		774 (8.8%)
MSM	245 (31.9%)	3702 (46.3%)		3947 (45.1%)
Heterosexual contacts	342 (44.6%)	3172 (38.7%)		3514 (39.2%)
Other/Unknown	31 (4.0%)	492 (6.2%)		523 (6.0%)
Nationality, n(%)			<.001	
Not Italian	89 (11.6%)	1607 (19.6%)		1696 (18.9%)
AIDS diagnosis, n(%)			<.001	
Yes	95 (12.4%)	673 (8.2%)		768 (8.6%)
HBsAg[a], n(%)			0.020	
Negative	496 (64.7%)	4999 (61.0%)		5495 (61.3%)
Positive	6 (0.8%)	29 (0.4%)		35 (0.4%)
Not tested	265 (34.6%)	3165 (38.6%)		3430 (38.3%)
HCVAb[a], n(%)			<.001	
Negative	396 (51.6%)	4562 (55.7%)		4958 (55.3%)
Positive	128 (16.7%)	528 (6.4%)		656 (7.3%)
Not tested	243 (31.7%)	3103 (37.9%)		3346 (37.3%)
Hepatitis B/C coinfection[a], n(%)			<.001	
No	373 (48.6%)	4306 (52.6%)		4679 (52.2%)
Yes	133 (17.3%)	553 (6.7%)		686 (7.7%)
Not tested	261 (34.0%)	3334 (40.7%)		3595 (40.1%)
Calendar year of ART initiation			<.001	
Median (IQR)	2007 (1998, 2012)	2015 (2012, 2017)		2014 (2011, 2017)
CD4 count nadir, cells/mmc			<.001	
Median (IQR)	276 (131, 383)	323 (170, 475)		316 (165, 468)
Below 200, n(%)	275 (36.6%)	2237 (29.0%)	<.001	2512 (29.7%)
CD4/CD8 ratio			<.001	
Median (IQR)	0.3 (0.2, 0.5)	0.4 (0.2, 0.6)		0.4 (0.2, 0.6)
HIV-RNA, log10 copies/mL			<.001	
Median (IQR)	4.82 (4.27, 5.39)	4.71 (4.10, 5.25)		4.72 (4.11, 5.26)
PLWH with HIV RNA >100,000, n(%)	226 (38.8%)	2140 (35.5%)	0.119	2366 (35.8%)
Time from HIV diagnosis[a], months			<.001	
Median (IQR)	7 (1, 55)	2 (1, 21)		2 (1, 24)
Started 2DR before cART, n(%)	137 (17.9%)	209 (2.6%)	<.001	346 (3.9%)
Number of regimen lines received up to the most recent VL				
Median, (IQR)	6 (5, 9)	2 (1, 4)	<.001	3 (2, 4)
Antivirals received up to the most recent VL, n(%)				
Prior NRTI	455 (59.3%)	5.698 (69.5%)	<.001	6153 (68.7%)
Prior NNRTI	159 (20.7%)	2053 (25.1%)	0.008	2212 (24.7%)
Prior PI	160 (20.9%)	1205 (14.7%)	<.001	1365 (15.2%)
Prior INSTI	324 (42.2%)	2322 (28.3%)	<.001	2646 (29.5%)
Lamivudine	208 (27.1%)	2624 (33.0%)	<.001	2832 (32.4%)
Abacavir	83 (10.8%)	899 (11.3%)	0.694	982 (11.2%)
Tenofovir	36 (4.7%)	760 (9.5%)	<.001	796 (9.1%)
Emtricitabine	166 (21.6%)	1968 (24.7%)	0.058	2134 (24.4%)
Efavirenz	3 (0.4%)	150 (1.9%)	0.003	153 (1.8%)
Nevirapine	4 (0.5%)	105 (1.3%)	0.058	109 (1.2%)
Lopinavir/r	0 (0.0%)	14 (0.2%)	0.245	14 (0.2%)
Atazanavir/r	7 (0.9%)	67 (0.8%)	0.837	74 (0.8%)
Darunavir/r	138 (18.0%)	959 (12.0%)	<.001	1097 (12.6%)
Raltegravir	80 (10.4%)	294 (3.7%)	<.001	374 (4.3%)

[a] Meeting at least one definition.
[b] Chi-square or Kruskal-Wallis tests as appropriate.
ART: antiretroviral treatment; ARV: antiretroviral; cART: combined ART; MSM: males who have sex with males; HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibodies; INSTI: integrase strand transfer inhibitors; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-NRTI; PI: protease inhibitors; PWID: people who inject drugs; VL: viral load; 2DR: two-drugs regimens.

Among the group of HTE PLWH, 30 (18%) subjects had current evidence of immune immune-virological failure. The overall prevalence of these patients at high risk of clinical progression was 0.003% in the total population of PLWH actively followed up in the cohort. As expected, a more prolonged duration of ART, with a mean duration of 15 (±6) years, was observed in this subgroup, along with an impressive number of treatment line switches (a median of 9 [IQR 7-12]). Nearly all patients in this subgroup (27/30, 90%) had experienced at least one Virological Failure since enrollment in the cohort, while 12 out of 30 patients (40%) had reported four or more episodes of Virological Failure.

GRTs were available for 29/30 patients. Their cumulative analysis revealed the presence of major acquired resistance-associated mutations (RAMs) to at least one ARV drug class in 19 (63%) out of 30 cases. In particular, 13(43%) subjects had RAMs to NRTIs, 13(43%) to NNRTIs, 8 (27%) to PIs, and 5 (17%) displayed intermediate and high-level resistance mutations to first-generation INSTIs. Notably, five patients (17%) simultaneously presented with

Table 2
Factors associated with entering the HTE definition among patients features collected at the moment of ART initiation.

	Logistic regression estimates of factors associated with HTE status					
	Unadjusted		Adjusted[a]		Adjusted[b]	
Factor	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Nationality						
Not Italian vs Italian	0.43 (0.25, 0.73)	***0.002***	0.34 (0.20, 0.59)	***<.001***		
Mode of transmission						
PWID vs not	4.81 (3.42, 6.77)	***<.001***	4.71 (3.34, 6.65)	***<.001***		
AIDS						
Yes vs not	1.78 (1.14, 2.78)	***0.012***	1.77 (1.13, 2.79)	0.013	1.43 (0.87, 2.34)	0.153
HCVAb						
Positive vs negative	4.63 (3.23, 6.63)	***<.001***	4.14 (2.87, 5.98)	***<.001***	1.90 (1.16, 3.11)	***0.011***
Year of ART initiation						
per more recent	0.80 (0.77, 0.82)	***<.001***	0.80 (0.78, 0.82)	***<.001***		
CD4 count nadir						
below 200 vs >200 cells/mmc	1.51 (1.10, 2.07)	***0.012***	1.72 (1.24, 2.38)	***0.001***	1.60 (1.06, 2.41)	***0.026***
HIV-RNA						
>100,000 vs below 100,000 copies/ml	1.13 (0.78, 1.63)	0.528	1.29 (0.89, 1.87)	0.179		
2NNRTIas 1st line						
Yes vs no	9.70 (6.70, 14.03)	***<.001***	7.45 (5.11, 10.86)	<.001	1.05 (0.69, 1.60)	0.809

ART: antiretroviral treatment; CD: clusters of differentiation; CI: confidence interval; HCV Ab: hepatitis C virus antibodies; NNRTI: non-nucleoside reverse transcriptase inhibitors; OR, odds ratio; PWID: people who inject drugs.
[a] Adjusted for gender and age.
[b] -AIDS; adjusted for gender, age, and CD4 count nadir.
-HCV; adjusted for gender, age, and mode of transmission.
-CD4 nadir; adjusted for gender, age, HCV status, and HIV-RNA at ART initiation.
-2NNRTI before combination ART; adjusted for gender, age, and year of ART initiation.

Table 3
Factors associated with transitioning to HTE status with immune-virological failure among the features collected at the moment of ART initiation.

	Logistic regression estimates of factors associated with immune-virological failure					
	Unadjusted		Adjusted[a]		Adjusted[b]	
Factor	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Nationality						
Not Italian vs Italian	0.85 (0.32, 2.21)	0.734	0.72 (0.27, 1.95)	0.523		
Mode of transmission						
PWID vs not	3.95 (1.75, 8.91)	***<.001***	3.84 (1.70, 8.66)	***0.001***		
AIDS						
Yes vs not	0.77 (0.18, 3.25)	0.724	0.74 (0.17, 3.12)	0.678	0.53 (0.12, 2.36)	0.404
HCVAb						
Positive vs negative	4.85 (2.15, 10.93)	***<.001***	4.27 (1.88, 9.70)	***<.001***	2.61 (0.85, 8.00)	0.092
Year of ART initiation						
per more recent	0.83 (0.79, 0.87)	***<.001***	0.83 (0.79, 0.88)	***<.001***		
CD4 count nadir						
below 200 vs >200 cells/mmc	1.59 (0.77, 3.31)	0.212	1.75 (0.83, 3.70)	0.140	1.62 (0.67, 3.93)	0.284
HIV-RNA						
>100,000 vs below 100,000 copies/ml	0.95 (0.42, 2.14)	0.903	1.09 (0.48, 2.46)	0.838		
NNRTI as 1st line						
Yes vs no	10.16 (4.49, 23.00)	***<.001***	8.00 (3.48, 18.37)	***<.001***	1.56 (0.61, 3.99)	0.350

ART: antiretroviral treatment; CD: clusters of differentiation; CI: confidence interval; HCV Ab: hepatitis C virus antibodies; NNRTI: non-nucleoside reverse transcriptase inhibitors; OR, odds ratio; PWID: people who inject drugs.
[a] Adjusted for gender and age.
[b] -AIDS; adjusted for gender, age, and CD4 count nadir.
-HCV; adjusted for gender, age, and mode of transmission.
-CD4 nadir; adjusted for gender, age, HCV status, and HIV-RNA at ART initiation.
-2NNRTI before combination ART; adjusted for gender, age, and year of ART initiation.

intermediate and high-level resistance to NRTIs, NNRTIs, and PIs. Specifically, one patient exhibited resistance to all PIs (M46I, M46L, I54L, L76V), all NRTIs (M184V, K70R), and most NNRTIs, except for DOR (K103N). This same patient also carried a highly resistant virus against BIC) and DTG (mutation Q148H was detected, which has a score of 30 for BIC and 60 for other INSTIs in the Stanford algorithm). For this patient, a salvage regimen comprising DOR + DTG + MVC was chosen, which still is their current regimen. When we calculated the virtual StanfordGSS, 10 out of 29 with complete resistance data (34%) had no drugs in the INSTI class, which was predicted to be still active. Of note, the last genotypic test results used for this calculation were done on average 67 (26-115) months before the end of 2021.

More than half of them were indeed on triple regimens consisting of 2NRTIs + a boosted PI (four patients) or two NRTIs + a INSTIs (12 subjects), which generally do not conform to the traditional definition of "salvage" regimens and are single-tablet formulations. Other currently used combination regimens observed were: (i) the association of two NNRTIs + INSTI + boosted PI (four patients) or NRTI (one patient); (ii) the composite of a boosted PI with an NRTI (lamivudine, 3TC, two patients) or MVC (one patient); (iii) the combination of an NNRTI (specifically rilpivirine, doravirine, or ETV) + a boosted PI (two subjects) or an INSTI

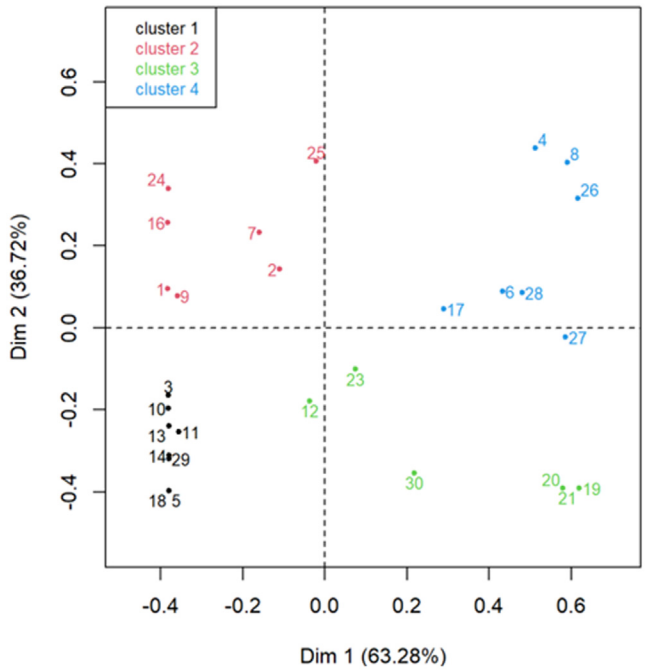

Figure 2. Ascending Hierarchical classification of HTE according to cluster dendrogram analysis. Each dot in the plot is a participant included in the subgroup of HTE with evidence of immune-virological failure, indicated by their patient ID, and specifically: Cluster 1: n = 8 patients with low viral loads and CD4 counts above 200 cells/mm^3, Cluster 2: n = 9 patients with viral loads above 200 cp/ml but good CD4 counts >200 cells/mm^3, Cluster 3: n = 6 subjects with CD4 counts <200 cells/mm^3 despite low viral loads, Cluster 4: n = 7 patients with CD4 count constantly <200 cells/mm^3 regardless of viral load.
ARV: antiretrovirals; CD: clusters of differentiation; HTE: heavily treatment-experienced.

(two subjects). In the latter two cases, this association was potentiated with MVC and (iv) the association of a fixed dose single table regimen such as TDF/3TC/DOR + DTG (one patient) or TAF/FTC/BIC + boosted DRV (one patient).

Finally, in the cluster analysis, looking at the trajectories of CD4 and VL after having met the HTE status, four distinct patient clusters emerged within this subgroup (Figure 2):

- Cluster 1: n = 8 patients with low viral loads and CD4 counts above 200 cells/mmc.
- Cluster 2: n = 9 patients with viral loads above 200 cp/ml but good CD4 counts >200 cells/mmc.
- Cluster 3: n = 6 subjects with CD4 counts < 200 cells/mmc despite low viral loads.
- Cluster 4: n = 7 patients with CD4 count constantly <200 cells/mmc, regardless of VL.

The last two clusters are particularly interesting as they include patients with an immediate higher risk of morbidity/mortality because of their low CD4 count. Cluster 3 is a group of patients often cited in the literature as 'immunological non-responders,' and their management is particularly challenging. Figures 1 to 4 in Supplementary Material depict the trajectories of VL and CD4+ cell count for each of the four patients' clusters.

Discussion

Among participants of our cohort who by the end of 2021 were still alive and under active follow-up, approximately 2% could be retrospectively classified as HTE based on their current and past ART history. Among these, 43% currently have a CD4 count <200 cells/mmc indicating that they are currently at risk of clinical progression, and a subset would benefit from using novel antiretroviral drugs to suppress VL and improve CD4 count. Our HTE-defined group showed extensive drug resistance accumulation even in the INSTI class.

Despite the lack of a universally agreed-upon definition for HTE PLWH, evidence from international cohort studies, such as the Centers for AIDS Research Clinical Network of Integrated Systems (CNICS), indicates a significant decrease in patients with limited treatment options from 2000-2006 [12]. Conversely, the EuroSIDA cohort, considering GRTs and medication history, observed an increasing proportion of HTE patients from 2010 to 2016 [13].

Our analysis outlined a notably low prevalence of patients on Italian PLWH enrolled in the ICONA cohort, even lower than in the two mentioned sizeable international cohort studies. This is because our analysis is restricted to a selected group of participants in the cohort who were under active follow-up until recently.

Patients meeting HTE criteria were mainly Italian females. The higher prevalence of females in HTE may stem from delayed treatment initiation in the mid-90s, impacting virological and immunological outcomes. This association could be partly due to survival bias [20].

We have documented a higher prevalence, among HTE patients, of individuals showing evidence of co-infection with Hepatitis B Virus and HCV, although not necessarily in active form. In particular, co-infection, whether past or still active with the HCV, was among the factors explored in the multivariate analysis and emerged as one of the most significantly associated with the risk of becoming HTE and also developing a condition of worsened immunovirological status.

This evidence may signify the detrimental effects of hepatitis co-infection on HIV-positive patients, resulting in decreased ART adherence, insufficient immunological recovery, and persistent inflammation. Additionally, it could be construed as an outcome of prolonged exposure to certain ARVs, such as TDF/3TC, necessitated by the treatment of Hepatitis B Virus co-infection [21,22].

Our analysis further shows that having a lower CD4 cell count at ARTinitiation is associated with a higher risk of becoming HTE during follow-up. This observation aligns with earlier findings by Priest and Katlama [13,14], who also found that immunological impairment in HTE subjects is relatively common. However, interestingly, they also reported that it does not necessarily translate into a greater likelihood of developing AIDS-related events. This finding has implications for HTE ICONA participants included in clusters #3 and #4 in our analysis.

A unique aspect of our research lies in focusing, within the group of HTE PLWH who were still alive and under follow-up in our cohort, on a group of subjects currently experiencing either virological or immunological failure and in their comprehensive characterization in terms of the entire history of CD4 count, VL, and cumulated HIV drug resistance. This detailed inquiry was made possible by the large initial universe of PLWH enrolled in the ICONA cohort database and the rigorous data management and storage processes that have consistently maintained the quality of clinical and laboratory data over the years.

We discovered that this subset of participants made up approximately one-fifth of the entire cohort. The detailed analysis of this group of patients also revealed two crucial aspects of their immune-virological and therapeutic profile.

From the perspective of VL control, about half of the population had detectable viral loads >200 copies/ml. Additionally, nearly all patients exhibited major RAMs to at least one primary ARV class. Overall, 34% of them did not have active drugs in the INSTI class. Of note, possibly because they transitioned the HTE status sometime before the end of 2021, most patients in this subgroup were

currently on standard regimens (often single-tablet formulations) with three or, in some cases, two medications.

These findings suggest that thanks to the tolerability and ease of modern antiretroviral regimens, even patients with complex and ineffective treatment histories can achieve therapeutic success. However, caution is needed because virologically active drugs may not always be usable due to specific concerns like DDIs, toxicities, or intolerance. In addition, it is essential to note that for most patients, the last genotypic test had been performed many months before the end of 2021, and therefore the number of drugs predicted to be still active was most likely overestimated. This raises questions about the potential impact of these findings on treatment outcomes, underscoring the importance of our study in clarifying these intricate dynamics.

Regarding immunological impairment, examining CD4 trends of HTE patients with ongoing evidence of inadequate immune-virological conditions revealed that nearly half of them, despite an undetectable VL and an effective regimen, had low CD4 counts, indicating unsatisfactory immunological recovery (clusters #3 and #4). The management of this type of patient (the so-called 'immunological non-responders') is particularly challenging as there is little data on strategies able to increase their CD4 count (i.e., ART intensification, interleukin-2 treatment, etc. [23,24]), and they potentially remain at increased risk of morbidity/mortality. It is unclear whether these individuals could also benefit from the new treatments recently introduced to the market, such as fostemsavir and lenacapavir [25–27], or whether these new drugs should be left only to those with currently elevated HIV-RNA. A thorough assessment of the characteristics of HTE patients currently under follow-up is hence of significant importance.

Our study has limitations. First, results are specific to the Italian context and not easily generalizable. Moreover, the main inclusion criteria (HIV-1 positive patients in care on December 31, 2021) hindered unbiased estimates of prevalence, incidence, and trends of HTE cases, as well as descriptions of subjects lost to follow-up or deceased due to this condition. This selection may explain the low HTE prevalence observed in our analysis and is probably further biased by the impact that the SARS-CoV-2 pandemic has had on PLWH. Substantial cohort studies have indeed highlighted an elevated burden of COVID-19-related morbidity and mortality among PHWL, particularly those of older age and with compromised immunological assessments [28,29]. Considering the vulnerability of the HTE PLWH population, our decision to include in the analysis only those alive and in follow-up by the end of December 2021 may have led to a marginal underestimation of their number. However, this choice was motivated by the necessity to furnish updated evidence on the matter of HTE.

Another notable limitation is that the ICONA cohort enrolls only treatment-naive adults, excluding those with vertically acquired HIV. This may slightly underestimate HTE cases, especially those on complex regimens with unsatisfactory immune-virological recovery, typical of vertically transmitted cases. Finally, our analysis extracted the group of the as a time-fixed feature based on participants' history for their date of entry in the cohort up to a recent date; on the other hand, the concept of HTE, regardless of its exact definition, is fluid. Just as the prevalence of this group of patients is likely to increase over time due to issues such as long-term virological failure, toxicity, intolerance, adherence challenges, or other factors, it may also diminish as new therapeutic options emerge on the market as a result of patients transitioning back from HTE to non-HTE.

For this reason, despite the reassuring landscape regarding HIV treatment in high-income patients, reliable estimates of the burden of HTE over time, which consider its time-varying nature, are still lacking and should be the focus of future analyses.

Conclusion

Despite limitations, our analysis enhances understanding of HTE patients. Modern antiretrovirals have reduced the impact on a small subset of patients with long treatment histories. Yet, within this group, roughly one-tenth face challenges, despite undetectable viral loads, with compromised immune status, increasing morbidity and mortality risk. Identifying suitable candidates for advanced treatments is crucial, holding the potential to extend life expectancy and improve the quality of life for most PLWHs.

Declarations of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Sergio Lo Caputo: Methodology, Writing – original draft, Writing – review & editing, Project administration. **Mariacristina Poliseno:** Methodology, Writing – original draft, Writing – review & editing. **Alessandro Tavelli:** Formal analysis, Investigation, Data curation, Writing – original draft. **Roberta Gagliardini:** Investigation, Data curation. **Stefano Rusconi:** Investigation, Data curation. **Giuseppe Lapadula:** Investigation, Data curation. **Andrea Antinori:** Investigation, Data curation. **Daniela Francisci:** Investigation, Data curation. **Loredana Sarmati:** Investigation, Data curation. **Andrea Gori:** Investigation, Data curation. **Vincenzo Spagnuolo:** Investigation, Data curation. **Francesca Ceccherini-Silberstein:** Investigation, Data curation. **Antonella d'Arminio Monforte:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Alessandro Cozzi-Lepri:** Formal analysis, Investigation, Data curation, Writing – original draft, Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

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Ethical approval statement

The Italian Cohort Naïve Antiretrovirals Foundation study has been approved by the Institutional Review Boards of all the participating centers. All people living with HIV signed an informed consent for study participation and processing of data.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.01.023.

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