Burden of advanced HIV disease among antiretroviral therapy-experienced persons with HIV in Italy over the past 20 years

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ABSTRACT

Objectives: Data on the burden of advanced HIV disease (AHD) among people with HIV (PWH) already in care remain limited in high-income settings.

Methods: We included all PWH from the Icona Cohort who started ART between 2004 and 2024, with CD4$\geq$200 cells/mm^3 and no prior AIDS-defining event (ADE). Probability of AHD (CD4 < 200 cell/mm^3 or ADE) occurring $\geq$3 months after ART initiation was estimated by Kaplan-Meier curves. In a nested case-control study, AHD cases were matched 1:2 to controls by CD4 nadir, age, and ART duration. Predictors of AHD were evaluated by conditional logistic regression. Mortality risk in cases versus controls was also assessed.

Results: Among 9,972 ART-experienced PWH, 429 (4.3%) developed AHD. Incidence was highest during the first year of ART (1.6%) and increased linearly thereafter, with lower rates among more recent ART initiators. In the case-control study, female sex, lower education, unemployment, injecting drugs use, prolonged disengagement from care and suboptimal virologic control were associated with an increased AHD risk. AHD cases exhibited an over 8-fold higher risk of all-cause mortality, particularly within two years post-diagnosis.

Conclusions: Although declining, the risk of AHD following ART, remains a concern in Italy. Efforts to improve sustained care engagement, especially among women and socio-economically vulnerable groups, are critical.

Introduction

Despite the significant progress in HIV management [1], the burden of advanced HIV disease (AHD), defined by the World Health Organization (WHO) as a CD4 count below 200 cells/mm³ or WHO Stage 3/4 AIDS-defining illness [2], remains high, involv-

ing approximately one-third of individuals presenting to healthcare settings [3]. AHD has been largely associated to an increased risk of morbidity and mortality [4] and worse clinical outcomes following hospital discharge, even after ART initiation [5]. Consequently, there is a pressing need to prevent, promptly recognize, and effectively manage this stage of infection [3,6].

Until recently, AHD has been perceived as related to late presentation to care. In response, public health initiatives in the last decades have focused on promoting early HIV diagnosis, particularly among high-risk demographic groups [6,7]. However, recent evidence from resource-limited settings suggests a shift in this paradigm, indicating that AHD is now increasingly observed among people with HIV (PWH) already on ART but not adequately engaged in care [8,9]. This trend highlights a critical challenge in the continuum of care, revealing its cyclical rather than linear nature—marked by recurring patterns of (re)engagement and disengagement—and underscores the urgent need for targeted interventions to enhance adherence and retention [10].

Data on the incidence of AHD following ART initiation in resource-rich settings remain limited, and risk factors for progressing to the advanced disease despite ART remain poorly investigated. The aim of this study was to assess the burden of AHD after ART initiation in a high-income setting and to identify potential predictors within a large cohort of PWH seen for care in Italy over the last two decades. A secondary objective was to evaluate the impact of incident AHD after ART initiation on the long-term risk of mortality from any cause.

Material and methods

Study design and population

The study was conducted within the ICONA (Italian Cohort Naïve Antiretrovirals) Foundation Study cohort, an Italian nationwide observational cohort set up in 1997, including adult PWH who were ART-naïve at the enrolment. Details of the cohort have been described elsewhere [11].

We included all PWH enrolled in Icona who started ART between January 1st, 2004, and July 31st, 2024 with a pre-treatment CD4 count $\geq$ 200 cells/mm^3 and no prior AIDS-defining events (ADE). Participants without at least one follow-up visit after treatment initiation were excluded. Longitudinal analysis on the overall cohort and a case-control study nested in the cohort were performed on the prospectively collected data.

Statistical analysis

The data of the whole cohort were used to estimate the incidence of AHD (defined as a CD4 cell count <200 cells/mm^3 or an ADE, regardless of CD4 count, occurring more than 3 months after ART initiation). For this first aim, Kaplan–Meier curves were used to estimate the probability of progressing towards AHD after ART initiation over both the entire observation period and after stratifying by two consecutive time decades (2004-2013, 2014-July 2024).

To address the second aim of identifying time-varying factors associated with the risk of AHD, we performed a nested case-control study within the identified cohort. Participants who developed AHD, identified in the prospective part of the analysis, were defined as cases and matched 1:2 with controls, defined as subjects selected from the ICONA cohort who, after the same duration of time from baseline (ART initiation) to the date of developing AHD of the corresponding case (index date), still had a CD4 count $\geq$200 cells/mm^3 and were free from ADE. Matching variables were age, the nadir of CD4 count measured up to baseline and the time elapsed from ART initiation. We used a fuzzy matching with continuous variables allowing a maximum difference in

age of 10 years and 35 cells/mm^3 for CD4 count. The main characteristics of participants were compared between cases and controls using an univariable conditional logistic regression model. For time-varying factors, we used baseline values or the value closest to the index date or both, as appropriate. We performed an exposure-wide analysis with AHD as a single outcome, assessing several pre-specified potential risk factors using conditional unadjusted and adjusted logistic regression models. The following predictors were analysed in separate models: sex at birth, nationality, mode of HIV transmission, education, employment, previous gaps in care, virologic control (since ART initiation and within the year before the index date) and ART regimen taken within 3 months prior the index date. Gap in care was defined as having experienced at least one period of more than 18 months before the index date in which no laboratory tests or clinical visits occurred, regardless of ART. Participants with a total follow-up of less than 21 months were classified as not having experienced a gap in care.

We defined participants with a history of virological failure as those who had spent more than 4 months with an HIV-RNA > 400 copies/mL while receiving ART prior to the index date. This definition was used solely to describe prior virological failure, aiming to minimize the misclassification of transient viral blips as true failures and to account for limitations in historical datasets, where consecutive viral load measurements were not always available. Conversely, for the purpose of defining suboptimal virological control as a covariate in the logistic regression analysis, we used the more standard HIV-RNA threshold of >200 copies/mL.

Potential interactions between covariates were explored descriptively through stratified analyses, rather than formal statistical interaction testing. Specifically, we examined variations in the effect of care gaps across viral load trajectory groups, as well as differences in the effect of female sex across strata defined by education level, employment status, pregnancy, and nationality. Sex was modelled as a 3-way categorical exposure with cisgender male as the fixed comparator and stratifying women by secondary potential risk factors. In separate multivariable models, we included a set of potential confounders for each predictor based on associations previously shown in the literature or subject-matter knowledge.
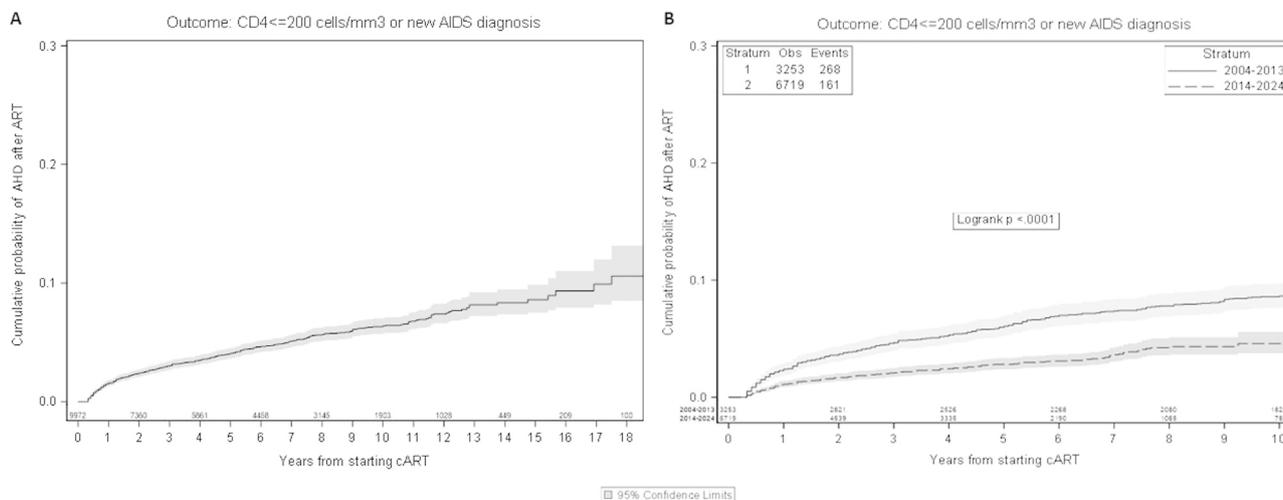
Finally, still using the data of the nested case-control study, cases and matched controls were re-classified as exposed and not exposed for a further prospective survival analysis. In this analysis, time zero was set to the index date for both groups: for the cases, this was the date of AHD diagnosis, and for the matched controls, it corresponded to the same duration since ART initiation. Matched sets were excluded from the analysis if the case or any of its controls had less than 1 month of clinical follow-up after the index date. Specifically, we used standard Kaplan-Meier and Cox regression analysis to compare the cumulative risks and hazards of all-cause mortality in exposed vs not-exposed.

All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA). All P-values presented are two-sided and a P-value <0.05 indicates conventional statistical significance.

Results

Prospective analysis: incidence of AHD

Of the 15,358 participants enrolled in the Icona Cohort who initiated first-line ART between January 2004 and July 2024, 9,972 PWH without AHD at ART initiation were included in the analysis. Over a five-year median follow-up, 429 individuals (4.3%) developed AHD at least 3 months after starting ART. Among these, 111 cases (26%) were associated to an ADE, while 318 cases (74%) were due to a decline in CD4 cell count below 200 cells/mm^3 (Supplementary Figure S1). The most frequently observed ADEs were:

Figure 1. Kaplan-Meier estimates the time to progress to AHD after ART initiation over the whole period **(1a)** and after ART initiation by calendar decade of ART initiation **(1b)**.

non-Hodgkin lymphoma (22.5%), Kaposi's sarcoma (19.8%), tuberculosis (18.9% — of which 81% were pulmonary and 19% extrapulmonary), esophageal candidiasis (10.8%), and atypical mycobacterial disease (4.5%). The probability of progression to AHD increased rapidly within the first year (1.6% [95% confidence intervals {CI}: 1.3%-1.8%] by 1 year) and then increased linearly over follow-up (4.1% [95% CI: 3.6%-4.5%] by 5 years and 6.4% [95% CI: 5.4%-7.0%] by 10 years) (Figure 1a). After stratifying by the decade of ART initiation, we found a lower risk of developing AHD among participants who started ART in the most recent decade. In fact, the probability of progression to AHD halved from 2.4% (95% CI: 1.9%-2.9%) by 1 year and 6.0% (95% CI: 5.2%-6.9%) by 5 years during 2004–2013, to 1.1% (95% CI: 0.8%-1.4%) by 1 year and 2.8% (95% CI: 2.4%-3.3%) by 5 years in the most recent decade (2014-July 2024) (Figure 1b). Of note, for PWH who initiated ART after 2014, we could only provide the incidence of AHD by 10 years from baseline.

Retrospective analysis: nested case-control study

In the nested case-control study, 424 of the 429 participants who developed AHD were matched with 844 controls, resulting in total of 1,268 PWH. All matched sets had two controls per case, apart from four sets in which we could only identify one control. No suitable matched controls were found for five participants who developed AHD.

The distribution of the main baseline characteristics among cases and matched controls is reported in Supplementary Table S1. The subjects included in the nested case-control study were mostly male (79%), Italian (83%), with a median age of 41 years. They started ART with a median CD4 count of 394 cells/mm^3, with a three-drug regimen in 90% of cases. A history of gaps in care was reported in 143 (11%) participants, 53 (37%) of whom were off ART during the care interruption.

Table 1 summarizes key sociodemographic and clinical characteristics of the study population, overall and stratified by prior gaps in care. Significant differences were observed: gaps in care were more common among women ($P = 0.009$), individuals who acquired HIV through injecting drug use ($P < 0.001$), those with lower education ($P < 0.001$), and those without stable employment (i.e., unemployed or in occasional work, $P = 0.001$). As expected, participants with prior care interruptions also exhibited poorer viro-immunological control and a higher incidence of virological failure (before the index date $P < 0.001$).

Predictors of advanced HIV disease

After controlling for confounding factors, cisgender females (adjusted odds ratio, aOR = 1.37, 95% CI: 1.03-1.82, $P = 0.03$), lower education (aOR = 1.51, 95% CI: 1.06-2.16, $P = .02$), unemployment ($P < 0.001$), and HIV acquisition via injection drug use (aOR = 1.74, 95% CI: 1.12-2.68, $P < 0.001$, compared to homosexual intercourse) were all significantly associated with increased risk of progression to AHD after ART initiation (Table 2A). To investigate the role of female sex as a predictor of AHD, we evaluated its interaction with nationality, socio-economic factors, and pregnancy. While the history of pregnancy was not associated with an increased risk of AHD, a trend toward higher risk of clinical progression was observed in women with lower education (aOR = 1.44, 95% CI: 0.92-2.25 vs women with high education 1.29, 95% CI: 0.81-2.06, $P = 0.05$), housewives (aOR = 1.78, 95% CI: 0.74-4.30 vs employed women 1.17, 95% CI: 0.81-1.79, $P = 0.09$) and those of Italian nationality (aOR = 1.44 95% CI: 1.03-2.00 vs foreign aOR = 1.19 95% CI: 0.68-2.08, $P = 0.03$) (Table S2 Supplementary Material).

In addition, a history of prolonged (>18 months) disengagement from care (aOR = 5.51 95% CI:3.54-8.59, $P < 0.001$) and suboptimal virologic control defined as either failure to achieve virologic suppression since ART initiation (aOR = 2.69, 95% CI 1.83-3.96, $P < 0.001$) or incomplete virologic suppression within the prior year (aOR = 5.50, 95% CI: 3.15-9.61, $P < 0.001$) were both strong predictors of AHD (Table 2A)'. Notably, when we redefined exposure as having a history of a gap in care with no evidence of ART use during the longest gap period, based on chart review, the results remained consistent. The prevalence of off-ART care gaps was higher among cases (62%, $n = 33$) than controls (38%, $n = 20$), with an aOR of 3.36 (95% CI: 1.72–6.58; $P = 0.0004$) [data not shown]. We also investigated the possible interaction between discharge from care and suboptimal virologic control finding a clear dose-response relationship between having none of these factors, only one of them (gap in care being the most predictive), and both factors and the risk of AHD. The interaction between these two factors was evaluated using both the most two recent values of HIV-RNA within the year before the index date (Table 2B, model 1) and the duration of HIV-RNA suppression before the index date (Table 2B, model 2). Finally, taking a single-tablet ART regimen (STR) within 3 months from the index-date, compared to a multi-tablet regimen (MTR), was associated with a 50% reduction in the risk of clinical progression (aOR = 0.48, 95% CI: 0.38–0.62; $P < 0.001$) [Table 2a]. A detailed list of the STR regimens has been reported in Supplementary Materials (Supplementary Table S3).

Table 1
Main characteristics of the population included in the nested case-control study stratified by previous history of a gap in care.

Participant's characteristics	Gap In Care N = 143	No Gap in Care N = 1,125	P-value*	Total N = 1268
Gender, n (%)			**0.009**	
Female	42 (29.4%)	224 (19.9%)		266 (21.0%)
Mode of HIV Transmission, n (%)			**<0.001**	
PWID	26 (18.2%)	113 (10.0%)		139 (11.0%)
Homosexual contacts	41 (28.7%)	521 (46.3%)		562 (44.3%)
Heterosexual contacts	63 (44.1%)	422 (37.5%)		485 (38.2%)
Other/Unknown	13 (9.1%)	69 (6.1%)		82 (6.5%)
Nationality, n (%)			0.076	
Foreign	32 (22.4%)	185 (16.4%)		217 (17.1%)
Calendar year of ART initiation			**<0.001**	
Median (IQR)	2011 (2009, 2016)	2013 (2010, 2016)		2013 (2010, 2016)
Age$^{\&}$, years			**0.045**	
Median (IQR)	39 (31, 46)	42 (33, 49)		41 (33, 49)
CD4 count nadir, cells/mmc			0.701	
Median (IQR)	308 (255, 414)	323 (254, 423)		321 (254, 422)
CD4 count at ART$^{\&}$, cells/mmc			0.219	
Median (IQR)	370 (279, 487)	398 (282, 527)		394 (281, 525)
CD4 count 1y prior to index date, cells/mmc			**<0.001**	
Median (IQR)	484 (349, 679)	581 (414, 781)		564 (405, 767)
CD4 count 6 m prior to index date, cells/mmc			**0.002**	
Median (IQR)	464 (332, 666)	560 (369, 758)		544 (366, 749)
Viral load at ART, log10 copies/mL			0.934	
Median (IQR)	4.51 (4.10, 5.05)	4.59 (3.98, 5.08)		4.57 (3.99, 5.08)
Viral load 1y prior to index date, log10 copies/mL			**<0.001**	
Median (IQR)	1.77 (1.30, 4.16)	1.49 (0.00, 2.05)		1.57 (0.00, 2.47)
Viral load 6 m prior to index date, log10 copies/mL			**<0.001**	
Median (IQR)	1.69 (1.30, 4.12)	1.57 (0.00, 2.29)		1.57 (0.00, 2.70)
Viral load at index date, log10 copies/mL			**<0.001**	
Median (IQR)	1.59 (1.04, 2.81)	1.30 (0.00, 1.60)		1.46 (0.00, 1.70)
Psychiatric comorbidities, n (%)			0.486	
Yes	6 (4.2%)	63 (5.6%)		69 (5.4%)
Education, n (%)			**<0.001**	
Primary school	18 (12.6%)	53 (4.7%)		71 (5.6%)
Secondary school	34 (23.8%)	216 (19.2%)		250 (19.7%)
College	33 (23.1%)	346 (30.8%)		379 (29.9%)
University	5 (3.5%)	141 (12.5%)		146 (11.5%)
Other/Unknown	53 (37.1%)	369 (32.8%)		422 (33.3%)
Employment, n (%)			**0.001**	
Unemployed	29 (20.3%)	105 (9.3%)		134 (10.6%)
Employed	61 (42.7%)	509 (45.2%)		570 (45.0%)
Self-employed	16 (11.2%)	171 (15.2%)		187 (14.7%)
Occasional	7 (4.9%)	26 (2.3%)		33 (2.6%)
Student	3 (2.1%)	38 (3.4%)		41 (3.2%)
Retired	4 (2.8%)	39 (3.5%)		43 (3.4%)
Housewife	5 (3.5%)	18 (1.6%)		23 (1.8%)
Other/unknown	18 (12.6%)	217 (19.3%)		235 (18.5%)
First-line ART			0.257	
2 drugs	9 (6.3%)	83 (7.4%)		92 (7.3%)
3 drugs	133 (93.0%)	1009 (89.7%)		1142 (90.1%)
4+ drugs	1 (0.7%)	33 (2.9%)		34 (2.7%)
Anchor drug in first ART regimen			0.064	
3TC+DTG	9 (6.3%)	83 (7.4%)		92 (7.3%)
PI/r	54 (37.8%)	358 (31.8%)		412 (32.5%)
NNRTI	50 (35.0%)	379 (33.7%)		429 (33.8%)
INSTI	23 (16.1%)	253 (22.5%)		276 (21.8%)
other	1 (0.7%)	33 (3.0%)		34 (2.7%)
Time from HIV diagnosis to ART, months			**<0.001**	
Median (IQR)	21 (2, 117)	4 (1, 36)		5 (1, 42)
Time from ART to index date$^{\&}$, months			**<0.001**	
Median (IQR)	59 (21, 107)	23 (9, 58)		26 (9, 62)
Number of previous VF, n (%)			**<0.001**	
≥1	25 (17.5%)	51 (4.5%)		76 (6.0%)
Active injecting drug use, n (%)			0.202	
Yes	7 (5.9%)	31 (3.5%)		38 (3.8%)

Abbreviations: PWID, people who inject drugs; ART, antiretroviral treatment; IQR, interquartile range; 3TC, lamivudine; DTG, dolutegravir; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; VF, virological failure.
$^{\$}$AIDS or CD4 count
$^{\&}$Matched factors,
*Chi-square or Kruskal-Wallis test as appropriate.

Table 2

Unadjusted and adjusted odds ratio of advanced HIV disease from fitting separate conditional logistic regression models with single exposures (table 2a) and composite exposures (table 2b).

TABLE 2A:

MODEL	EXPOSURE	CASES N (%)	CONTROLS N (%)	ORS OF ADVANCED HIV DISEASE			
				UNADJUSTED[&]	p-value	ADJUSTED[&*]	p-value
1.	**Sex at birth**				**0.009**		**0.031**
	- Male	317 (75%)	685 (81%)	1		1	
	- Female	107 (25%)	159 (19%)	1.44 (1.0-1.90)		1.37 (1.03-1.82) *Nationality	
2.	**Nationality**				**0.043**		0.158
	- Italians	339 (80%)	712 (84%)	1		1	
	- Migrants	85 (20%)	132 (16%)	1.38 (1.01-1.88)		1.26 (0.91-1.74) *Sex	
3.	**Mode of HIV transmission**				**<0.001**		**<0.001**
	- Homosexual	160 (38%)	402 (47%)	1		1	
	- Heterosexual	165 (39%)	320 (38%)	1.33 (1.01-1.73)		1.06 (0.77-1.46)	
	- PWID	68 (16%)	71 (8%)	2.53 (1.70-3.75)		1.74 (1.12-2.68)	
	- Other/Unknown	31 (7%)	51 (6%)	1.57 (0.96-2.55)		1.32 (0.79- 2.19) * Nationality, sex, alcohol, education, year of starting ART	
4.	**Education level**				**0.002**		**0.023**
	-University or higher	152 (53%)	373 (67%)	1		1	
	- Primary or secondary school	136 (47%)	185 (33%)	1.73 (1.23-2.44)		1.51 (1.06-2.16) *Nationality and year of starting ART	
5.	**Employment status**				**0.026**		**<.001**
	- Unemployed	60 (14%)	74 (9%)	1		1	
	- Employed	239 (56%)	518 (61%)	0.55 (0.38, 0.81)		0.68 (0.45, 1.03)	
	Student/occasional	25 (6%)	49 (6%)	0.64 (0.35, 1.18)		0.65 (0.35, 1.21)	
	-Other (housewives, retired, invalids)	100 (24%)	203 (24%)	0.58 (0.38, 0.90)		0.79 (0.50, 1.26) *Sex, alcohol, mode of HIV transmission, nationality, year of starting ART	
6.	**Gap in care (>18 months)**				**<0.001**		**<0.001**
	- Yes	330 (78%)	795 (94%)	1		1	
	- No	94 (22%)	49 (6%)	5.58 (3.66-8.51)		5.51 (3.54-8.59) *Sex, nationality, mode of HIV transmission, year of ART initiation, alcohol use, education, employment	
7.	**Viral suppression (<50 cp/mL)**				**<0.001**		**<0.001**
	- Yes	311 (73%)	718 (85%)	1		1	
	- No	113 (27%)	126 (15%)	2.88 (2.01-4.14)		2.69 (1.83-3.96) * Nationality, mode of HIV transmission, year of ART initiation, alcohol use, education, employment	
8.	**Viral dynamics from 12 to 6 months from index date**				**<0.001**		**<0.001**
	- Stable < 200 cp/mL	206(62%)	514 (79%)	1		1	
	-Current <200 -Previous ≥ 200 cp/mL	31 (9%)	58 9%)	2.85 (1.36-5.96)		2.57 (1.19- 5.52)	
	-Current ≥200- Previous < 200 cp/mL	5 (2%)	7 (1%)	2.22 (0.65-7.58)		1.82 (0.49- 6.74)	
	-Stable ≥ 200 cp/mL	88 (27%)	71 (11%)	6.35 (3.70-10.91)		5.50 (3.15 -9.61) *Nationality, mode of HIV transmission, alcohol, education, employment, year of starting ART	
9.	**ART formulation (n° of pills) [§]**				**<0.001**		**<0.001**
	-MTR	270 (64%)	392 (46%)	1		1	
	-STR	154 (36%)	452 (54%)	0.48 (0.38-0.62)		0.54 (0.40-0.73) * Nationality, mode of HIV transmission, year of ART initiation, alcohol use, education, employment, HIV-RNA at baseline	

TABLE 2B:

MODEL	EXPOSURE	CASES N (%)	CONTROLS N (%)	ORS OF ADVANCED HIV DISEASE			
				UNADJUSTED[&]	p-value	ADJUSTED[&*]	p-value
1.	**Gap in care and viral control 6 months before index date**				**<0.001**		**<0.001**
	- No gap in care/ VL^≤200 cp/mL	206 (52%)	582 (73%)	1		1	
	-No gap in care/ VL^>200 cp/mL	98 (25%)	163 (21%)	2.45 (1.57-3.81)		2.16 (1.35-3.45)	
	- Gap in care/ VL^≤200 cps/mL	51 (13%)	36 (5%)	4.75 (2.84-7.95)		4.55 (2.66-7.77)	
	- Gap in care/ VL^>200 cps/mL	42 (11%)	12 (2%)	11.93 (5.91- 24.07)		10.78 (5.20-22.35) * Nationality, mode of HIV transmission, alcohol, education, employment status and year of starting ART	

Table 2 (*continued*)

2.	Gap in care and duration of viral suppression			<0.001	<0.001
	- No gap in care/ VL ≤ 50 cps/mL for >12 months$^£$	148 (35%)	428 (51%)	1	1
	- No gap in care/ VL ≤ 50 for ≤ 12 months$^£$	182 (43%)	367 (44%)	2.02 (1.2- 3.29)	1.74 (1.05-2.89)
	- Gap in care/ VL ≤ 50 for >12 months$^£$	38 (9%)	30 (3%)	3.75 (2.14-6.57)	3.82 (2.15-6.79)
	- Gap in care/ VL ≤ 50 for ≤ 12 months$^£$	56 (13%)	19 (2%)	11.91 (6.15- 23.06)	10.23 (5.16-20.26)
					* Nationality, mode of HIV transmission, year of ART initiation, alcohol use, education, employment

Abbreviations: N, number; OR, odds ratio; cps, copies; PWID, people who inject drugs; ART, antiretroviral therapy; cp, copies; MTR multi tablet regimen; STR single tablet regimen; VL, viral load.

Notes: $^&$ matched for age and CD4 nadir; *confounders adjustment set; § ART formulation 3 months before index date; ^ HIVRNA 6 months before the index date, £ counting all HIV-RNA between ART initiation and index date

Figure 2. Kaplan–Meier curves for all-cause mortality in subjects with AHD (exposed) and not-exposed.

Survival analysis with the baseline index date

Of the 1,268 participants included in the nested study, 1,191 (94%) have at least 1 month of clinical follow-up after the index date. These comprised 398 matched sets, each consisting of one case and at least one control for a total of 398 exposed (cases) and 793 not exposed (controls) individuals. Over a median follow-up of 4.6 years (IQR: 1.8-7.8), 54 participants died (5.9% by 10 years, 95% CI: 4.2%-7.7%). The leading causes of death were malignancies (26%), AIDS-related events (22%), cardiovascular disease (9%) and infections (9%). A detailed breakdown of causes of death is provided in Supplementary Table S4. ART regimen changes were common (250/398, 63%), with no significant difference between exposed and non-exposed groups (P = 0.93).

By 10 years, mortality risk was significantly higher among participants with AHD (14.5%, 95% CI: 10.1%-18.9%) compared to those who were free from AHD (1.3%, 95% CI: 0.3%-2.4%; P < 0.0001), with the highest excess risk in the first 2 years after AHD diagnosis. One-year mortality was 4.9% in the exposed vs 0.4% in the nonexposed, rising to 10.9% vs 1% at 5 years (Figure 2). After adjusting for potential confounders, individuals with AHD exhibited a strikingly more than 8-fold higher risk of death for any cause compared to those who were free from AHD (Table 3).

Discussion

Our analysis, conducted on a large multicentre national cohort of PWH in Italy, showed that the risk of progression to AHD after ART initiation over the past two decades is low yet not negligible (4.3%) and has nearly halved in the most recent years (2014-

2023). In particular, this incidence appears to be lower than estimates of late HIV presentation in the same cohort over the same period [12].

Our findings are in contrast with evidence from sub-Saharan Africa showing that AHD is currently predominantly observed among individuals who, after initially engaging in care and initiating ART, experience treatment interruptions or failure [8,9,13,14]. Conversely, in high-income settings the burden of AHD appears to be primarily driven by late presentation to care. In Europe, the proportion of late HIV diagnosis has remained steadily high, with approximately 53% and 32% of subjects diagnosed in late and advanced stages of infection in 2023, respectively [15]. These divergent epidemiological patterns likely reflect differences in healthcare infrastructure, treatment accessibility, and patient monitoring systems, underscoring the heterogeneous challenges that HIV care must address across different contexts.

Although the increasing prevalence of AHD among ART-experienced subjects appears to predominantly affect low-resource countries, and our data suggest that the risk of developing AHD post ART initiation has declined over time, the identification of factors associated with clinical progression in PWH already engaged in care is essential for informing targeted interventions. This is particularly relevant in the light of a recent study from Latin America reporting worse clinical outcomes in ART-experienced individuals hospitalized with AHD compared to ART-naïve ones [16]. Among the limited data available from high-resource countries, a previous study from the UK found that PWH who developed AIDS after entering care (PHDA) had higher rates of psychiatric comorbidities, social challenges, and substance use compared to AIDS-presenters. Furthermore, they often experienced ART interruptions and gaps from care prior to the development of AIDS [17]. Consistent with these findings, our study found that ART-experienced individuals who developed AHD were more likely to exhibit signs of social disadvantage compared to those who did not progress. Specifically, these individuals were more likely to have a history of injecting drug use and a lower socio-economic status (unemployment and lower levels of education). These results align with prior evidence that socio-demographic factors significantly influence HIV outcomes, suggesting that vulnerable subpopulations not only encounter barriers to healthcare access, but also face an increased risk of poorer outcomes once enrolled in care, due to lower engagement and retention—even in high-income countries [18–20].

In addition, unsurprisingly, we found that suboptimal virologic control and prolonged disengagement from care played a key role in the development of AHD. Individuals with suboptimal virologic control who had also disengaged from care for longer than 18 months had a fivefold higher risk of progression compared to those consistently engaged. These findings are consistent with previous studies showing that even brief care interruptions heighten progression risk [21–23]. In particular, recent

Table 3
Unadjusted and adjusted relative hazards of all-cause mortality in subjects with AHD (exposed) versus not-exposed by fitting a Cox regression model.

	Unadjusted HR	P-value	Adjusted* HR	P-value
Not-AHD (not-exposed)	1		1	
AHD (exposed)	8.74 (4.40, 17.37)	**<0.001**	8.58 (4.29, 17.19)	**<0.001**

Abbreviations: HR, hazard ratio; AHD, advanced HIV disease;
Adjusted for age, gender, nationality, mode of HIV transmission, year of AHD/index time, and hepatitis co-infection.

data from the Swiss cohort showed that most PWH who were re-engaged in care following ART interruption return to care at a late stage of the disease [23]. Notably, the sociodemographic factors associated with AHD development in our study have been previously recognized as predictors of poor retention in care and non-adherence to ART [18,21,23,24], emphasizing the critical role of sustained engagement in care, particularly among disadvantaged subpopulations. To this regard, a recent review revealed a lack of data on re-engagement strategies from Europe, with most evidence coming from the U.S., where engagement barriers may differ [25], underscoring the need for context-specific research in Europe.

Additionally, our results support the significant impact of pill burden on clinical and viro-immunological outcomes [26] showing that individuals taking STR close to the index date had half the risk of progression compared to those on MTR. This finding likely reflects the better adherence and higher treatment acceptability associated with STRs, as consistently reported in previous studies [26].

In line with earlier studies [27,28], we did not observe an increased risk of clinical progression among migrants, even after restricting the analysis to women. Indeed, although migrants' status has been widely associated with delayed presentation to care, higher rates of loss to follow-up and virological failure [12,21,29], its influence on long-term clinical outcomes after ART initiation remains uncertain [28,29,30]. Conversely, we observed an increased risk of progression of AHD in women, which was not previously consistently reported. The role of female gender as a risk factor for poor clinical outcomes among PWH remains controversial [18]. Although men have been linked to poorer retention in care [21,23], several factors, as the post-partum period or the fear of stigma, can increase the risk of interruption of HIV care for women [31,32]. Our analysis found no evidence that women with a history of pregnancy carried a higher risk of developing AHD. On the contrary, socio-economic factors and, particularly, lower education and housewife status showed a trend toward an increased risk of clinical progression.

Finally, as expected, ART-experienced individuals who developed AHD exhibited an 8-fold increased risk of all-cause mortality compared to controls. Notably, as previously reported in studies conducted in late presenters, the mortality risk was highest in the period immediately following the diagnosis of AHD [12]. Particularly, in our study, the risk of all-cause of death was the highest in the 2 years following AHD diagnosis.

Our study has several limitations. First, due to its observational nature, unmeasured or residual confounding cannot be ruled out. In this regard, we were unable to control for important confounders such as socioeconomic status (SES) or housing/family issues, as these data were unavailable in our database. However, we used education level and employment as proxies for SES. Second, our database did not include direct measures of clinical attendance or ART adherence. Therefore, we used the number of viral load measurements and HIV-RNA values as surrogate markers for engagement in care and adherence to therapy. Third, data on key components of AHD management—such as antimicrobial prophy-

laxis and rapid diagnostic tools—were not available in our dataset, limiting the generalizability of our findings to current clinical settings and preventing assessment of their impact on survival within our cohort. Additionally, the prevalence of AHD may be underestimated, as individuals who experienced gaps in care and later re-engaged at different centers or in other countries were not captured in our analysis. Finally, we used a case-control study nested in the cohort to evaluate the association with time-varying factors measured prior to the AHD event. This was done to simplify an otherwise complicated analysis in the context of time-varying exposures, potential time-varying confounders as well as mediators and unmeasured common causes of intermediates and outcome, a setting in which standard regression techniques are likely to provide biased results [33].

Despite these limitations, our study has notable strengths. To the best of our knowledge, this is the largest recent study examining the prevalence, predictors, and outcomes of AHD among ART-experienced PWH in a high-income setting. By leveraging real-world data from a large national cohort with extended follow-up, our work provides a comprehensive and up-to-date depiction of the burden and evolution of AHD in Italy over the past two decades. Importantly, it identifies key factors associated with progression to AHD in PWH engaged in care, thereby advancing understanding of how vulnerability and adherence interact to influence disease trajectories in a context where ART is widely accessible.

Conclusions

In conclusion, our findings indicate a decreasing, yet persistent, risk of progression to AHD among PWH on ART in Italy over the last two decades. Continued engagement in HIV care has a crucial role in preventing AHD after discharge and should focus on women and vulnerable subpopulations with signs of social deprivation. Future research should focus on developing targeted re-engagement strategies that also address the broader social and behavioural factors influencing care retention, with the aim of minimizing the risk of AHD progression further.

Funding

Ethical approval

The Icona Foundation study was approved by the ethics committees of participating centers. All participants provided written informed consent. The study adhered to the Declaration of Helsinki

(last amended in October 2013). The proposal was shared with patient representatives at the annual Icona Foundation Study meeting (2023). The reporting of the study follows the Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines20.

Data Availability Statement

The data sets generated during the current study are not publicly available because they contain sensitive data to be treated under data protection laws and regulations. Appropriate agreement of data sharing can be arranged after a reasonable request to the corresponding author.

Declaration of competing interest

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108016.

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