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Persistent poor clinical outcomes of people living with HIV presenting with AIDS and late HIV diagnosis – results from the ICONA cohort in Italy, 2009-2022

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ABSTRACT

Objectives: Limited data are available on the long-term outcomes in recent years for late HIV diagnosis (LD).

Methods: All subjects with HIV enrolled in the ICONA cohort in 2009-2022 who started antiretroviral treatment (ART) within 4 months from diagnosis were included and divided into: (i) pre-ART CD4 count ≥350/mm^3 without AIDS (non-LD), (ii) pre-ART CD4 count <350/mm^3 without AIDS (LD asymptomatic), and (iii) with AIDS events pre-ART (LD-AIDS). The estimated probability and independent risk for mortality (all-cause and cause-specific) and treatment failure were evaluated.

Results: Of 6813 participants (2448 non-LD, 3198 LD asymptomatic, and 1167 LD-AIDS), 161 (2.4%) died after ART initiation. At survival analysis, a higher probability of all-cause mortality has been identified for LD than non-LD (P <0.001) and within the former, for LD-AIDS over LD asymptomatic (P <0.001). After adjusting for confounders, LD showed a higher risk of all-cause mortality (vs non-LD adjusted hazard ratio (aHR) 5.51, P <0.001) and, in particular, being an AIDS presenter predicted a greater risk of all-cause (aHR = 4.42, P <0.001), AIDS-related (adjusted subhazard ratio [aSHR] = 16.86, P <0.001), and non-AIDS–related mortality (aSHR = 1.74, P = 0.022) than the rest of the late presenters. Among the short-term survivors in the LD-AIDS group, the long-term mortality was mediated by the lack of immune recovery at 2 years. Finally, LD compared with non-LD and, particularly, among the former, LD-AIDS over LD asymptomatic showed a greater risk of treatment failure.

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Conclusions: In recent years, LD subjects, particularly, AIDS presenters, remained at a higher risk of poorer outcomes. Public health strategies for early HIV diagnosis are urgently needed to constrain the mortality gap.

Introduction

Despite universal access to HIV testing and antiretroviral treatment (ART), diagnosis of HIV at a late stage of the disease is still a significant challenge, even in high-income countries [1,2]. Late HIV diagnosis (LD) has been defined as a person first diagnosed with HIV with a CD4 count below 350 cells/mm^3 or with an AIDS-defining event (ADE), regardless of the CD4 count, excluding individuals with evidence of recent HIV infection [3,4]. In 2021, according to the European and Italian HIV surveillance data, 54% of newly diagnosed subjects with HIV in Europe and 63% in Italy were diagnosed late [1,2]. Furthermore, more than 80% of new AIDS diagnoses still occurred within a few months from HIV diagnosis [1,2].

LD has been widely associated with poor clinical outcomes at the individual and community levels. In fact, late presenters have a greater risk of morbidity and mortality, mostly but not only due to ADEs, particularly, over the first year of diagnosis [5–8], suboptimal virological control and immunological recovery, and treatment discontinuation [9–12]. The role of immune recovery after ART initiation in people living with HIV (PLWH) with a late diagnosis on clinical progression is still highly debated; a recent study from the Spanish PISCIS cohort, showed that CD4 counts nadir do not necessarily fully explain the long-term survival in late presenters and, after an early high risk of mortality, LD who achieved CD4 >500 cells/mm^3 2 years after ART start had a long-term mortality comparable to the rest of naïve PLWH [13]. Conversely, another recent study reported that subjects starting ART with a low CD4 cell count remained at a greater risk for clinical progression and death, even after the restoration of immunocompetence [14].

In addition, LD leads to high health care costs and enhances the risk of onward transmission owing to the lack of awareness of HIV positivity [12,15].

Although late presentation is still a relatively frequent condition, data on long-term clinical outcomes of PLWH who have been diagnosed late in recent years and who started ART with more potent and tolerable antiretroviral drugs are limited. In this study, we aimed to assess the impact of LD on mortality and treatment outcomes in a large national cohort of newly diagnosed PLWH who started ART in Italy over the last 14 years (2009-2022).

Material and methods

Study design and population

This is a retrospective analysis of prospectively collected data from the ICONA (Italian Cohort Naïve Antiretrovirals) Foundation cohort, an Italian nationwide observational cohort, set up in 1997, including adult subjects infected with HIV-1 who were ART-naïve at the time of enrollment. Details of the cohort have been described elsewhere [16].

We included all consecutive PLWH enrolled in the ICONA cohort who started ART within 4 months from HIV diagnosis from January 1, 2009 to December 31, 2022, who had an available measure of CD4 before ART initiation and at least 1-month follow-up after treatment start. The included patients were classified according to CD4 count and clinical presentation before ART initiation into two exposure groups: (i) subjects with CD4 count <350 cells/mm^3 or a diagnosis of ADE regardless of CD4 count (LD) and (ii) subjects with CD4 count ≥350 cells/mm^3 without a history of ADE (non-late diagnosis [non-LD]). We further divided the former group into two subgroups: (i) subjects with pre-ART CD4 count <350/mm^3 without a history of ADE (asymptomatic late diagnosis, LD asymptomatic) and (ii) subjects with diagnosis of ADE before ART start (AIDS presenters [LD-AIDS]). The CD4 count considered for the classification of the exposure was the closest available pre-ART measurement.

Subjects who started treatment more than 4 months after HIV diagnosis were excluded to guarantee consistency in the definition of late diagnosis, avoiding classifying as LD someone who was diagnosed with high CD4 counts but started ART many months later. This could have frequently occurred, especially before 2015 when ART was guided by current CD4 count. Furthermore, individuals who had a previously available CD4 count that was discordant with the group into which they were classified (i.e. subjects classified as either LD with a previous CD4 count ≥350/mm^3 or non-LD with a previous count <350/mm^3) were excluded from the analysis to avoid potential misclassification.

Follow-up accrued from the date of ART initiation to the achievement of the defined primary endpoint or the last follow-up visit, whichever came first.

Objectives–endpoint definitions

The primary study objective was to estimate the impact of LD on survival in ART-naïve individuals starting ART between 2009 and 2022 within 4 months from diagnosis. Deaths for any reason, whether AIDS-related or not, all counted as events. The secondary objectives were to evaluate the probabilities and the independent risks for the exposure groups of (i) mortality due to ADEs, (ii) mortality due to non-AIDS, and (iii) treatment failure (TF), a composite outcome defined as virological failure (VF) (confirmed HIV RNA >200 copies/ml 6 months after ART start) or treatment discontinuation (TD) (discontinuation of at least one drug in the initial regimen for failure or toxicity, as reported by the treating physician). As a final objective, we evaluated how much of the total effect of LD on mortality risk might be mediated by the failure to restore immune competence by 2 years from starting ART. Of note, the reasons of death were classified into two main groups of AIDS-related and non-AIDS–related death and specific subgroups based on HIV Cohort Data Exchange Protocol codes (Supplementary Materials).

Statistical analysis

Descriptive characteristics at baseline were compared between the exposure groups using the chi-square test (Fisher's exact test when applicable) for categorical variables and the Mann–Whitney or Kruskal–Wallis test, as appropriate, for continuous variables.

Cumulative probabilities of all-cause mortality and TF were estimated by Kaplan–Meier analysis and compared between the exposure groups (non-LD vs LD group and non-LD vs LD asymptomatic vs LD-AIDS) by log-rank test. Kaplan–Meier curves have been also

used to estimate the median survival time to reach CD4 >500 cells/mm^3 in LD asymptomatic and LD-AIDS groups.

Crude and adjusted standard Cox regression models were used to evaluate the risks of all-cause mortality and TF associated with LD. The covariates included were identified under a set of assumptions regarding the causal relations between variables, specifically, the following time-fixed factors measured at baseline were identified as potential confounders: age, sex, mode of HIV transmission, nationality, calendar year for ART initiation, hepatitis coinfections, and type of third drug class included in the initial ART (non-nucleoside reverse transcriptase inhibitors vs protease inhibitors [PIs] vs integrase strand transfer inhibitors [INSTIs]).

A competing risk analysis was also conducted after classifying the reasons of deaths into ADEs and non-AIDS, as reported by the treating physician. The cumulative probabilities of AIDS-related and non-AIDS–related mortality were estimated and compared between the exposure groups (LD-AIDS vs LD asymptomatic vs non-LD) by competing risk Kaplan–Meier curves. Fine–Gray regression models were used to assess the independent risks of death because of ADEs/non-AIDS by the three exposure groups, in which deaths because of AIDS and non-AIDS were handled as competing events.

An interaction test between the calendar year and exposure groups was performed for the main outcomes to investigate whether the calendar year of ART initiation was an effect measure modifier of the association between LD and risk of death. In case of a significant statistical interaction, the results were reported stratified by periods of ART initiation constructed using two consecutive 7-year time windows (2009-2014 and 2015-2022), the latter period reflecting the years after the introduction of treatment guidelines of universal ART initiation, irrespective of CD4 count [17].

Finally, to expand the analysis to factors measured after ART initiation and to gain maximum insight into how much of the effect of LD and AIDS presentation on long-term mortality in those surviving for the first 2 years post-ART might be mediated by an optimal immune recovery (reaching CD4 >500 cells/mm^3 at 2 years from ART start), we used a counterfactual framework four-way decomposition method for the analysis. This mediation analysis allows us to understand the extent to which the overall effect of an exposure (e.g. LD-AIDS) on an outcome (e.g. long-term mortality) in the presence of a mediator with which the exposure may interact (e.g. optimal immune recovery 2 years after ART start) is because of mediation, interaction, both of them, or neither [18].

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.

Ethics statement

The ICONA Foundation study was approved by the local ethics committees of participating clinical sites. All patients signed a consent form for study participation and processing of data in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amended in October 2013).

Results

Baseline characteristics

Of the 13571 ICONA participants who began first-line ART between 2009 and 2022, 6,145 (45%) were excluded from the analysis because they started treatment more than 4 months after diagnosis. An additional 613 (4.5%) were excluded because of the lack of available pre-ART CD4 count (n = 65), lack of follow-up after ART initiation (n = 221), or discordance between exposure group and CD4 count before that which was used for group classification (n = 327) (Supplementary Figure 1). The study population (n=6813) consisted mostly of men (81%), with a median age of 40 years (interquartile range [IQR] 31-49) who mainly acquired HIV infection through sexual intercourse (87%). LD subjects accounted for 64.1% (n = 4365) of the included patients, with 3198 LD asymptomatic (73.3% of LDs) and 1167 LD-AIDS (26.7% of LDs). The exposure groups significantly differed for most of the baseline characteristics (Table 1). Particularly, LD subjects, compared with non-LD ones, were more likely to be female (20.9% vs 15.6%, *P* <0.001) and Italian (44.3% vs 39.4%, *P* <0.001) and to have a lower education level (post-secondary school degree in 37.5% vs 45.1%, *P* < 0.001). In addition, compared with non-LD, PLWH LD, and, particularly, AIDS presenters, were significantly older (LD-AIDS 45 years vs LD asymptomatic 41 years vs non-LD 36 years, *P* <0.001), heterosexuals (LD-AIDS 53.1% vs LD asymptomatic 47.7% vs non-LD 30.5%, *P* <0.001), and with comorbidities at ART initiation (LD-AIDS vs LD asymptomatic vs non-LD: diabetes, 4.2% vs 2.4% vs 1.3%, *P* <0.001; cardiovascular disease, 1.5% vs 0.8% vs 0.4%, *P* = 0.003; and hypertension 7.5% vs 4.7% vs 3.6%, *P* <0.001). The median baseline CD4 count was 528 (IQR 435-680) cells/mm^3 for non-LD and 138 (IQR 49-247) cells/mm^3 for LD patients (*P* <0.001). Among the latter, as expected, AIDS presenters had a worse immunological status than LD asymptomatic individuals (49 [IQR 21-125] cells/mm^3 and 181 [IQR 80-265] cells/mm^3, *P* <0.001). The median baseline HIV viral load was higher in LD, particularly, AIDS presenters, compared to non-LD subjects (median HIV RNA, $\log_{10}$: LD-AIDS 5.32 copies/ml vs LD asymptomatic 5.05 vs non-LD 4.51 copies/ml, *P* <0.001).

Antiretroviral treatment

As per the inclusion criteria, ART was started within a median of 1 month (IQR 0-2) from HIV diagnosis, mostly with a three-drug regimen (92.3%). A detailed description of ART regimens is shown in Table 1. LD subjects were more likely to start a triple regimen (94.5% vs 88.4%, *P* <0.001) than non-LD ones. Among LD patients, INSTI-based (LD asymptomatic 47.3%, LD-AIDS 45.4%, *P* <0.001) and PI-based (LD asymptomatic 33.8%, LD-AIDS 38.9%, *P* <0.001) triple therapies were the most prescribed regimens. Non-LD subjects preferentially started INSTI-based (53.0%) three-drug regimens. Among LD patients boosted, darunavir (DRV/b) and dolutegravir (DTG) were the most prescribed anchor drug (LD asymptomatic: DRV/b 22.5% and DTG 22.6%; LD-AIDS: DRV/b 28.2% and DTG 23.2%), whereas non-LD subjects received more frequently DTG as the third drug (26.7%).

All-cause mortality

Over a median follow-up of 46 (IQR 17-83) months, a total of 161 (2.4%) patients died: 11 (0.4%) in the non-LD and 150 (3.4%) in the LD group, including 99 (8.4%) LD-AIDS and 51 (1.6%) LD asymptomatic. The Kaplan–Meier curves revealed a significantly higher probability of all-cause mortality for LD than non-LD patients (*P* <0.001, Figure 1a) and for AIDS presenters with respect to the rest of the study population (*P* <0.001, Figure 1b). Specifically, after 5 years since ART initiation, the estimated probabilities (95% confidence interval [CI]) for all-cause mortality were 9.2% (7.4-11.1%) for LD-AIDS, 1.5% (1.0-2.0%) for LD asymptomatic, and 0.6% (0.2-1.1%) in the non-LD group. In the LD-AIDS group, the estimated risk was already 5.0% at 1 year, 6.6% at 2 years, 7.5% at 3 years, and 8.2% at 4 years, indicating a large increase in risk over the first year, followed by a gradual increase of approximately 1% per year.

After adjusting for potential confounders, LD individuals compared with non-LD ones showed a significantly higher risk of death for any cause (adjusted hazard ratio [aHR] 5.51, 95% CI 2.87-10.60,

Table 1
Main characteristics (a) and first-line ART regimens (b) of total population and according to the treatment group at ART initiation.

(A)	Total N = 6813	Non-LD N = 2448 (35.9%)	LD N = 4365 (64.1%)	LD-asymptomatic N = 3198 (46.9%)	LD-AIDS N = 1167 (17.1%)	*P*-value[a]	*P*-value[b]
Female sex, n (%)	1295 (19.0)	382 (15.6)	913 (20.9)	660 (20.6)	253 (21.7)	**<0.001**	**<0.001**
Age, years, median (IQR)	40 (31-49)	36 (29-45)	42 (34-51)	41 (33-50)	45 (37-53)	**<0.001**	**<0.001**
Mode of HIV transmission, n (%)						**<0.001**	**<0.001**
Men sex with men	3040 (44.6)	1408 (57.5)	1632 (37.4)	1256 (39.3)	376 (32.2)		
Heterosexual	2892 (42.4)	746 (30.5)	2146 (49.1)	1526 (47.7)	620 (53.1)		
Intravenous drug user	322 (4.7)	118 (4.8)	204 (4.7)	140 (4.4)	64 (5.5)		
Other/Unknown	559 (8.2)	176 (7.2)	383 (8.8)	276 (8.6)	107 (9.2)		
Not Italian nationality, n (%)	3916 (57.5)	1484 (60.6)	2432 (55.7)	1805 (56.4)	627 (53.7)	**<0.001**	**<0.001**
Hepatitis B surface antigen, n (%)						**<0.001**	**<0.001**
Negative	1913 (28.1)	778 (31.8)	1135 (26.0)	850 (26.6)	285 (24.4)		
Positive	4 (0.1)	2 (0.1)	2 (0.0)	2 (0.1)	0 (0.0)		
Not tested	4896 (71.9)	1668 (68.1)	3228 (74.0)	2346 (73.4)	882 (75.6)		
Hepatitis C virus antibody, n (%)						**<0.001**	**<0.001**
Negative	1784 (26.2)	724 (29.6)	1060 (24.3)	800 (25.0)	260 (22.3)		
Positive	128 (1.9)	57 (2.3)	71 (1.6)	49 (1.5)	22 (1.9)		
Not tested	4901 (71.9)	1667 (68.1)	3234 (74.1)	2349 (73.5)	885 (75.8)		
Calendar year of baseline, median (IQR)	2016 (2014-2019)	2017 (2015-2019)	2016 (2013-2019)	2016 (2013-2019)	2016 (2012-2018)	**<0.001**	**<0.001**
CD4 count nadir, cells/mm³, median (IQR)	257 (95-451)	512 (425-655)	136 (48-242)	179 (78-264)	49 (20-120)	**<0.001**	**<0.001**
Baseline CD4 count, cells/mm³							
Median (IQR)	258 (96-452)	528 (435-680)	138 (49-247)	181 (80-265)	49 (21-125)	**<0.001**	**<0.001**
≤200 *cells*/mm³, *n (%)*	2818 (41.4)	-	2818 (64.6)	1792 (56.0)	1026 (87.9)	**<0.001**	**<0.001**
HIV-RNA, log₁₀ copies/ml, median (IQR)	4.91 (4.18-5.52)	4.51 (3.73-5.14)	5.12 (4.50-5.66)	5.05 (4.45-5.57)	5.32 (4.63-5.86)	**<0.001**	**<0.001**
AIDS diagnosis, n (%)	1167 (17.1)	-	1167 (26.7)	-	1167 (100.0)	**<0.001**	**<0.001**
Comorbidities and habits							
Diabetes, n (%)	160 (2.3)	33 (1.3)	127 (2.9)	78 (2.4)	49 (4.2)	**<0.001**	**<0.001**
Cardiovascular disease, n (%)	56 (0.8)	11 (0.4)	45 (1.0)	27 (0.8)	18 (1.5)	**0.011**	**0.003**
Hypertension, n (%)[c]	326 (4.8)	89 (3.6)	237 (5.4)	150 (4.7)	87 (7.5)	**<0.001**	**<0.001**
Dyslipidemia, n (%)[d]	104 (1.5)	30 (1.2)	74 (1.7)	49 (1.5)	25 (2.1)	0.129	0.110
Smoking, n (%)	1942 (28.5)	788 (32.2)	1,154 (26.4)	888 (27.8)	266 (22.8)	**<0.001**	**<0.001**
Social determinants							
Education, n (%)						**<0.001**	**<0.001**
Primary school	320 (4.7)	65 (2.7)	255 (5.8)	161 (5.0)	94 (8.1)		
Secondary school	940 (13.8)	251 (10.3)	689 (15.8)	490 (15.3)	199 (17.1)		
College	1880 (27.6)	699 (28.6)	1181 (27.1)	869 (27.2)	312 (26.7)		
University	857 (12.6)	404 (16.5)	453 (10.4)	339 (10.6)	114 (9.8)		
Other/Unknown	2816 (41.3)	1029 (42.0)	1787 (40.9)	1339 (41.9)	448 (38.4)		
Employment, n (%)						**<0.001**	**<0.001**
Unemployed	866 (12.7)	307 (12.5)	559 (12.8)	409 (12.8)	150 (12.9)		
Employed/Self-employed	3489 (51.2)	1238 (50.6)	2251 (51.6)	1649 (51.6)	602 (51.6)		
Occasional	168 (2.5)	42 (1.7)	126 (2.9)	86 (2.7)	40 (3.4)		
Student	214 (3.1)	138 (5.6)	76 (1.7)	64 (2.0)	12 (1.0)		
Retired/Invalid	229 (3.3)	45 (1.8)	186 (4.3)	121 (3.8)	63 (5.4)		
Housewife	112 (1.6)	31 (1.3)	81 (197)	51 (1.6)	30 (2.6)		
Other/Unknown	1,735 (25.5)	647 (26.4)	1,088 (24.9)	818 (25.6)	270 (23.1)		
Follow-up time, months, median (IQR)	46 (17- 83)	40 (16-73)	50 (19-90)	50 (18-90)	53 (20-90)	**<0.001**	**<0.001**
First-line ART regimens							
Months from HIV diagnosis to ART start, median (IQR)	1 (0-2)	1 (0-2)	1 (0-1)	1 (0-1)	1 (0- 1)	**<0.001**	**<0.001**
Type of regimen started, number of drugs, n (%)						**<0.001**	**<0.001**
Two-drug regimen (lamivudine+DTG)	130 (1.9)	89 (3.6)	41 (0.9)	38 (1.2)	3 (0.3)		
Three-drug regimen	6332 (92.9)	2171 (88.7)	4161 (95.3)	3043 (95.2)	1118 (95.8)		
- *Integrase strand transfer inhibitor-based*	3319 (48.7)	1293 (52.8)	2026 (46.4)	1505 (47.1)	521 (44.6)		
- *Protease inhibitor-based*	1931 (28.3)	409 (16.7)	1522 (34.9)	1076 (33.6)	446 (38.2)		
- *Non-nucleoside reverse transcriptase inhibitor-based*	1032 (15.1)	460 (18.8)	572 (13.1)	441 (13.8)	131 (11.2)		
- *other*	50 (0.7)	9 (0.4)	41 (0.9)	21 (0.7)	20 (1.7)		
≥4-drug regimen	351 (5.2)	188 (7.7)	163 (3.7)	117 (3.7)	46 (3.9)		
Type of drug, n (%)						-	-
DTG	1648 (24.2)	653 (26.7)	995 (22.8)	724 (22.6)	271 (23.2)		
Bictegravir	820 (12.0)	340 (13.9)	480 (11.0)	376 (11.8)	104 (8.9)		
Raltegravir	631 (9.3)	245 (10.0)	386 (8.8)	260 (8.1)	126 (10.8)		
Boosted darunavir	1462 (21.5)	413 (16.9)	1049 (24.0)	720 (22.5)	329 (28.2)		
Boosted atazanavir	571 (8.4)	132 (5.4)	439 (10.1)	338 (10.6)	101 (8.7)		
Efavirenz	490 (7.2)	110 (4.5)	380 (8.7)	266 (8.3)	114 (9.8)		

Notes:
[a] Comparison non-LD vs LD
[b] comparison non-LD vs LD-asymptomatic vs LD-AIDS
[c] use of blood pressure lowering drugs
[d] use of statins.Abbreviations: ART, antiretroviral therapy; CD, clusters of differentiation; DTG, dolutegravir; IQR, interquartile range; LD, late diagnosis; non-LD, not late diagnosis.

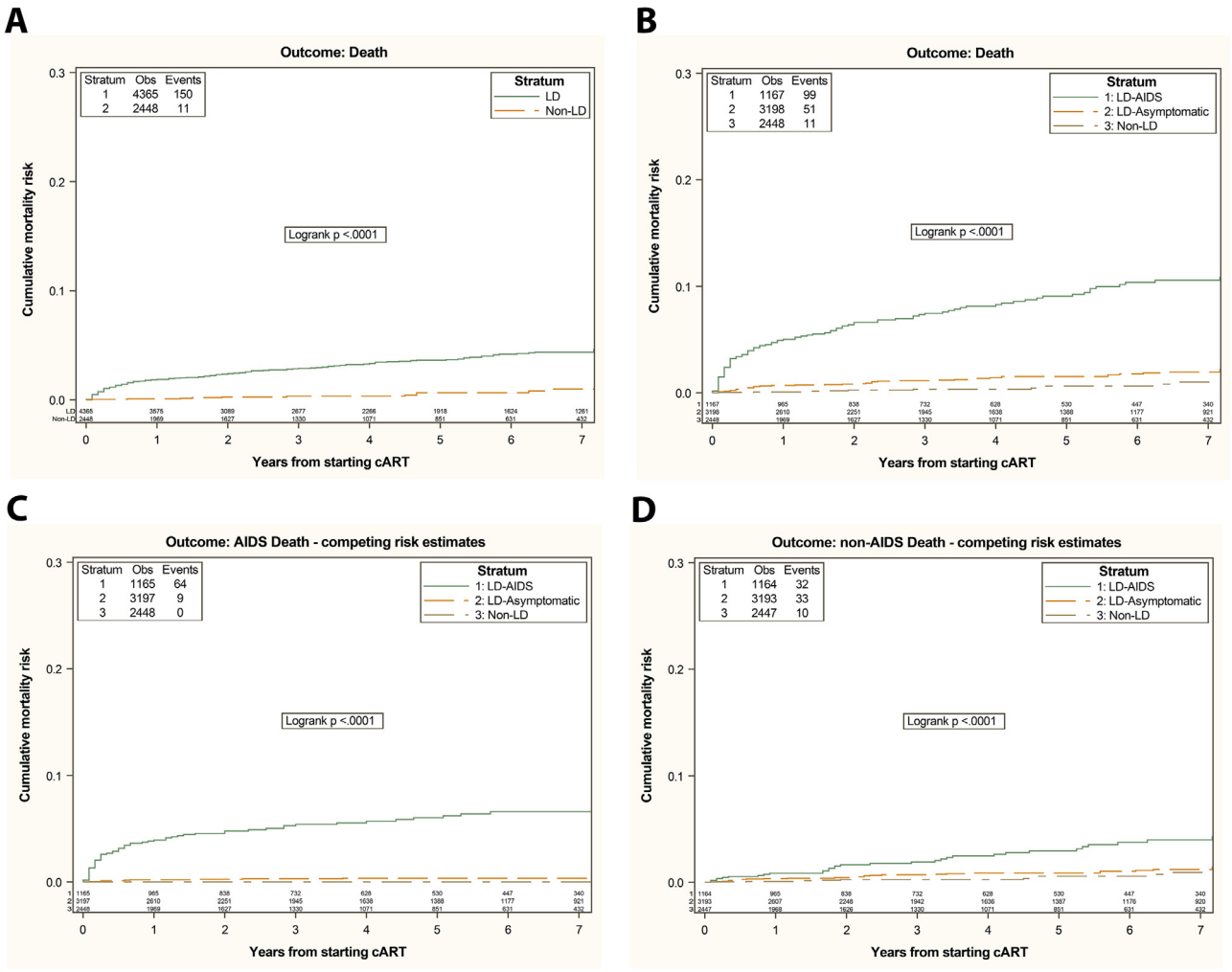

Figure 1. Kaplan–Meier curves for all-cause mortality (non-LD vs LD [a] and non-LD vs LD-asymptomatic vs LD-AIDS [b]) and cause-specific mortality[a] (AIDS-related deaths [c] and non-AIDS–related deaths [d]) according to the exposure group. [a]Competing risk Kaplan–Meier curves. cART, combined antiretroviral therapy; LD, late diagnosis; non-LD, non-late diagnosis.

P <0.001) (Table 2a). Furthermore, compared with LD asymptomatic, being an AIDS presenter was associated with a risk more than four times greater for all-cause mortality (aHR 4.42, 95% CI 3.14-6.22, P <0.001), whereas being non-LD significantly reduced this risk (aHR 0.35, 95% CI 0.17-0.59, P = 0.002) (Table 2b). No difference in the effect of LD on mortality risk by calendar year of ART initiation was observed (Table 2a and b).

Mediation analysis

A total of 2568 participants (1697 [66%] non-LD and 871 [34%] LD-AIDS) survived for more than 2 years after treatment initiation and they had a measure of CD4 count within the time window of 21 to 27 months after starting ART. Of these, 1065 (41%) did not achieve a CD4 count >500 cells/mm^3 by 2 years. Overall, 43 (2%) deaths were observed, 36 (84%) in the LD group and seven in the non-LD group. Interestingly, in this selected subset, we found evidence that the failure of achieving a CD4 count >500 cells/mm^3 was an effect measure modifier and a mediator for the effect of AIDS presentation on the long-term mortality risk. Particularly, the four-way decomposition analysis revealed that approximately 80% of the total effect of LD-AIDS (vs non-LD) on the risk of long-term mortality was because of mediation (of which 72% was interaction) with the 2-year CD4 count gain (Supplementary Figure 3). This suggests that in this group of short-term survivors, participants in the LD-AIDS group who did not achieve full immune recovery by 2 years have an even higher risk of long-term mortality than non-LD (i.e. there is an interaction) and, at the same time, the LD-AIDS condition is needed for a CD4 count ≤500 cells/mm^3 to be present at 2 years (i.e. LD-AIDS causes a CD4 count ≤500 cells/mm^3 at 2 years, which is necessary for LD-AIDS to have an effect on mortality). The estimated median time to full immune recovery (CD4 >500 cells/mm^3) was 4.1 years (95% CI 3.7-4.5) for the LD-AIDS and 2.2 years (95% CI 2.0-02.3) for the LD asymptomatic group (Supplementary Figure 2).

AIDS-related and non-AIDS–related mortality

Over the study period, we observed 73 (45.3%) deaths because of ADEs and 88 (54.6%) for non-AIDS events. As expected, when restricting the analysis to those who died, the proportion of AIDS-related deaths gradually decreased over time, accounting for 63.6% of total deaths during the first year after ART started, 35.1% between the second and fifth year, and 14.8% thereafter (Supplementary Table 1). AIDS-related deaths occurred exclusively in LD patients, particularly, AIDS presenters, for whom they accounted for 78% of all deaths during the first year, 52% between the second and fifth year, and 37% later (Supplementary Figure 4). Of the non-AIDS–related deaths, malignancies were the leading cause of death. In contrast, AIDS-related mortality was mainly driven by infections

Table 2
HR and aHR for all-cause mortality (non-LD vs LD [Table 3a] and non-LD vs LD-asymptomatic vs LD-AIDS [Table 3b]) and SHR and aSHR for specific-cause mortality (AIDS-related [Table 3c] and non-AIDS–related mortality [Table 3d]) associated with LD.

	HR	95% CI	*P*-value	aHR[a]	95% CI	*P*-value
Table 2a. All-cause mortality[b]						
Non-LD	1	-		1	-	
LD	6.86	3.72-12.67	**<0.001**	5.51	2.87-10.60	**<0.001**
X *interaction test exposure group and calendar year of ART start: P = 0.41*						
Table 2b. All-cause mortality[b]	**HR**	**95%CI**	**P-value**	**aHR[a]**	**95%CI**	**P-value**
LD-asymptomatic	1	-		1	-	
LD-AIDS	5.19	3.70-7.28	**<0.001**	4.42	3.14-6.22	**<0.001**
Non-LD	0.31	0.16-0.60	**<0.001**	0.35	0.17-0.69	**0.002**
X *interaction test exposure group and calendar year of ART start: P = 0.07*						
	SHR	**95% CI**	**p-value**	**aSHR[a]**	**95% CI**	**p-value**
Table 2c. AIDS-related mortality[c]						
LD-asymptomatic	1	-		1	-	
LD-AIDS	19.13	9.52-38.42	**<0.001**	16.86	8.24-34.46	**<0.001**
Non-LD	-	-	-	-	-	-
X *interaction test exposure group and calendar year of ART start: P = 0.42*	**SHR**	**95% CI**	**p-value**	**aSHR[a]**	**95% CI**	**p-value**
Table 2d. Not AIDS-related mortality[c]						
LD-asymptomatic	1	-		1	-	
LD-AIDS	2.09	1.32-3.33	**0.002**	1.74	1.08-2.78	**0.022**
Non-LD	0.42	0.22-0.82	**<0.001**	0.53	0.26-1.11	**0.093**
X *interaction test exposure group and calendar year of ART start: P = 0.65*						

[a] Adjusted for age, sex, mode of HIV transmission, nationality, calendar year for ART initiation, hepatitis coinfection, and type of ART regimen;
[b] standard Cox regression model;
[c] Fine-Gray Cox regression model.Abbreviations: aHR, adjusted hazard ratio; aSHR, adjusted sub-hazard ratio; ART, antiretroviral therapy; HR, unadjusted hazard ratio; CI, confidence interval; LD, late diagnosis; non-LD, non-late diagnosis; SHR, sub-hazard ratio.

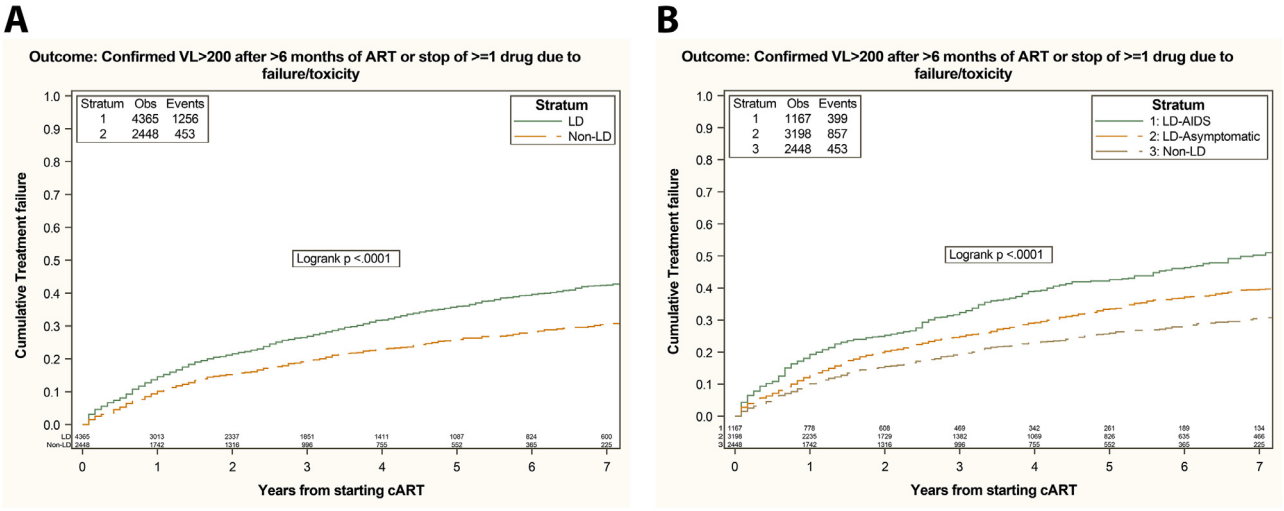

Figure 2. Kaplan–Meier estimates for treatment failure according to the exposure group: non-LD vs LD (a) and non-LD vs LD-asymptomatic vs LD-AIDS (b). LD, late diagnosis; non-LD, non-late diagnosis.

over the first year after ART initiation and by malignancies thereafter (Supplementary Table 1).

Competing risk Kaplan–Meier curves showed a significantly higher probability of AIDS-related and non-AIDS–related mortality for LD-AIDS than the other exposure groups (P <0.001) (Figure 1c and d). In LD patients, LD-AIDS showed an approximately 17-fold greater risk of dying because of ADEs (adjusted subhazard ratio [aSHR] 16.86, 95% CI 8.24-34.46, P <0.001) and about two times higher because of non-AIDS events than the LD asymptomatic group (aSHR 1.74, 95% CI 1.08-2.78, P = 0.022). The interaction test carried no evidence that this risk might be different in recent years as opposed to earlier periods for AIDS-related and non-AIDS–related mortality (Table 2c and d).

Treatment failure

Overall, 1709 (25.1%) subjects experienced TF: 453 (18.5%) in the non-LD and 1256 (28.8%) in the LD group, including 399 (34.2%) LD-AIDS and 857 (26.8%) LD asymptomatic. In all exposure groups, TF was mainly driven by TD (90.7%, 91.3%, and 87.0% of patients in the non-LD, LD asymptomatic, and LD-AIDS groups, respectively) rather than VF. Of note, after disaggregating the composite outcome, less than 10% of the study population experienced VF in the TF outcome (9.3%, 8.7% and 4.5% of subjects in the non-LD, LD asymptomatic, and LD-AIDS groups, respectively), which was mainly related to rebounds after the achievement of viral suppression (39 of 42 VFs in the non-LD group, 67 of 75 VFs in the LD asymptomatic group, and 48 of 52 VFs in the LD-AIDS group were because of viral rebound), with no evidence for a difference by exposure groups (P = 0.762).

The estimated probabilities of TF significantly differed among the exposure groups (log-rank P <0.001) (Figures 2a and b). From fitting the multivariable Cox regression models, LD individuals compared to non-LD (aHR 1.21, 95% CI 1.08-1.36, P = 0.001), as well as AIDS presenters compared to LD asymptomatic subjects (aHR 1.30, 95% CI 1.15-1.47, P <0.001), showed a higher risk of

Table 3
HR and aHR for treatment failure associated with late HIV diagnosis (non-LD vs LD, Table 3a and non-LD vs LD-asymptomatic vs LD-AIDS, Table 3b) from fitting a standard Cox regression model.

Table 3a. Treatment failure	HR	95% CI	*P*-value	aHR[a]	95% CI	*P*-value
Non-LD	1	-		1	-	
LD	1.51	1.35-1.68	**<0.001**	1.21	1.08-1.36	**0.001**
[X] *interaction test exposure group and calendar year of ART start: P <0.01*						
Table 3b. Treatment failure	**HR**	**95% CI**	**P-value**	**aHR[a]**	**95% CI**	**P-value**
LD-asymptomatic	1	-		1	-	
LD-AIDS	1.36	1.21-1.53	**<0.001**	1.30	1.15-1.47	**<0.001**
Non-LD	0.72	0.65-0.81		0.88	0.78-1.00	**0.046**
[X] *interaction test exposure group and calendar year of ART start: P <0.01*						

[a] Adjusted for age, sex, mode of HIV transmission, nationality, calendar year for ART initiation, hepatitis-coinfection, and type of ART regimen according to the third drug.Abbreviations: aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; HR, unadjusted hazard ratio; LD, late diagnosis; non-LD, non-late diagnosis.

TF. On the contrary, non-LD patients were associated with a lower risk of TF than LD asymptomatic (aHR 0.88, 95% CI 0.78-1.00, $P = 0.046$) (Tables 3a and b). The analysis stratified by calendar period, showed evidence of interaction with the year of ART start ($P < 0.001$); compared with LD asymptomatic, PLWH in the LD-AIDS group had a higher risk of TF in 2009-2014 and 2015-2022, whereas non-LD showed a lower risk only in the most recent calendar period (ARH 0.79, 95% CI 0.66-0.94) (Supplementary Table 3).

Discussion

In this observational study including 6813 PLWH who started ART within 4 months from diagnosis between 2009 and 2022, we showed that, even in more recent years, subjects presenting late to care and, in particular, AIDS presenters, despite a prompt linkage to care after diagnosis, remained at a substantially greater risk for mortality and TF.

Consistent with previous evidence [6–8,19], we found that the overall risk for all-cause mortality was approximately 5.5-fold higher in LD individuals than in those without a late diagnosis and 4.5-fold higher in AIDS presenters than the remaining late diagnosed patients, particularly, in the first year after diagnosis (1-year mortality risk: 5%). Specifically, the increased risk of mortality for AIDS presenters was mainly driven by ADEs, responsible for more than three-quarters of deaths within the first year after diagnosis, but also by non-AIDS events. Similarly, subjects in the LD asymptomatic group showed a higher risk of dying for reasons other than AIDS compared to non-LD ones.

Previous studies described an increased risk for non-AIDS events in subjects with LD or AIDS presentation compared with their counterparts [8,20–23]. A previous Italian study showed that the risk of non-AIDS events was specifically increased in patients with advanced HIV disease and in those with previous ADE who failed to restore their immunocompetence despite effective ART [20]. Preexisting immune dysfunction, immune activation, and persistent inflammation have been suggested as possible mechanisms for the development of non-AIDS events in this vulnerable population [20]. In addition, a higher burden of multimorbidity has been described in late presenters [15]. To the best of our knowledge, this is one of the few large cohort studies that separately analyzed mortality because of ADEs and non-AIDS events.

Recently, conflicting evidence on the role of immunological recovery after ART initiation as a protective factor for long-term mortality in patients with LD have emerged [13,14]. In our study, we performed a formal mediation analysis which showed that a large part of the effect of AIDS presentation on the risk of long-term mortality in those who survived the first 2 years after ART start was explained by the failure to restore immunocompetence, suggesting that a significant part of the excess mortality risk in patients with advanced HIV is possibly explained by their current immunological status. Of note, despite recent evidence suggesting a beneficial role of first-line INSTI-based regimens on survival in subjects with advanced HIV [13,24], in our study, the increased risk of all-cause and cause-specific mortality for LD and LD-AIDS persisted after adjustment for anchor drug class and calendar year of ART start (a proxy for change in therapeutic indications).

In our cohort, LD individuals and, in particular AIDS presenters, showed increased rates of TF, mostly driven by the discontinuation of one or more drugs in the initial regimen owing to toxicity/failure. This finding is in line with a recent observation reporting a higher risk of TD because of adverse events in late presenters [12]. The choice of ART in LD subjects, especially AIDS presenters, is challenging and very few data on the optimal first-line regimen are available because these patients are still poorly represented in clinical trials. Recently, large cohort studies described higher discontinuation rates in patients with advanced HIV starting PI-based than those on INSTI-based regimens [9,24–26]. However, this finding has not been confirmed by other reports [27,28] and needs to be clarified by the results of ongoing clinical trials [29,30]. Of note, in our study, INSTI (particularly, DTG)-based and PI (mostly DRV)-based regimens were the most prescribed first-line ART in patients in the LD and LD-AIDS group and, interestingly, the higher risk for TF persisted after adjustment for the third drug class.

Finally, the prevalence of LD in our cohort, despite being biased by the selection of patients who started ART within few months from diagnosis, is in line with data reported by cohort studies from other high-income countries and recent European and Italian surveillance reports in which rates of late HIV diagnosis and AIDS presentation ranged approximately from 40 to 60% and 8 to 20%, respectively [1,2,8,12,13]. In these settings, late presentation appears to disproportionally affect certain demographic groups, such as women, older adults, heterosexuals, migrants, and persons with low educational levels [7,8,12,19,31], suggesting that the risk of LD is greater in groups that are not traditionally considered to be at a high risk of acquiring HIV [32]. It is worth noting that in our study, the characteristics of the LD population mirror most of the risk factors that have been associated with delayed presentation to care.

Our study has some limitations. First, the observational nature of the study, which is subject to bias due to unmeasured confounders. In this regard, we did not include in the multivariable models potentially important confounders, such as the rate of access to health care services, fear of stigmatization, and health locus of control (the degree to which individuals believe that their health is controlled by internal or external factors), which were not covered by our data collection [33]. In addition, we did not adjust

for baseline comorbidities because they were considered mediators and not confounders for the considered outcomes. However, the results were similar after repeating the analyses for the main outcomes (all-cause mortality and TF), including baseline comorbidities, in the model. Second, the choice of ART initiation as the baseline for the survival analysis might have introduced immortal time bias (only the those who were late diagnosed who survived long enough to start ART were included), which was partially mitigated by restricting the analysis to participants who started ART within 4 months from the diagnosis. On the other hand, choosing the date of enrollment in the cohort as the baseline for the survival analysis might have led to non-proportional hazards because of the high risk of death in participants diagnosed late in absence of ART, as well as generated the issue of how to correctly control for time-varying ART initiation. If anything, immortal time bias could have conferred an advantage to those who were late diagnosed; therefore, our estimates of the difference in risk are potentially underestimated.

Furthermore, regarding the selection of study population, it needs to be noted that the inclusion of subjects with a short time from enrollment to ART initiation might have led to an artificially selected group of rapid starters in the non-LD patients enrolled before 2015 who are also likely to have a better prognosis than the average non-LD patient. Nonetheless, we did not find evidence for interaction between calendar periods (2009-2014 and 2015-2022) and the main study outcomes, except for TF. In fact, in the analysis restricted after 2015, the non-LD group had a lower risk of TF than the LD asymptomatic group, which was not identified in the period (2009-2014). Another limitation of the study is the potential misclassification of participants presenting with a low CD4 count as LD when he/she was a case of acute infection. This potential bias was partially mitigated by excluding subjects with an available previous CD4 count discordant with the exposure group of classification. Fifth, the change in the guidelines on the recommended first-line antiretroviral drugs and indication for ART initiation during the observation period might have introduced a bias (because the time from enrollment to ART initiation was shorter with the more recent calendar time), only partially attenuated by adjusting the analyses by the type of regimen started and calendar year. Finally, the lack of information about the reason of death for approximately one-fifth of deaths may have limited the detailed interpretation of the mortality outcomes.

Nevertheless, our analysis has also important strengths. First, the use of real-life data from a large national cohort makes our results highly representative of the situation of PLWH in Italy. In addition, the relevant length of the observation period and the 5-year follow-up gives a valuable representation of the changes in epidemiology and outcomes that occurred during the last 14 years.

Conclusion

Our study showed that PLWH presenting late to care, particularly, AIDS presenters, despite a rapid linkage to care and ART initiation, still presented significantly poorer outcomes in terms of survival and treatment durability than the rest of ART-naïve subjects. Of note, for early survivors, most of the long-term effect was mediated by the failure to achieve immunological recovery after ART initiation. Considering the persistent mortality gap of LD and patients who presented with AIDS, also in high-income countries, public health strategies for emerging unknown infections are urgently needed, including the extension of HIV testing beyond routine settings, the increase of indicator conditions–guided testing in all health care services, the development of public campaigns to normalize HIV testing and reduce the stigma, and the decrease of structural barriers for HIV testing [31,32,34].

Declarations of competing interest

A.M. received speaker honoraria from Gilead Sciences and ViiV Healthcare and travel fees and participated in advisory boards sponsored by ViiV Healthcare. A.C. received funding for scientific advisory boards, travel, or speaker honoraria from Gilead Sciences, ViiV Healthcare, Janssen-Cilag, and MSD. A. Giacomelli reports speaker honoraria for ViiV Healthcare and Gilead Sciences and is an adviser for Janssen-Cilag and Mylan. C.P. received personal fees from Gilead Sciences for a case presentation and a travel grant and has served on an advisory board for Janssen-Cilag; A. Gori received speaker honoraria and fees for attending advisory boards from ViiV Healthcare, Gilead Sciences, Janssen-Cilag, MSD, BMS, Pfizer, and Novartis and received research grants from ViiV, BMS, and Gilead Sciences. A.S. received speaker honoraria or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, MSD, and Janssen-Cilag. A.B. received speaker honoraria and fees for attending advisory boards from Astra-Zeneca, BioMerieux, Janssen-Cilag, Nordic Pharma, Pfizer, Qiagen, SOBI, and ViiV and received research grants from Gilead; G.M. participated in the advisory boards of Gilead Sciences, ViiV Healthcare, Angelini, and Janssen-Cilag and received travel grants from ViiV Healthcare, MSD, and Janssen-Cilag; E.G. received grant support from Gilead Sciences and Mylan and speaker honoraria from Gilead Sciences. C.M. received speaker honoraria or participated in advisory boards sponsored by Gilead Sciences, ViiV Healthcare, MSD, and Janssen-Cilag and received research grants from Gilead Sciences; A.d.M. participated in advisory board of Gilead Sciences, ViiV Healthcare, MSD, Pfizer, and GSK and received research grant from Gilead Science, ViiV Healthcare, Merck Sharp and Dohme, GSK, and Janssen-Cilag; A.A. received research grants from Gilead Sciences, AstraZeneca, and ViiV Healthcare and honoraria from Gilead Science, AstraZeneca, GSK, Pfizer, MSD, Moderna, Mylan, Janssen-Cilag, and ViiV Healthcare; A.C-L., A.T., G.D.G., and G.O. have no competing interest to declare.

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Author contributions

Conception: A.M., A.C-L., A.T., A.d.M., and A.A.; study design: A.M., A.C-L., and A.T.; statistical Analysis: A.C-L.; acquisition of data: A.T.; A.G., G.O., G.D.G., and C.P.; interpretation of the data: A.M., A.C-L., A.T., A.G., A.S., A.B., G.M., E.G., C.M., A.d.M., and A.A.; draft of the manuscript: A.M.; review of the article and critical revision for important intellectual content: all authors. Final approval of the submitted version: all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.106995.

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