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RESEARCH ARTICLE

Increased non-AIDS mortality among persons with AIDS-defining events after antiretroviral therapy initiation

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Abstract

Introduction: HIV-1 infection leads to chronic inflammation and to an increased risk of non-AIDS mortality. Our objective was to determine whether AIDS-defining events (ADEs) were associated with increased overall and cause-specific non-AIDS related mortality after antiretroviral therapy (ART) initiation.

Methods: We included HIV treatment-naïve adults from the Antiretroviral Therapy Cohort Collaboration (ART-CC) who initiated ART from 1996 to 2014. Causes of death were assigned using the Coding Causes of Death in HIV (CoDe) protocol. The adjusted hazard ratio (aHR) for overall and cause-specific non-AIDS mortality among those with an ADE (all ADEs, tuberculosis (TB), *Pneumocystis jiroveci* pneumonia (PJP), and non-Hodgkin's lymphoma (NHL)) compared to those without an ADE was estimated using a marginal structural model.

Results: The adjusted hazard of overall non-AIDS mortality was higher among those with any ADE compared to those without any ADE (aHR 2.21, 95% confidence interval (CI) 2.00 to 2.43). The adjusted hazard of each of the cause-specific non-AIDS related deaths were higher among those with any ADE compared to those without, except metabolic deaths (malignancy aHR 2.59 (95% CI 2.13 to 3.14), accident/suicide/overdose aHR 1.37 (95% CI 1.05 to 1.79), cardiovascular aHR 1.95 (95% CI 1.54 to 2.48), infection aHR (95% CI 1.68 to 2.81), hepatic aHR 2.09 (95% CI 1.61 to 2.72), respiratory aHR 4.28 (95% CI 2.67 to 6.88), renal aHR 5.81 (95% CI 2.69 to 12.56) and central nervous aHR 1.53 (95% CI 1.18 to 5.44)). The risk of overall and cause-specific non-AIDS mortality differed depending on the specific ADE of interest (TB, PJP, NHL).

Conclusions: In this large multi-centre cohort collaboration with standardized assignment of causes of death, non-AIDS mortality was twice as high among patients with an ADE compared to without an ADE. However, non-AIDS related mortality after an ADE depended on the ADE of interest. Although there may be unmeasured confounders, these findings suggest that a common pathway may be independently driving both ADEs and NADE mortality. While prevention of ADEs may reduce subsequent death due to NADEs following ART initiation, modification of risk factors for NADE mortality remains important after ADE survival.

Keywords: AIDS-defining events; non-AIDS mortality; tuberculosis; *Pneumocystis jiroveci* pneumonia; non-Hodgkin's lymphoma; marginal structural model

Additional Supporting Information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

In the era of antiretroviral therapy (ART), there have been striking decreases in acquired immune deficiency syndrome (AIDS)-related mortality [1–3] and prolongation of life expectancy [4–7] for people living with HIV infection (PLWH). With this, there has been a shift in distribution of causes of death toward non-AIDS-defining events (NADEs) [8–12]. Factors contributing to non-AIDS mortality include immunodeficiency [13,14], ART toxicity [15,16], increasing age [17–22], and lifestyle factors such as tobacco use and obesity [18,21,23]. However, chronic inflammation and immune activation produced by chronic HIV infection as well as many AIDS-defining events (ADEs) are now recognized as significant drivers in the pathogenesis of non-AIDS-related deaths [14,24–28].

A previous Antiretroviral Therapy Cohort Collaboration (ART-CC) study sought to examine variation in mortality associated with specific ADEs among patients receiving ART. The study found that overall mortality rates after an ADE were dependent on the specific ADE diagnosis and a classification scheme for ADE severity (mild, moderate, severe) was proposed [29]. This study demonstrated that not all ADEs have the same consequences with regards to overall mortality. However, studies to determine if this finding holds true for mortality due to non-AIDS deaths are lacking.

Our objective was to estimate the overall effect of ADEs as well as three specific ADEs of differential severity on the risk of NADE mortality after ART initiation in high-income settings. We sought to appropriately control for time-updated diagnosis of ADEs and immune status (CD4+ count and HIV-1 RNA). Moreover, we evaluated the overall and ADE-specific effects on differing subtypes of NADE deaths.

2 | METHODS

2.1 | Patient population

We conducted an observational cohort analysis among PLWH enrolled in the ART-CC from 1996 to 2014 (http://www.bris.ac.uk/art-cc) [30]. Data were contributed by 19 cohorts in Europe and North America. Patients were included if they were ART-naïve, had CD4+ and HIV-1 RNA values available at ART initiation, and were ≥18 years of age at ART initiation. Ethics approval was obtained from all participating study sites, the National Health Service Health Research Authority South West-Cornwall and Plymouth Research Ethics Committee, United Kingdom (REC reference 12/SW/0253). Informed consent or a waiver of informed consent were obtained as required by local site ethics committees. Patients were assigned a random study number at the local sites and a limited dataset was transmitted to the ART-CC Data Coordinating Center.

2.2 | Study definitions

Person-time was contributed beginning at ART initiation (study baseline) until the earliest of loss to follow-up, death, or administrative censoring (May 2012 to December 2015, depending on cohort). ART was defined as a regimen that contained ≥3 drugs including nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or integrase inhibitors. Baseline CD4+ and HIV-1 RNA values were defined as the first value <90 days before or <7 days after ART initiation. Loss to follow-up (LTFU) was defined as >12 months between available laboratory results; these patients were censored at 12 months after the date of their last results. Persons were not allowed to re-enter the analysis after meeting LTFU criteria.

Information on cause of death was recorded using the International Classification of Diseases Ninth Revision (ICD-9) code, the ICD-Tenth Revision (ICD-10) code, a classification based on the Coding of Death in HIV (CoDe) project (http://www.cphiv.dk/Tools-Standards/CoDe/About), or free text. Causes of death were classified using an adapted version of the CoDe protocol into mutually exclusive categories. Clinicians classified deaths using information on death (ICD-9/ICD-10 codes or free text), patient characteristics at ART initiation (age, sex, HIV transmission risk group, ADEs, and hepatitis C status), time from ART initiation to death, ADEs after starting ART, latest CD4 (within six months of death), and whether a patient was on ART at the time of death. A computer algorithm and a clinician classified deaths using ICD codes when these codes were available. Otherwise, two clinicians independently classified each death. Disagreements between clinicians and/or computer-classifications were resolved via panel discussion as per the CoDe protocol [1,31].

The exposure of interest was an ADE after ART initiation, defined according to the US Centers for Disease Control and Prevention [32]. Diagnosis of ADEs after ART initiation and the dates of diagnosis were validated by local site investigators. In addition to evaluating ADEs overall, two mild ADEs (tuberculosis (TB) and *Pneumocystis jiroveci* pneumonia (PJP)) and one severe ADE (non-Hodgkin's lymphoma (NHL)) according a previous classification scheme [29], were evaluated to elucidate differences in NADE mortality based on ADE severity.

The outcome of interest was NADE mortality. We evaluated both overall non-AIDS deaths as well as cause-specific non-AIDS deaths, including cardiovascular, hepatic, metabolic, non-AIDS malignancy, non-AIDS infection, renal, respiratory, central nervous, accident/suicide/overdose, and other NADE deaths not falling into one of the previous categories.

2.3 | Statistical analysis

For continuous variables, median and interquartile range (IQR) are shown. For categorical variables, number (n) and percent (%) are shown. Crude NADE mortality rates per 1000 person-years (p-y) of follow-up were calculated for the overall population as well as for persons with ADE and without an ADE after ART initiation.

To model the association between ADEs and NADE mortality while appropriately adjusting for baseline and time-dependent confounders, marginal structural models were constructed [33]. Patient exposure status was assessed monthly until censoring or death. Patients were classified as unexposed for each month prior to their first ADE after ART initiation and exposed in each subsequent month. As we were interested in ADEs after ART initiation, patients with an ADE prior to ART initiation were classified as unexposed at baseline. Inverse probability weights (IPW) for the primary model of interest were determined based on four components. Each component was a pooled logistic regression model predicting probability of the following events each month: 1) ADE diagnosis; 2) LTFU; 3) administrative censoring; 4) a competing event, including death due to other NADEs (in the case of cause-specific NADE deaths), death due to ADEs, and death from unknown causes. These models included time since ART initiation, age at ART initiation, sex, cohort, year of ART initiation, baseline ART regimen (PI-based, NNRTI-based, other), HIV transmission risk group (heterosexual, men who have sex with men (MSM), injection drug use (IDU), blood transfusion, other/unknown), presence of ADE at or prior to ART initiation, baseline CD4+ count, baseline HIV-1 RNA, and current CD4+ count and HIV-1 RNA; restricted cubic splines were used for all continuous variables. Both current CD4+ count and HIV-1 RNA were time-dependent variables. If a patient had more than one measurement during a given month, the value from the latest date was utilized; if a patient did not have a measurement during a given month, the value from the previous month was carried forward.

A weighted pooled logistic regression model including robust standard errors was used to estimate the hazard ratio (HR) for NADE mortality comparing those who did and did not experience the ADE. This weighted pooled logistic regression model approximates a marginal structural Cox regression model when certain conditions are met (short intervals and low event rates) [33,34]. The weights from the four components above were multiplied to obtain the single time-updated weight incorporated into this model. This model included current ADE status (current or previous ADE diagnosis), time since initial visit date in months, age at ART initiation, sex, cohort, year of ART initiation, baseline ART regimen, HIV transmission risk factor, presence of ADE at or prior to ART initiation, baseline CD4+ count, and baseline HIV-1 RNA. Results are reported with stabilized weights [33] truncated at the 1st and 99th percentiles. The median of the untruncated stabilized weights was 0.98 (IQR 0.90 to 1.02) for the model including all ADEs as the exposure; weights for models corresponding to specific ADE exposures were similar (results not shown).

In a sensitivity analysis, we fitted several alternative models of the association between ADEs and non-AIDS mortality, including an unadjusted model that did not adjust for any covariates and a model that only adjusted for baseline covariates. For both models, we did not include any IPW and thus did not account for time-dependent covariates. We also refitted the marginal structural model after excluding observations from sites with >50% missing codes of death, after excluding those with AIDS at or prior to baseline, and after limiting the cohort to only patients with a baseline CD4+ count above 500 cells/mm^3. All statistical tests were two-sided. Statistical analyses were performed using R version 3.2. Analysis code is available at http://biostat.mc.vanderbilt.edu/ArchivedAnalyses.

3 | RESULTS

There were 124,587 patients included and followed up for a total of 770,259 p-y (median 5.18 years) in this study. The median age at ART initiation was 38 years, 76% were male, and 12% reported IDU as an HIV transmission factor. The median baseline CD4+ count was 244 cells/mm^3 (IQR 117 to 369 cells/mm^3) and the median baseline HIV-1 RNA was 66,580 copies/ml (IQR: 14,000 to 200,000 copies/ml) (Table 1). There were 14,245 patients (11%) who developed at least one ADE after ART initiation. Of these, 2174 (15%) had TB, 1864 (13%) had PJP, and 939 (7%) had NHL (patients could contribute to >1 ADE category). Among patients with an ADE, 6588 (46.2%) were on a PI-based regimen, 3955 (27.8%) were on an NNRTI-based regimen, 1114 (7.8%) were another regimen, and 2588 (18.2%) were not on ART at the time of the ADE. The proportion of patients with an ADE after ART initiation was higher among patients with a baseline a CD4+ count less than 500 cells/ml^3 (13,324/110,412; 12.1%) compared to those with a baseline CD4+ count greater than 500 cells/ml^3 (921/14,175; 6.5%).

Table 1. Demographic characteristics of the study population, ART-CC

	Overall (N=124,587)
Age (years)-median (IQR)	38 (32 to 46)
Male sex	95,001 (76%)
Year of ART initiation-median (IQR)	2005 (2001 to 2009)
Baseline ART regimen	
NNRTI	49,936 (40%)
PI	64,306 (52%)
Other	10,345 (8%)
ADE at or prior to baseline	24,849 (20%)
Transmission risk	
Heterosexual	43,644 (35%)
MSM	43,387 (35%)
IDU	15,347 (12%)
Blood transfusion	980 (1%)
Other/unknown	21,229 (17%)
Baseline CD4+ count (cells/ml), median (IQR)	244 (117 to 369)
Baseline HIV-1 RNA (copies/ml), median (IQR)	66,580 (14,000 to 200,000)
Years of follow-up, median (IQR)	5.18 (2.28 to 9.42)

ADE, AIDS-Defining Event; IQR, interquartile range; ART, antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; HIV, human immunodeficiency virus; MSM, male-male sexual contact; IDU, injection drug use; ml, millilitre.

There were 11,280 deaths during the study period; 2661 (24%) were AIDS-related deaths, 4051 (36%) were non-AIDS related deaths, and 4568 (40%) were unknown types of deaths. Among non-AIDS related deaths, 956 (24%) were due to a non-AIDS malignancy, 673 (17%) were due to accident/suicide/overdose, 649 (16%) were due to cardiovascular disease, 598 (15%) were non-AIDS infection, 529 (13%) were hepatic, 121 (3%) were respiratory, 68 (2%) were renal, 41 (1%) were metabolic, 57 (1%) were central nervous system (CNS) and 359 (9%) were due to other causes (Table 2). The proportion of missing death codes varied by cohort (10% to 92%) (Table S1). Among those who died, death codes were missing for 41% of persons without an ADE after ART initiation compared to 39% of persons with an ADE after ART initiation (p=0.03).

The crude overall non-AIDS mortality rate was 5.26/1000 p-y (95% confidence interval (CI) 5.09 to 5.42). Persons with any ADE after ART initiation had a higher crude overall non-AIDS mortality rate (14.90/1000 p-y (95% CI 13.99 to 15.79)) compared to persons without any ADE after ART initiation (4.28/1000 p-y (95% CI 4.12 to 4.43)). This finding of a

Table 2. Classification of deaths, ART-CC

	CoDe* codes	Number (%)
AIDS coded deaths		2661 (24%)
AIDS infection	01.1	1036
AIDS malignancy	01.2	635
AIDS unspecified	01	990
NADE coded deaths		4051 (36%)
Non-AIDS malignancy	04	956
Accident/suicide/overdose	16, 17, 19	673
Cardiovascular	08, 09, 12, 24	649
Non-AIDS infection	02	598
Hepatic	03, 14	529
Respiratory	13, 25	121
Renal	15	68
Central nervous	23	57
Metabolic	05, 06, 07	41
Other	10, 11, 18, 20, 22, 26, 27, 28, 29, 90	359
Unknown death		4568 (40%)
Coded, unknown	91, 92	1253
Uncoded (no information)		3315
Total deaths		11,280

*Coding of Death in HIV (CoDe) project (http://www.cphiv.dk/Tools-Standards/CoDe/About). AIDS, acquired immunodeficiency syndrome; NADE, non-AIDS-defining event.

higher crude overall non-AIDS mortality rate held true for each of the specific ADEs evaluated (Table 3). The median time from diagnosis of any ADE after ART initiation to NADE mortality was 702 days (IQR: 147 to 1661 days). This time from ADE to NADE mortality for the three specific ADEs of interest was 902 days for TB (IQR: 377 to 1912 days), 568 days for PJP (IQR 170 to 1413 days) and 225 days for NHL (IQR 89 to 1534 days).

Table 3. Crude non-AIDS related mortality rate per 1000 person-years, ART-CC

	NADE deaths	Follow-up (years)	NADE mortality rate per 1000 person-years (95% CI)
Overall	4051	770,259	5.26 (5.09 to 5.42)
Persons with ADE	1057	70,917	14.88 (13.99 to 15.79)
Persons without ADE	2994	699,342	4.28 (4.12 to 4.43)
Persons with TB	131	11,587	11.17 (9.28 to 13.07)
Persons without TB	3920	758,573	5.17 (5.00 to 5.32)
Persons with PJP	129	8247	15.62 (13.05 to 18.44)
Persons without PJP	3922	762,013	5.15 (4.98 to 5.30)
Persons with NHL	44	2886	15.12 (10.88 to 20.02)
Persons without NHL	4007	767,373	5.22 (5.05 to 5.38)

NADE, non-AIDS defining event; ADE, AIDS-defining event; CI, confidence interval; TB, tuberculosis; PJP, *Pneumocystis jiroveci* pneumonia; NHL, non-Hodgkin's lymphoma.

In the marginal structural model which adjusted for time-updated covariates, the adjusted hazard of death due to any NADE was significantly higher among patients with any ADE after ART initiation (adjusted hazard ratio (aHR) 2.21, 95% CI 2.00 to 2.43) compared to patients without any ADE after ART initiation. This finding was true for overall NADE deaths and for each NADE death category except for metabolic NADE deaths. The association of cause-specific NADE mortality differed depending on the specific ADE of interest. TB was associated with a higher risk of cardiovascular, metabolic, and non-AIDS infection NADE mortality. PJP was associated with a higher risk of non-AIDS infection, respiratory and accident/suicide/overdose NADE deaths. NHL was associated with a higher risk of renal NADE deaths. All three ADEs (TB, PJP and NHL) were associated with a higher risk of death due to non-AIDS malignancies (Table 4).

The results from the marginal structural model were somewhat attenuated although largely unchanged when compared to the results of the unadjusted model with a hazard ratio of 3.50 (95% CI 3.26 to 3.75) for death due to any NADE among patients with any ADE after ART initiation compared to patients without any ADE after ART initiation (Table S2). Similarly, in the model adjusted only for baseline covariates the adjusted ratio for death due to any NADE was 2.68 (95% CI 2.47 to 2.90) among patients with any ADE after ART initiation compared to patients without any ADE after ART initiation (Table S3).

The results of sensitivity analyses with alternative exclusion criteria as described in the methods were largely unchanged as well. In the model excluding all sites with >50% missing codes of death (Table 5), the aHR for death due to any NADE was 2.23 (95% CI 1.97 to 2.53). In the model excluding those individuals with ADEs at or prior to baseline (Table S4), the aHR for death due to any NADE was 2.37 (95% CI 2.10 to 2.67). Notably, among 14,175 (11%) patients in this cohort with a baseline CD4 cell count >500 cells/ml^3, the aHR for overall NADE mortality following any ADE was 2.66 (95% CI 1.84 to 3.87).

4 | DISCUSSION

In this large, multi-centre cohort collaboration with standardized assignment of causes of death, the risk of death due to NADEs overall was over two times higher for patients with any ADE after ART initiation compared to without an ADE following ART initiation. This finding held true for each of the three selected individual ADEs (TB, PJP and NHL). However, there was heterogeneity in the risk of cause-specific NADE mortality across the individual ADEs evaluated, consistent with previous studies of all-cause mortality. These findings suggest that prevention of ADEs, perhaps with more frequent HIV testing and early treatment with ART as recommended by current guidelines, may decrease subsequent NADE mortality.

Overall, the crude mortality rate per 1000 p-y due to NADEs (5.26 (95% CI 5.09 to 5.42)) was slightly higher than that reported from other cohorts in high-income countries, including South Korea (3.71, 95% CI 2.52 to 5.48) [35], Spain (3.75, 95% CI 2.84 to 4.94) [36], and from the Data collection on Adverse Events of anti-HIV Drugs (D:A:D) cohort in

Table 4. Adjusted marginal structural models for hazard ratios of cause-specific mortality

Type of death	N=6712 coded deaths	aHR (95% CI) Tuberculosis	aHR (95% CI) Pneumocystis	aHR (95% CI) Non-Hodgkin Lymphoma	aHR (95% CI) All ADEs
ADEs	2661	2.65 (2.20 to 3.19)	5.10 (4.36 to 5.97)	29.49 (25.48 to 34.13)	7.51 (6.64 to 8.49)
NADEs	4051	1.68 (1.38 to 2.04)	2.21 (1.78 to 2.73)	2.95 (2.12 to 4.10)	2.21 (2.00 to 2.43)
NADE malignancy	956	1.84 (1.23 to 2.76)	2.12 (1.30 to 3.47)	5.63 (3.46 to 9.16)	2.59 (2.13 to 3.14)
Accident, suicide, overdose	673	1.39 (0.81 to 2.38)	2.60 (1.54 to 4.38)	2.37 (0.90 to 6.26)	1.37 (1.05 to 1.79)
Cardiovascular	649	1.88 (1.15 to 3.08)	1.74 (0.96 to 3.15)	0.95 (0.20 to 4.46)	1.95 (1.54 to 2.48)
NADE infection	598	1.63 (1.05 to 2.54)	2.66 (1.74 to 4.06)	1.57 (0.45 to 5.47)	2.17 (1.68 to 2.81)
Hepatic	529	1.36 (0.77 to 2.40)	1.06 (0.52 to 2.19)	2.48 (0.79 to 7.76)	2.09 (1.61 to 2.72)
Respiratory	121	0.85 (0.24 to 2.92)	6.76 (3.03 to 15.09)	1.78 (0.44 to 7.16)	4.28 (2.67 to 6.88)
Renal	68	3.13 (0.88 to 11.19)	0.95 (0.22 to 4.05)	9.31 (2.25 to 38.45)	5.81 (2.69 to 12.56)
Central nervous	57	0.74 (0.10 to 5.47)	0.66 (0.09 to 5.04)	[a]	2.53 (1.18 to 5.44)
Metabolic	41	4.30 (1.35 to 13.69)	[a]	[a]	1.53 (0.67 to 3.47)
NADE, other	359	1.77 (0.86 to 3.66)	3.20 (1.40 to 7.30)	2.45 (0.96 to 6.25)	2.98 (2.14 to 4.16)

[a]Denotes that no deaths occurred in these categories.
+Models were adjusted for baseline CD4+ count, baseline HIV-1 RNA, sex, HIV transmission risk group, age, calendar year of ART initiation, baseline ART regimen (PI/NNRTI/other), ADE at or prior to the time of enrolment, and ART-CC cohort.

Table 5. Adjusted marginal structural models for hazard ratios of cause-specific mortality (excluding all sites with >50% missing codes of death)

Type of death	N=4,664 coded deaths	aHR (95% CI) tuberculosis	aHR (95% CI) pneumocystis	aHR (95% CI) non-Hodgkin lymphoma	aHR (95% CI) All ADEs
ADEs	1841	3.34 (2.64 to 4.23)	7.48 (6.06 to 9.23)	31.23 (26.83 to 36.36)	9.24 (8.08 to 10.58)
All NADEs	2823	1.82 (1.41 to 2.36)	1.58 (1.14 to 2.18)	2.48 (1.74 to 3.53)	2.23 (1.97 to 2.53)
NADE malignancy	674	1.86 (1.10 to 3.15)	0.70 (0.22 to 2.18)	3.68 (2.10 to 6.46)	2.14 (1.65 to 2.77)
Accident, Suicide, Overdose	491	0.87 (0.33 to 2.31)	1.18 (0.50 to 2.81)	2.57 (0.98 to 6.72)	1.14 (0.78 to 1.67)
Cardiovascular	413	2.90 (1.57 to 5.36)	0.99 (0.41 to 2.40)	1.02 (0.23 to 4.64)	2.11 (1.50 to 2.96)
Hepatic	384	1.06 (0.52 to 2.19)	1.08 (0.45 to 2.63)	1.70 (0.42 to 6.83)	1.83 (1.31 to 2.57)
NADE infection	352	2.03 (1.09 to 3.77)	3.01 (1.69 to 5.37)	1.70 (0.49 to 5.98)	2.50 (1.76 to 3.54)
Respiratory	98	1.70 (0.50 to 5.80)	4.81 (2.02 to 11.43)	2.02 (0.50 to 8.08)	4.72 (2.86 to 7.80)
Renal	52	5.03 (1.41 to 17.94)	1.23 (0.16 to 9.28)	10.00 (2.51 to 39.88)	9.19 (4.03 to 20.97)
Central nervous	47	1.11 (0.15 to 8.12)	1.31 (0.17 to 10.20)	[a]	2.52 (1.15 to 5.50)
Metabolic	28	1.57 (0.20 to 12.36)	[a]	[a]	1.47 (0.54 to 3.99)
NADE, other	284	2.09 (0.93 to 4.71)	3.11 (1.16 to 8.32)	2.75 (1.07 to 7.07)	3.16 (2.18 to 4.57)

[a]Denotes that no deaths occurred in these categories.
+Models were adjusted for baseline CD4+ count, baseline HIV-1 RNA, sex, HIV transmission risk group, age, calendar year of ART initiation, baseline ART regimen (PI/NNRTI/other), ADE at or prior to the time of enrolment, and ART-CC cohort.

Australia, Europe, and the United States (4.28, 95% CI 4.06 to 4.53) [12,37]–the latter two have some overlap with our dataset. It is possible this finding is related to differences in baseline CD4+ count (342 cells/mm^3 (IQR 163 to 546) in Spain, 400 (IQR 242 to 590) in D:A:D, and 244 (IQR 116 to 369) for ART-CC, respectively) as several previous studies have described lower CD4+ counts as risk factors for NADE mortality [13,14]. In addition, there may be background differences in NADE prevalence and NADE risk factors within the study populations as well as changes in these populations over time.

Over 60% of the coded causes of death in ART-CC were due to NADEs. This is consistent with the findings from a recent systematic review and meta-analysis which estimated the pooled proportion of patients with death due to NADEs in high-income countries during the ART era was 54% (95% CI 46% to 62%) [37]. The most frequent cause of NADE death in our study was non-AIDS malignancies (24%) followed by accidents/suicides/overdoses (17%), cardiovascular deaths (16%), non-AIDS infections (15%) and hepatic deaths (13%). These cause-specific findings are also consistent with this recent systematic review and meta-analysis (non-AIDS malignancies 28% (95% CI 23% to 33%), cardiovascular deaths 15% (95% CI 13% to 17%), non-AIDS infections 10% (95% CI 6% to 14%) and hepatic deaths 14% (95% CI 10% to 19%)) [37]. Pooled findings for accidents (n=187; 28%), suicides (n=180; 27%)

and overdoses (n=306; 45%) were not reported although these types of deaths were the second most common NADE death in our population.

A previous study conducted within the ART-CC found that overall mortality rates (deaths due to both ADEs and NADEs) subsequent to an ADE were dependent on the specific ADE diagnosis; NHL was classified as severe and TB and PJP were classified as mild [29]. In this study, while the associations between specific ADEs and overall NADE mortality were all statistically significant, we note that the strength of that association varied. The point estimate for the risk of NADE mortality overall was highest for NHL (2.95, 95% CI 2.12 to 4.10), previously designated as a severe ADE [29].

However, the risk of cause-specific NADE mortality differed between the three ADEs evaluated (TB, PJP, and NHL). For example, only TB was associated with cardiovascular NADE deaths. Previous epidemiologic studies have described an association between TB and cardiovascular disease. A large retrospective study in Taiwan reported a 40% increased risk of cardiovascular events among patients with TB compared to patients without TB after controlling for important co-morbidities [38]. Several possible mechanisms of the association include direct mycobacterial tissue invasion, auto-immunity mediated by antibodies against mycobacteria, as well as increased inflammation and immune activation, [39], although prospective studies are needed.

Only PJP was associated with subsequent death due to respiratory events and accident/suicide/overdoses. In the Pulmonary Complications of HIV Study, PJP was associated with declines in lung function that persisted even after the acute infection resolved [40]. However, the association of PJP with accidents/suicides/overdoses suggests that not all of these associations may be mechanistic and that unmeasured confounders such as mental illness and alcohol/drug use are likely important.

There are some limitations to this study. First, there are likely unmeasured confounders not accounted for in these analyses. The ART-CC does not collect information on other important lifestyle factors such as tobacco use, alcohol use, active IDU and body mass index (BMI). PLWH who smoke have higher rates of cardiovascular disease, respiratory disease and malignancies than people without HIV infection who smoke. A recent modelling study showed that PLWH in the US who smoke lose as much or more life expectancy from smoking than from HIV infection itself. Moreover, this study showed that smoking cessation would result in a greater gain in life expectancy than early HIV testing and treatment or improved ART adherence [41]. It is unclear if the associations we found would remain after controlling for such potentially important unmeasured variables.

Second, it is possible that some causes of death may be coded inaccurately as the coding was performed retrospectively without access to complete medical histories. It is also possible that we categorized diseases of different aetiologies in the same cause-specific categories. For example, it is possible that a dysrhythmia due to ischemic heart disease and a dysrhythmia due to drug overdose may have both been categorized as a cardiovascular cause of death. However, given the rigorous standardized process used for coding of deaths it is likely that the majority were coded correctly. Moreover, some deaths could not be coded and therefore some deaths due to NADEs may have been missed.

Thirdly, cause of death was not available for 40% of deaths within the cohort over the study period. Therefore, we performed a sensitivity analysis in which we excluded all sites with >50% missing codes of death. Compared to the main results, the results of the sensitivity analysis were largely unchanged. However, causes of death in the main analysis were differentially missing between those with and without ADEs after ART initiation, which may have led to biased results.

5 | CONCLUSIONS

In conclusion, in this cohort of persons initiating ART, NADE mortality rates were higher among those with an ADE after ART initiation compared to those without an ADE after ART initiation. Consistent with previous studies of overall mortality, NADE mortality rates after an ADE depended on the specific ADE diagnosed. Although there may be unmeasured confounders and associations may not be mechanistic, these findings suggest that a common pathway may be independently driving both ADEs and NADE mortality. ADE prevention, perhaps by more frequent HIV testing and initiating treatment at higher CD4+ counts, as well as the continued modification of risk factors such as tobacco use, may reduce subsequent NADE mortality. In addition, these findings underscore the need for future studies to elucidate a potential mechanism for this association, including that of chronic inflammation and immune activation due to ADEs. In these future studies it will be important to address potential confounders including important modifiable lifestyle factors such as tobacco use.

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COMPETING INTERESTS

All authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

Study conception and design: AP, MG, SI, MM, BS, JS, TS. Acquisition of data: SI, MM, MG, GF, SA, MS, JD, JM, MC, FD, AM, PR, JG, DM, LS, NO, HC, CS, RT, RZ, JS, TS. Data analysis and interpretation: AP, MG, SI, MM, BS, JS, TS. Drafting of manuscript: AP, MG. Revising manuscript for important intellectual content: AP, MG, SI, MM, BS, MG, GF, SA, MS, JD, JM, MC, FD, AM, PR, JG, DM, LS, NO, HC, CS, RT, RZ, JS, TS. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Missing cause of death codes by cohort
Table S2. Unadjusted models for hazard ratios of cause-specific mortality
Table S3. Adjusted models for hazard ratios of cause-specific mortality (non-marginal structural models)+
Table S4. Adjusted marginal structural models for hazard ratios of cause-specific mortality+ (excluding those with ADE at or prior to baseline)