Mortality using raltegravir versus other integrase strand-transfer inhibitors in people with HIV in Europe and Australia: a prospective multicentre study

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Summary

Background Integrase strand-transfer inhibitors (INSTI) are a key part of contemporary antiretroviral therapy (ART). Raltegravir (RAL) was the first INSTI and remains recommended for some people with HIV. We investigated all-cause mortality between RAL-based ART and other INSTIs in the RESPOND cohort consortium among both ART-naïve and treatment experienced individuals.

Methods RESPOND, a multicenter prospective cohort study, includes approximately 40,000 adults (≥18 years) with HIV from 17 cohorts across Europe and Australia. Individuals eligible for inclusion into RESPOND had ≥1 clinical visit at a site participating in RESPOND after January 01, 2012, and a CD4 count and HIV viral load measurement available at inclusion. Participants in RESPOND who started their first INSTI between JAN 01, 2012 and DEC 31, 2021 were included. All-cause mortality among those starting RAL was compared to those starting any other INSTI using Cox proportional hazards regressions: one model adjusting for age and another weighted by inverse probability of treatment weights (IPTW). Predictors of starting RAL were estimated by logistic regression.

Findings Among 20,349 participants starting an INSTI (15,429 (75.8%) male, 4879 (24.0%) female, and 41 (0.2%) transgender), 938 (4.6%) died during 94,677 person-years of follow-up (PYFU). Crude mortality rates (MR) were higher for participants starting RAL (MR 12.9 per 1000 PYFU; 95% CI 11.5–14.5) than other INSTIs (MR 9.1 per

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1000 PYFU; 95% CI 8.4, 9.8). Starting RAL was significantly associated with higher mortality when controlling for age (adjusted hazard ratio (aHR) 1.43; 95% CI 1.25, 1.65). However, after applying IPTW, there was insufficient evidence for a difference in mortality in the full cohort (hazard ratio (HR) 1.13; 95% CI 0.93, 1.34) or among ART-naïve participants (HR 1.23; 95% CI 0.71, 2.12). Starting RAL was associated with higher HIV viral load, hepatitis C positive status (aOR 2.07; 95% CI 1.82, 2.37), prevalent end-stage renal disease (aOR 2.58; 95% CI 1.58, 4.19), chemotherapy near baseline (aOR 1.58; 1.01, 2.48), and cardiovascular disease (aOR 1.58; 95% CI 1.30, 1.91).

Interpretation In this large and well-characterised cohort we found no evidence of an association between all-cause mortality and use of RAL compared to other INSTIs after accounting for confounding at the time of starting the INSTI. Our findings suggest that prior reports of such an association could have been confounded by indication and channelling bias. While a large number of potential confounders were accounted for, the results presented are an estimation of average treatment effect using IPTW which is still vulnerable to uncontrolled confounding.

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Keywords: HIV; Integrase strand-transfer inhibitors (INSTI); Raltegravir; All-cause mortality

Research in context

Evidence before this study

A recent study showing an association between starting the integrase strand inhibitor (INSTI) raltegravir (RAL), and all-cause mortality compared to several other antiretrovirals was published in Lancet HIV in 2022 by Trickey et al. We searched PubMed for additional studies investigating association between use of RAL and mortality. Searches were limited to studies published before September 1, 2024, in English. The literature presents mixed evidence with some studies reporting an association between use of RAL and all-cause mortality, though no mechanism has been suggested, while others found insufficient evidence for an association.

Added value of this study

RAL was the first available INSTI and remains recommended for people with HIV including those who experience adverse effects to other ART, are at risk of drug-drug interactions, or during pregnancy. Whilst use of RAL is declining over time a large proportion of individuals in Europe and Australia have been/are currently using the drug. Therefore, it is important to determine whether the safety signal for RAL in the literature may be better explained by channelling bias or confounding by indication.

Implications of all the available evidence

This multinational study provides an important negative safety finding of no evidence of an association between use of RAL and incident mortality after controlling for confounding at INSTI start (baseline). Though age-adjusted survival analysis indicated an association between use of RAL and all-cause mortality, accounting for baseline confounding using inverse propensity of treatment weights indicates no association. In secondary analysis of the baseline risk factors, several mortality risk factors are strongly associated with starting RAL, as compared to any other INSTI, namely, end-stage renal disease, hepatitis C, use of chemotherapy near baseline, cardiovascular disease, and higher levels of HIV viral load. Taken in light of the mixed evidence in the literature, these results provide a strong explanation that confounding by indication and/or channelling bias may have been driving the observed associations between starting RAL and all-cause mortality.

Introduction

Since the introduction of antiretroviral therapy (ART), mortality among people with HIV has dramatically declined.[1–3] Integrase strand-transfer inhibitors (INSTI), one of the newer classes of antiretrovirals (ARV), are effective in maintaining viral suppression[4–6] and are currently recommended as part of first-line treatment worldwide.[7–9] Raltegravir (RAL) was the first INSTI to be approved by the European Medicines Agency in 2007. As RAL was the first drug of its class, it was commonly

used for people with HIV with an intolerance to other non-INSTI ARVs or as salvage therapy for those failing other drug classes.[6,10] RAL is generally well tolerated, has low potential for drug-drug interaction, and can be used in people with renal failure without dose adjustment.[7,11,12]

Past work within the International Cohort Consortium of Infectious Disease (RESPOND) showed that the initiation of RAL as a first INSTI, compared to other INSTIs, declined from 2012 through 2017.[13] This was due, in part, to the introduction of a wider range of INSTIs with a higher genetic barrier for resistance[14–16] and/or available as fixed-dose combinations. RAL is not available in fixed-dose combinations and administration in adults requires two tablets per day (as 1 × 400 mg bid or 2 × 600 mg qd).[7] However, RAL is still noted to be of clinical use in specific populations, especially in persons with adverse effects to other ARVs, those at risk for drug-drug interactions,[11] including treatment for tuberculosis (TB) or malignancies, and during pregnancy.[7]

Use of RAL has been associated with increased all-cause mortality in some cohorts,[4,17] though not in others.[18–20] Importantly, no biological mechanism to date has been suggested that could drive this association. In emulated target trial analyses comparing starting bictegravir (BIC) among ART-naïve people with HIV and switching to BIC among ART-experienced participants, the rate of viral suppression was lower among ART-naïve who started RAL and among those who continued RAL, compared to those who switched to BIC, among treatment-experienced.[21,22] In the RESPOND study, several mortality risk factors have been shown to be associated with the initiation of RAL, compared to the currently most commonly used INSTI dolutegravir (DTG): older age, HIV exposure by injection drug use, hepatitis C (HCV) or B (HBV) co-infection, prior AIDS, cardiovascular disease (CVD), and fracture.[13] Given the history of RAL use among people with HIV with intolerance to other non-INSTI antiretrovirals or as salvage therapy, as well as the mortality risk factors that have been shown to be associated with RAL use, uncontrolled baseline confounding due to indication or channelling may contribute to the reported association between RAL and mortality.

We investigated the potential link between RAL use and mortality risk using data from RESPOND. RESPOND is a prospective multi-cohort collaboration of people with HIV across Europe and Australia with a central aim to conduct systematic pharmacovigilance of ART. In both ART naïve and ART experienced people with HIV starting an INSTI for the first time, we investigated the risk of mortality in individuals starting RAL compared to those starting any other ARV within the INSTI class. As RESPOND is an observational study wherein the likelihood of baseline confounding is high, in addition to age-adjusted analyses, we used inverse probability of treatment weights (IPTW) to account for baseline confounding which could explain an apparent association between RAL and mortality.[23,24] Additionally, we investigated the characteristics associated with initiating RAL as a first INSTI to better understand any possible confounding.

Methods

Study population and data collection

The results from this multicenter cohort study are reported following the Strengthening the Reporting of Observation Studies in epidemiology (STROBE) guidelines. RESPOND was initiated in 2017 and includes approximately 40,000 people with HIV from 17 cohorts across Europe and Australia. Clinical and demographic data are collected prospectively during routine clinical care. Cohorts contributing data to RESPOND supplied retrospective data from 2012 to 2017 and prospectively collected data from 2017 onward; approximately 2000 new participants are added each year.[25] For this analysis, the last year of follow-up was omitted due to possible delays in mortality reporting,[1,26] leaving a follow-up period from JAN 01, 2012 through DEC 31, 2021.

Only participants who initiated their first INSTI treatment while under follow-up from 2012 through 2021 were eligible for inclusion. Baseline was defined as the date of first INSTI initiation. Participants were considered exposed to RAL or other INSTI from first date of ART initiation and remained in the same exposure group for mortality analyses, i.e., they were not censored and did not switch groups if they discontinued RAL or other INSTI. Other inclusion criteria were ≥18 years of age at baseline, known sex/gender, and recorded CD4 count and HIV viral load (HIV-VL) measurement within one year prior- or three months post-baseline, as per RESPOND inclusion criteria.[25] Loss to follow-up date was defined as two years after the last clinic visit. Participants were followed until the first of death, study dropout, loss to follow-up date, or end of the follow-up period (31 December 2021). As such, participants were censored due to dropout, which may occur due to changing clinics, voluntary withdrawal, or other reasons, as well as loss to follow-up, where there is no recorded reason for dropout.

Statistical analysis

Descriptive statistics

Participant characteristics at the time of starting their first INSTI (baseline) were described for all participants and separately for those who started RAL and any other INSTI. Cumulative exposure to ART regimens containing RAL, another INSTI, or not containing any INSTI was tabulated by calendar year of follow-up.

Crude and age-standardised mortality analysis

To assess whether there were any apparent mortality differences between participants who started RAL and those who started other INSTIs, crude and age-adjusted analyses were conducted first. Crude and age-standardised mortality rates were calculated for all participants, separately for participants who initiated RAL and any other INSTI, and in two time periods (early: 2012–2016 vs. late: 2017–2021). Time period was included to account for changes over time in uptake of different INSTIs.[13] Age-standardisation was estimated using the age distribution for all participants over the entire follow-up period, using Dobson's approach to calculate confidence intervals.[27,28] Cox proportional hazard regression was used to compare the risk of all-cause mortality between participants who initiated RAL as the first INSTI vs. any other INSTI, controlled for age at baseline, smoothed by penalised spline.[29,30] Participants who discontinued first INSTI during the follow-up period remained under follow-up, assigned to the same group. In terms of target trial emulation, this would be considered an intent to treat analysis. The specifications for a target trial and components of our study in an emulated trial framework are outlined in the Supplemental Material.

IPTW analysis

In order to address as many known confounders as possible, we conducted IPTW-weighted Cox proportional hazard regression. Covariate balancing propensity score (CBPS) regression estimates the propensity score such that it maximises the resulting covariate balance as well as the prediction of treatment assignment.[31,32] CBPS regression with starting RAL as first INSTI as the outcome was used to estimate standardised IPTW. Weighted distributions of baseline covariates were calculated for RAL and other-INSTI groups and compared by average mean difference (AMD). Covariates were considered balanced if AMD was less than 10%.[24,33] A Cox proportional hazard regression was then conducted with IPTW weighting to estimate the average treatment effect on mortality between participants who started RAL as first INSTI compared to those who started any other INSTI. The 95% confidence interval was calculated by bootstrapping over 999 iterations.

Predictors of starting RAL

Least absolute shrinkage and selection operator (LASSO) regression was used to perform feature selection, i.e., to select covariates that are sufficiently associated with starting RAL, using the caret package in R[34,35]; see Supplemental Material for details. The selected covariates were included in multivariable logistic regression predicting starting RAL vs. other INSTIs to identify possible confounders in the association between the use of RAL and mortality.

Baseline covariates

Demographic characteristics included age, sex/gender, race/ethnicity, geographic region, HIV exposure group, and time period of INSTI start (2012–2016 vs. 2017–2021). Time periods were chosen to divide the follow-up time in half and allow for a simple, dichotomous presentation of trends over time. Geographic regions were defined as in previous research.[26,36] Sex/gender was not collected consistently in the participating cohorts. Gender information is included where available, otherwise sex assigned at birth.

Immunologic and virologic measures at baseline included HIV-VL and both nadir and baseline CD4 count. HIV-VL and CD4 count at baseline were defined as the measurement closest to baseline within one year prior- or three months post-baseline.

ART-related data includes ART exposure (naïve vs. ever-exposed), total number of different individual ARVs exposed to pre-baseline, and reason for discontinuation of previous ART regimen (in ART-experienced). ART adherence was not measured, as it is not collected by the contributing cohorts of the RESPOND collaboration. Reason for discontinuation in previous ART regimen was grouped into categories used in previous research[13]: patient/physician choice, treatment failure, treatment simplification, toxicity, other, or unknown. As different ARVs may have been discontinued on the same day with different reasons for discontinuation, each category is counted separately, and each participant may have more than one reason for discontinuation of the pre-baseline regimen.

Other clinical characteristics of interest, measured at baseline, included prior AIDS-defining event,[37] prior AIDS- or non-AIDS-defining malignancy (ADM and NADM), history of tuberculosis (TB), HBV, HCV, hypertension, diabetes mellitus (DM), dyslipidemia, smoking history, liver fibrosis, chronic kidney disease (CKD), end-stage liver and kidney disease (ESLD and ESRD), CVD, use of chemotherapy near baseline (within 12 months prior- or 3 months post-baseline), indication of pregnancy at baseline, and number of prescribed co-medications. Due to RESPOND requirements, the only reported specific, individual co-medications are those for cardiometabolic comorbidities and co-infection including TB and HBV/HCV. The following risk factors included 'unknown' levels for missing information: HIV exposure group, liver fibrosis stage, hepatitis C status, chronic kidney disease, smoking history, hypertension, dyslipidemia, diabetes, and reason for discontinuation of prior ART regimen. CBPS regression to estimate IPTW for starting RAL as first INSTI included all the above demographic, immunologic, virologic, ART-related, and clinical covariates.

As the majority of this data was unlikely to be missing at random but rather due to several different factors such as engagement in care and differences in clinical practice, excluding individuals missing this

information may have biased our sample. For HIV exposure group, it would not be appropriate to exclude participants who did not know how they acquired HIV, as they are an important and vulnerable population to study. For the clinical conditions diagnosed, at least in part, by laboratory tests, there are varying clinical standards of practice across the contributing cohorts, and a lack of laboratory test for e.g. diabetes can be generally interpreted as a lack of indication. Though there is poor reporting of smoking history, it is nevertheless an important risk factor for mortality and removing it from the model would not be justified. Definitions of all variables are included in Supplemental Material.

Median baseline date and full ART regimen at baseline were described separately and not included in statistical models. ART regimens at baseline reported by at least 1% of participants are described individually. Rare ART regimens reported by fewer than 1% of participants were grouped as "other, with RAL" or "other, without RAL".

Sensitivity analyses

We prespecified the same set of analyses in early (2012–2016) and late (2017–2021) time periods. Analyses were also repeated in a sub-group of individuals who were ART-naïve at first INSTI initiation. Time to switching off the first INSTI was analysed in a Cox proportional hazards model comparing participants starting RAL as first INSTI vs. any other INSTI.

All statistical analyses were performed using R version 4.4.1.[35]

Ethical considerations

Ethical approval and consent from participants for collection and sharing of data was obtained, if required, from the relevant bodies according to national and local requirements of the participating cohorts. Participants were pseudonymised at enrolment by assignment of a unique identifier by the participating cohort before data transfer to the main RESPOND database. All cohorts have approval to share data with RESPOND.

Role of the funding source

As per RESPOND governance, the funders of the study were also academic collaborators, and employees or associates could be included as co-authors if they met the ICJME criteria. However, neither funding bodies, nor employees or associates thereof, were in a position to in any way veto study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all data and was responsible for submission for publication.

Results

From 39,271 participants enrolled in RESPOND, 20,931 started an INSTI during follow-up. After applying exclusion criteria (see flow chart in Fig. 1), a cohort of 20,349 participants, contributing 94,677 person-years of follow-up (PYFU) (median 4.8 years; 95% CI 2.9, 6.4), were included in the analysis. Distributions of demographic and clinical characteristics are included in Table 1, the majority were male (75%, n = 15,429), 24.0% female (n = 4879), and 0.2% transgender (0.2%). A total of 4184 participants contributing 24,480 PYFU (median 6.2 years; 95% CI 3.7, 8.1) started RAL as their first INSTI; of these, 819 (19.6%) were ART-naive. There were 16,165 participants contributing 70,197 PYFU (median 4.6 years; 95% CI 2.7, 6.1) who started another INSTI as their first INSTI; of these, 3785 (23.4%) were ART-naive. Baseline date and ART regimens at baseline are included in Supplemental Table S1.

Fig. 2 shows the cumulative exposure among included participants to ART regimens containing RAL, other INSTIs, or no INSTIs, per calendar year of follow-up. Regimens containing RAL were most prevalent from 2012 through 2014, while those containing any other INSTI were most prevalent from 2015 through the end of follow-up. In 2021, the last year of follow-up, 1385 (8%) participants in the cohort were on RAL at some point.

Descriptive mortality estimates

A total of 938 (4.6%) people died during follow-up, 312 (7.5%) of 4184 who initiated RAL as first INSTI and 626 (3.9%) of 16,165 who initiated another INSTI as their first INSTI. Age-standardised mortality rates were higher among participants starting RAL (12.7 per 1000 PYFU; 95% CI 11.3, 14.1) compared to those starting other INSTIs (9.1 per 1000 PYFU; 95% CI 8.4, 9.9). Fig. 3 shows cumulative mortality curves between the two groups. After adjusting for age, but not controlling for any other possible confounders, in Cox-proportional hazards regression, there was a 43% higher mortality rate in individuals starting RAL as first INSTI compared to any other INSTI: adjusted hazard ratio (aHR) 1.43; 95% CI 1.25, 1.65.

Age-standardised mortality rates were higher in the full cohort in the earlier period (2012–2016 age-standardised mortality rate (SMR) 11.8 per 1000 PYFU; 95% CI 10.3, 13.4) compared to the later period (2017–2021 SMR 9.6 per 1000 PYFU; 95% CI 8.9, 10.3); see Table 2. Though age-standardised mortality was higher over the full-time period among participants who initiated RAL as first INSTI, this difference was primarily in the earlier time period (2012–2016).

IPTW mortality estimates

After applying IPTW weights to each group, the covariate balance between RAL and other-INSTI participants was very good: 72 out of 75 covariates (96%) were balanced, where each level of non-dichotomous categorical covariates was considered separately. Weighted

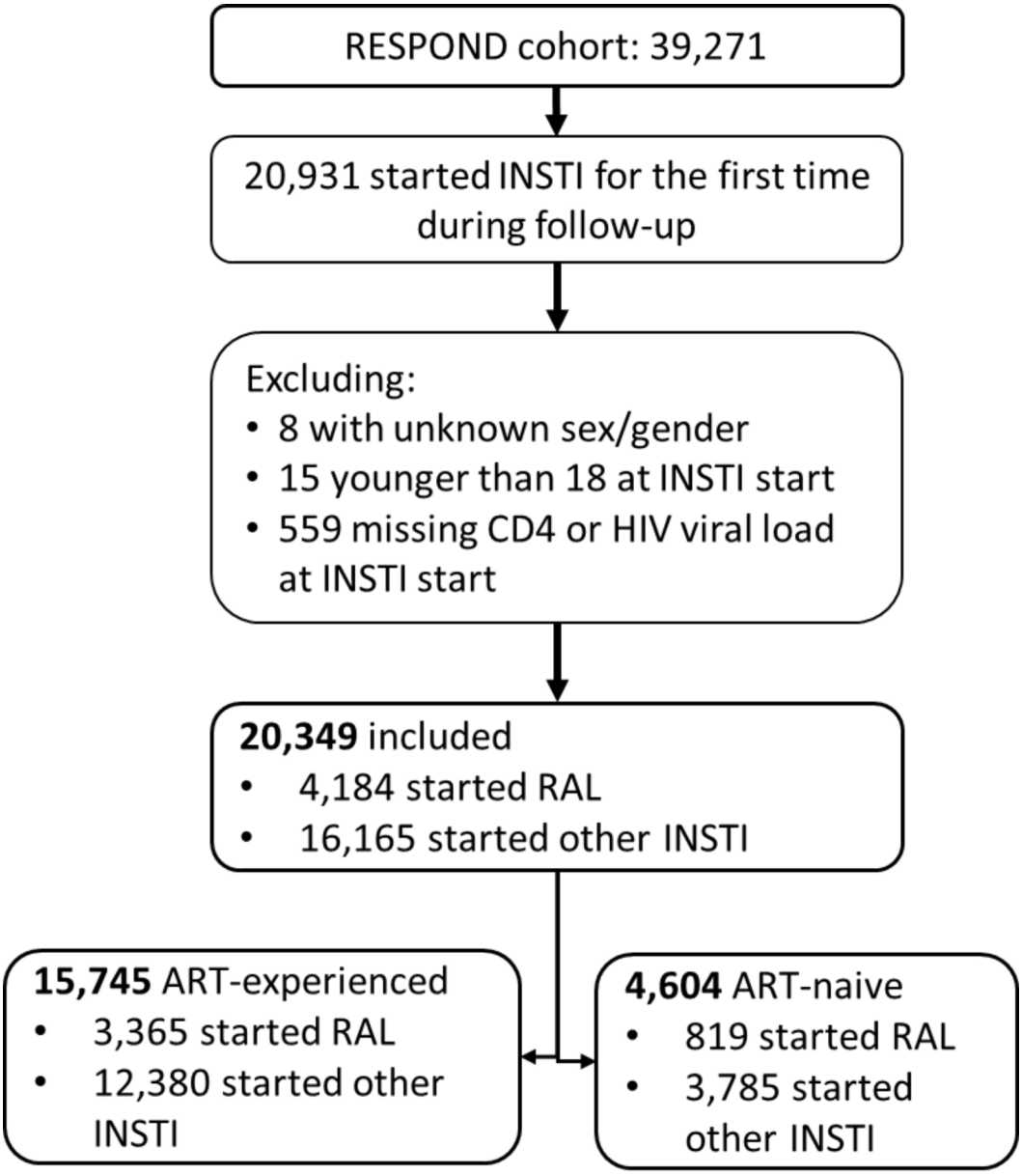

Fig. 1: Flow chart for participant inclusion.

covariate distributions are described in Table 1. Note that, in applying IPTW weights to the RAL and other-INSTI groups, the number of participants in the new pseudo-population groups is increased: from 16,165 to 20,475 in the other-INSTI group, and from 4184 to 17,560 in the RAL group. The most unbalanced covariate in the weighted pseudo-population was discontinuation of the prior ART regimen for treatment simplification (AMD 16.9%), with fewer participants in the RAL group discontinuing their previous regimen for treatment simplification, followed by time period (AMD 14.4%), with more participants in the RAL group in the earlier time period, and Central West European region (AMD 12.7%), with fewer participants in the RAL group in Central Western Europe. In weighted Cox regression, there was insufficient evidence for an average treatment effect on mortality between participants who started RAL compared to those who started any other INSTI (HR 1.13, 95% CI 0.94, 1.34). While the quoted hazard ratio represents a weighted average of the time-varying hazard ratio, the Kaplan–Meier survival curves present in Fig. 4, support this conclusion across the study period. Note that the number at risk in Fig. 4 corresponds to the weighted population.

Baseline covariate	All participants	Other INSTI group	RAL group	AMD between groups	Weighted other INSTI group	Weighted RAL group	AMD between weighted groups
Age in years, median (IQR)	47 (38, 54)	47 (38, 55)	48 (39, 54)	3.5%	47 (38, 55)	48 (38, 54)	1.1%
Sex/gender							
Male	15,429 (75.8%)	12,378 (76.6%)	3051 (72.9%)	8.4%	15,445 (75.4%)	12,713 (72.4%)	7%
Female	4879 (24%)	3750 (23.2%)	1129 (27%)	8.7%	4986 (24.4%)	4783 (27.2%)	6.7%
Transgender	41 (0.2%)	37 (0.2%)	<5 (0.1%)	3.3%	45 (0.2%)	64 (0.4%)	3.6%
Region							
Central West Europe	10,484 (51.5%)	8977 (55.5%)	1507 (36%)	39.9%	10,651 (52%)	8046 (45.8%)	12.7%
South Europe	4016 (19.7%)	3203 (19.8%)	813 (19.4%)	1%	4096 (20%)	3786 (21.6%)	3.9%
North Europe	3592 (17.7%)	2274 (14.1%)	1318 (31.5%)	42.5%	3454 (16.9%)	3542 (20.2%)	8%
Central East Europe	714 (3.5%)	504 (3.1%)	210 (5%)	9.6%	731 (3.6%)	722 (4.1%)	2.7%
East Europe	1227 (6%)	950 (5.9%)	277 (6.6%)	3.1%	1223 (6%)	1221 (7%)	4.1%
Australia	316 (1.6%)	257 (1.6%)	59 (1.4%)	1.5%	321 (1.6%)	243 (1.4%)	1.5%
Race/ethnicity							
White	13,822 (67.9%)	11,085 (68.6%)	2737 (65.4%)	6.7%	13,918 (68%)	11,674 (66.5%)	3.2%
Non-White	3741 (18.4%)	2838 (17.6%)	903 (21.6%)	10.2%	3716 (18.1%)	3137 (17.9%)	0.7%
Unknown	514 (2.5%)	410 (2.5%)	104 (2.5%)	0.3%	531 (2.6%)	461 (2.6%)	0.2%
Collection of race data prohibited[a]	2272 (11.2%)	1832 (11.3%)	440 (10.5%)	2.6%	2311 (11.3%)	2288 (13%)	5.6%
HIV exposure group							
MSM	9606 (47.2%)	7743 (47.9%)	1863 (44.5%)	6.8%	9544 (46.6%)	7699 (43.8%)	5.6%
IDU	2608 (12.8%)	1986 (12.3%)	622 (14.9%)	7.5%	2692 (13.1%)	2527 (14.4%)	3.6%
Heterosexual contact	6857 (33.7%)	5444 (33.7%)	1413 (33.8%)	0.2%	6929 (33.8%)	6060 (34.5%)	1.4%
Other/unknown	1278 (6.3%)	992 (6.1%)	286 (6.8%)	2.8%	1310 (6.4%)	1274 (7.3%)	3.5%
Time period							
Early (2012–2016)	11,656 (57.3%)	8312 (51.4%)	3344 (79.9%)	62.9%	11,672 (57%)	11,159 (63.5%)	14.4%
Indication of pregnancy at baseline[b]	231 (1.1%)	139 (0.9%)	92 (2.2%)	10.9%	271 (1.3%)	257 (1.5%)	1.1%
CD4 count (cells/mm^3)							
≤50	648 (3.2%)	465 (2.9%)	183 (4.4%)	8%	660 (3.2%)	599 (3.4%)	0.9%
>50 & ≤200	1571 (7.7%)	1142 (7.1%)	429 (10.3%)	11.4%	1597 (7.8%)	1413 (8%)	4.3%
>200 & ≤350	2544 (12.5%)	1928 (11.9%)	616 (14.7%)	8.2%	2551 (12.5%)	2445 (13.9%)	0.6%
>350 & ≤500	3726 (18.3%)	2951 (18.3%)	775 (18.5%)	0.7%	3778 (18.5%)	3200 (18.2%)	3.4%
>500	11,860 (58.3%)	9679 (59.9%)	2181 (52.1%)	15.7%	11,890 (58.1%)	9903 (56.4%)	0.9%
CD4 count nadir (cells/mm^3)							
≤200	9072 (44.6%)	6919 (42.8%)	2153 (51.5%)	17.4%	9130 (44.6%)	8099 (46.1%)	3.1%
>200 & ≤500	8994 (44.2%)	7369 (45.6%)	1625 (38.8%)	13.7%	9041 (44.2%)	7453 (42.4%)	3.5%
>500	2283 (11.2%)	1877 (11.6%)	406 (9.7%)	6.2%	2305 (11.3%)	2009 (11.4%)	0.6%
HIV viral load (copies/mL)							
≤50	13,307 (65.4%)	10,740 (66.4%)	2567 (61.4%)	10.6%	13,392 (65.4%)	11,284 (64.3%)	2.4%
>50 & ≤200	1054 (5.2%)	751 (4.6%)	303 (7.2%)	11%	1046 (5.1%)	967 (5.5%)	1.7%
>200 & ≤10,000	1669 (8.2%)	1241 (7.7%)	428 (10.2%)	8.9%	1709 (8.3%)	1615 (9.2%)	3%
>10,000 & ≤100,000	2143 (10.5%)	1745 (10.8%)	398 (9.5%)	4.2%	2138 (10.4%)	1831 (10.4%)	0%
>100,000	2176 (10.7%)	1688 (10.4%)	488 (11.7%)	3.9%	2191 (10.7%)	1863 (10.6%)	0.3%
Prior AIDS diagnosis	4600 (22.6%)	3432 (21.2%)	1168 (27.9%)	15.6%	4684 (22.9%)	4276 (24.4%)	3.4%
AIDS-defining malignancy	1001 (4.9%)	745 (4.6%)	256 (6.1%)	6.7%	1015 (5%)	837 (4.8%)	0.9%
Non-AIDS-defining malignancy	926 (4.6%)	685 (4.2%)	241 (5.8%)	7%	954 (4.7%)	805 (4.6%)	0.4%
Use of chemotherapy near baseline	127 (0.6%)	91 (0.6%)	36 (0.9%)	3.5%	131 (0.6%)	123 (0.7%)	0.7%
TB history	826 (4.1%)	599 (3.7%)	227 (5.4%)	8.2%	878 (4.3%)	893 (5.1%)	3.8%
Number of prescribed medication, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	3.6%	0 (0, 0)	0 (0, 1)	0.7%
Liver fibrosis stage							
0/1	16,807 (82.6%)	13,652 (84.5%)	3155 (75.4%)	22.7%	16,863 (82.4%)	13,936 (79.4%)	7.5%
2	180 (0.9%)	120 (0.7%)	60 (1.4%)	6.7%	183 (0.9%)	183 (1%)	1.4%
3	122 (0.6%)	88 (0.5%)	34 (0.8%)	3.3%	126 (0.6%)	118 (0.7%)	0.7%
4	385 (1.9%)	244 (1.5%)	141 (3.4%)	12.1%	404 (2%)	394 (2.2%)	1.8%
Unknown	2855 (14%)	2061 (12.7%)	794 (19%)	17.1%	2899 (14.2%)	2929 (16.7%)	6.9%

(Table 1 continues on next page)

Baseline covariate	All participants	Other INSTI group	RAL group	AMD between groups	Weighted other INSTI group	Weighted RAL group	AMD between weighted groups
(Continued from previous page)							
Hepatitis C status							
Antibody negative and either RNA negative or RNA unknown	14,593 (71.7%)	11,936 (73.8%)	2657 (63.5%)	22.4%	14,678 (71.7%)	12,064 (68.7%)	6.5%
Antibody positive and either RNA positive or RNA unknown	2475 (12.2%)	1604 (9.9%)	871 (20.8%)	30.6%	2517 (12.3%)	2440 (13.9%)	4.5%
Antibody positive and RNA negative	1747 (8.6%)	1515 (9.4%)	232 (5.5%)	14.6%	1759 (8.6%)	1625 (9.3%)	2.5%
Unknown	1534 (7.5%)	1110 (6.9%)	424 (10.1%)	11.7%	1522 (7.4%)	1431 (8.2%)	2.6%
End-stage liver disease	148 (0.7%)	92 (0.6%)	56 (1.3%)	7.9%	158 (0.8%)	141 (0.8%)	0.3%
Chronic kidney disease							
No CKD	14,078 (69.2%)	11,218 (69.4%)	2860 (68.4%)	2.2%	14,066 (68.7%)	11,554 (65.8%)	6.3%
CKD	693 (3.4%)	495 (3.1%)	198 (4.7%)	8.6%	699 (3.4%)	651 (3.7%)	1.5%
Unknown	5578 (27.4%)	4452 (27.5%)	1126 (26.9%)	1.4%	5711 (27.9%)	5355 (30.5%)	5.9%
End-stage renal disease	95 (0.5%)	42 (0.3%)	53 (1.3%)	11.6%	99 (0.5%)	103 (0.6%)	1.2%
Smoking history							
Never smoker	3755 (18.5%)	3168 (19.6%)	587 (14%)	14.9%	3792 (18.5%)	3046 (17.3%)	3.1%
Former smoker	3419 (16.8%)	2805 (17.4%)	614 (14.7%)	7.3%	3451 (16.9%)	2669 (15.2%)	4.5%
Current smoker	6738 (33.1%)	5475 (33.9%)	1263 (30.2%)	7.9%	6785 (33.1%)	5651 (32.2%)	2%
Unknown smoking history	6437 (31.6%)	4717 (29.2%)	1720 (41.1%)	25.2%	6448 (31.5%)	6194 (35.3%)	8%
Hypertension							
No HTN	9510 (46.7%)	7980 (49.4%)	1530 (36.6%)	26.1%	9648 (47.1%)	8144 (46.4%)	1.5%
HTN	6952 (34.2%)	5741 (35.5%)	1211 (28.9%)	14.1%	7061 (34.5%)	5776 (32.9%)	3.4%
Missing BP	3887 (19.1%)	2444 (15.1%)	1443 (34.5%)	46%	3767 (18.4%)	3640 (20.7%)	5.5%
Dyslipidemia							
No dyslipidemia	10,381 (51%)	8353 (51.7%)	2028 (48.5%)	6.4%	10,378 (50.7%)	8607 (49%)	3.3%
Dyslipidemia	7726 (38%)	6069 (37.5%)	1657 (39.6%)	4.2%	7788 (38%)	6626 (37.7%)	0.6%
Unknown	2242 (11%)	1743 (10.8%)	499 (11.9%)	3.6%	2310 (11.3%)	2327 (13.3%)	6.2%
Diabetes mellitus							
No diabetes	16,857 (82.8%)	13,579 (84%)	3278 (78.3%)	14.5%	16,913 (82.6%)	14,099 (80.3%)	5.9%
Diabetes	1175 (5.8%)	872 (5.4%)	303 (7.2%)	7.6%	1210 (5.9%)	1111 (6.3%)	1.7%
Unknown	2317 (11.4%)	1714 (10.6%)	603 (14.4%)	11.5%	2353 (11.5%)	2350 (13.4%)	5.7%
Cardiovascular disease	804 (4%)	564 (3.5%)	240 (5.7%)	10.7%	806 (3.9%)	707 (4%)	0.4%
ART-experienced pre-baseline	15,745 (77.4%)	12,380 (76.6%)	3365 (80.4%)	9.4%	15,841 (77.4%)	13,432 (76.5%)	2.1%
Number of ARVs previously exposed,[c] median (IQR)	5 (3, 8)	5 (3, 8)	6 (3, 9)	18.7%	5 (3, 8)	5 (3, 8)	0.6%
Reason for discontinuation of prior ART regimen							
Patient/physician choice	3357 (16.5%)	2693 (16.7%)	664 (15.9%)	2.1%	3392 (16.6%)	3282 (18.7%)	5.8%
Treatment failure	950 (4.7%)	638 (3.9%)	312 (7.5%)	15.2%	964 (4.7%)	888 (5.1%)	1.5%
Treatment simplification	2972 (14.6%)	2824 (17.5%)	148 (3.5%)	46.7%	3006 (14.7%)	1693 (9.6%)	16.9%
Toxicity	3915 (19.2%)	2780 (17.2%)	1135 (27.1%)	24.1%	3912 (19.1%)	3510 (20%)	2.1%
Unknown	1960 (9.6%)	1376 (8.5%)	584 (14%)	17.3%	1997 (9.8%)	1966 (11.2%)	4.6%
Other (not including pregnancy-related)	3455 (17%)	2751 (17%)	704 (16.8%)	0.5%	3482 (17%)	2975 (16.9%)	0.2%

Abbreviations: RAL: Raltegravir; INSTI: Integrase strand-transfer inhibitor; AMD: Average mean difference; IQR: Inter quartile range; MSMS: Men who have sex with men; IDU: Injecting drug use; CKD: Chronic kidney disease; HTN: Hypertension; BP: Blood Pressure; ART: Antiretroviral therapy; ARV: Antiretroviral drug; TB: Tuberculosis. [a]Participants from countries where collection of ethnicity data is legally prohibited. [b]Reported pregnancy any day within the same or next calendar year, or a pregnancy-related reason for switching off the most recent ART regimen before baseline. [c]Calculated including both ART-experienced and ART-naïve participants.

Table 1: **Unweighted and weighted distributions of participant characteristics at the start of the first INSTI regimen (baseline).**

Predictors of initiating RAL as first INSTI

In feature selection for multivariable logistic regression predicting RAL initiation, 3 out of 34 (8.8%) covariates from the full set were regularised to zero in LASSO regression, indicating no relationship between these risk factors and the outcome, and therefore excluded from the model used to estimate IPTW: history of TB, ART-naïve, and unknown reason for discontinuation of pre-baseline ART regimen. The full results of the multivariable logistic regression are presented in Supplemental Table S2.

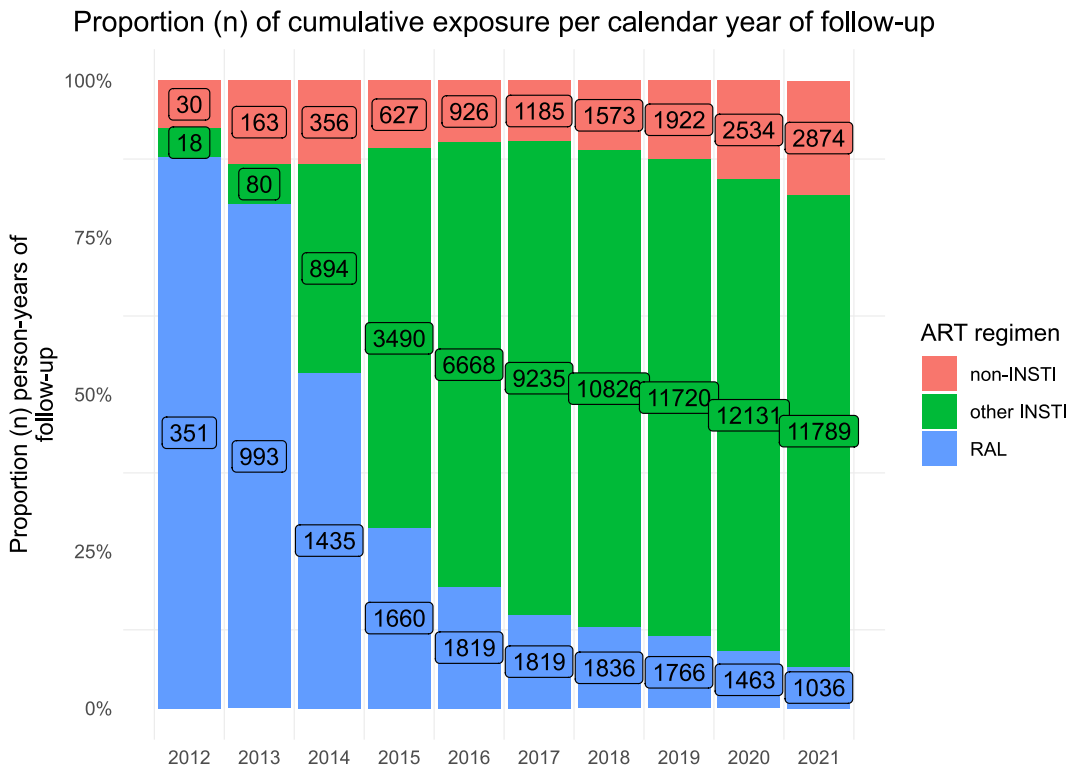

Fig. 2: Distribution of ART exposure among individuals under follow-up after initiating their first INSTI based regimen.

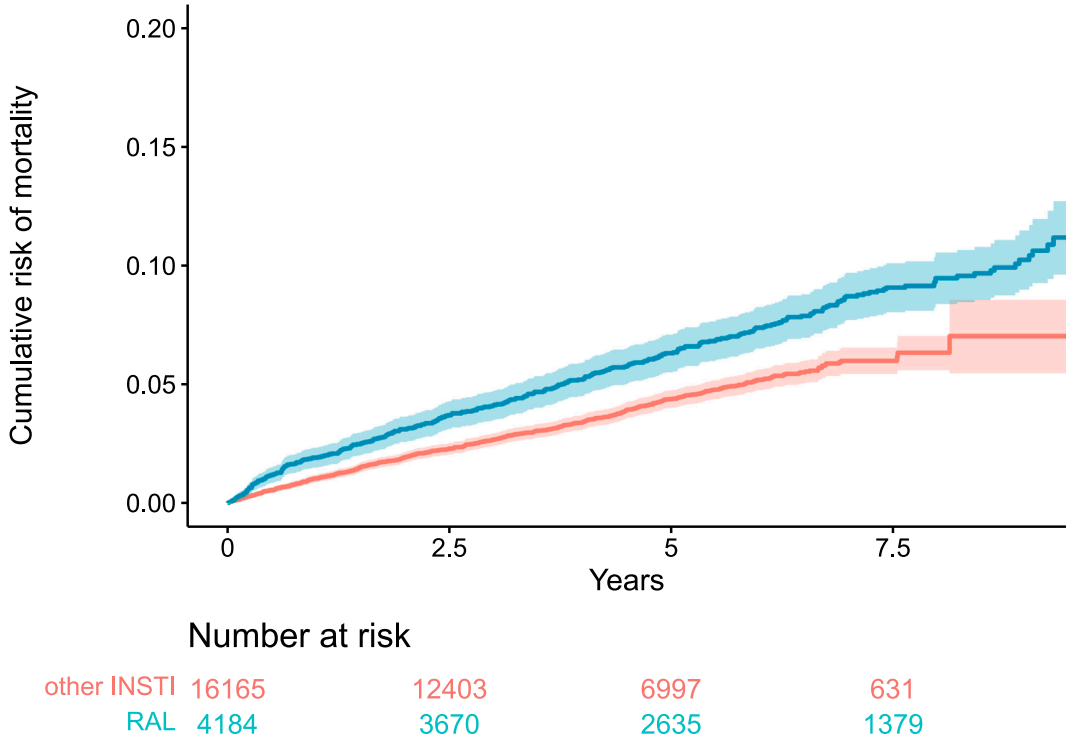

Fig. 3: Kaplan–Meier crude cumulative risk of mortality between use of RAL vs. other INSTI groups.

First INSTI	Full time period	Early (2012–2016)	Late (2017–2021)
All participants	10.1 (9.4, 10.7)[a]	11.8 (10.3, 13.4)	9.6 (8.9, 10.3)
RAL	12.7 (11.3, 14.1)	15.6 (13.1, 18.5)	11.0 (9.4, 12.8)
Other INSTI	9.1 (8.4, 9.9)	8.6 (6.9, 10.5)	9.2 (8.5, 10.0)

Abbreviations: RAL: Raltegravir; INSTI: Integrase strand-transfer inhibitor. [a]Crude mortality rate, not age-standardised.

Table 2: **Age-standardised all-cause mortality rate per 1000 person-years of follow-up (95% Confidence Interval).**

The strongest predictors of starting RAL as first INSTI were treatment simplification as reason for discontinuation of prior ART regimen and time period. Participants who started RAL had more than 80% lower odds of doing so for treatment simplification (adjusted odds ratio (aOR) 0.19; 95% CI 0.16, 0.23), and participants starting their first INSTI in the earlier period (2012–2016) had over four times greater odds of starting RAL than in the later period (2017–2021) (aOR 4.17; 3.85, 4.55).

The clinical characteristics most strongly linked to starting RAL were indication of pregnancy at baseline (aOR 3.87; 95% CI 2.81, 5.32), ESRD (aOR 2.58; 95% CI 1.58, 4.19), HCV positive status (vs. anti-HCV negative: aOR 2.07; 1.82, 2.37), use of chemotherapy near baseline (aOR 1.58; 95% CI 1.01, 2.48), and CVD (aOR 1.58; 95% CI 1.30, 1.91). Higher levels of HIV-VL were also associated with starting RAL as first INSTI, e.g., HIV-VL >100,000 vs. ≤50 aOR 1.27; 95% CI 1.07, 1.51 (see Supplemental Table S2).

Multivariable logistic regressions performed separately in each time period (2012–2016 and 2017–2021) show that, in the later time period, starting RAL was more strongly associated with an indication of pregnancy at baseline (late aOR: 9.08; 95% CI 5.63, 14.64; early aOR: 1.88; 95% CI 1.23, 2.86), ESRD (late aOR: 3.59; 95% CI 1.13, 11.43; early aOR: 2.87; 95% CI 1.65, 5.00), and HCV positive vs. HCV antibody and/or RNA negative (late aOR: 2.28; 95% CI 1.72, 3.02; early aOR: 1.94; 95% CI 1.66, 2.26). Higher baseline HIV-VL was associated with starting RAL in the early time period, but not later. See Supplemental Table S1 for full results multivariable logistic regressions in each time period.

Sensitivity analyses

Among 4604 ART-naïve participants, a total of 136 (3.0%) died during follow-up: 45 (5.5%) of 819 who started RAL as first INSTI and 91 (2.4%) of 3785 who started any other INSTI. Crude mortality rates were higher among ART-naïve participants who started RAL (10.3 per 1000 PYFU; 95% CI 7.5, 13.8) compared to those who started other INSTIs (5.8 per 1000 PYFU; 95% CI 4.6, 7.1). After adjusting for age in Cox-proportional hazards regression, mortality risk among ART-naïve participants was found to be 75% higher in individuals starting RAL as first INSTI: aHR 1.75; 95% CI 1.22, 2.53.

After applying IPTW estimated among ART-naïve participants, covariate balance was similar to the full cohort. There was insufficient evidence for an average

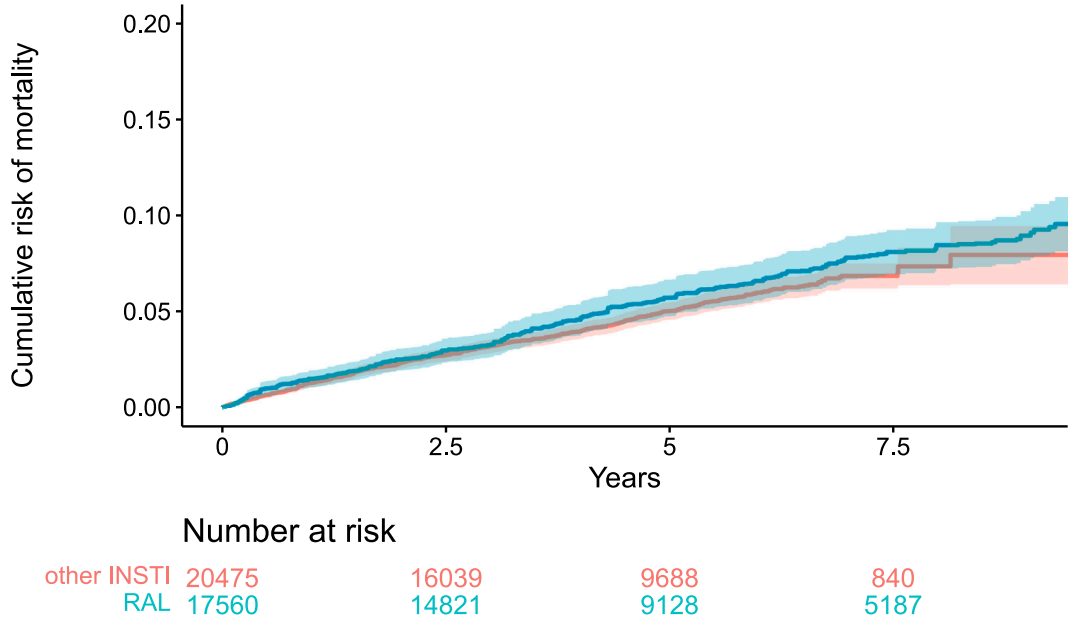

Fig. 4: Kaplan–Meier cumulative risk of mortality between IPTW-weighted use of RAL vs. other INSTI groups. Note: number at risk represents weighted population.

treatment effect on mortality in weighted Cox regression (HR 1.23; 95% CI 0.71, 2.12).

Time to switching off first INSTI differed between participants who started RAL and those who started any other INSTI. In crude Cox regression, people who started RAL switched off earlier (HR 1.62; 95% CI 1.54, 1.69); median time to switch off was 3.66 years (95% CI 3.38, 3.90), compared to 5.77 years (95% CI 5.61, 6.01) among people who started any other INSTI.

Discussion

In this observational study of over 20,000 persons starting their first INSTI during follow-up in RESPOND, RAL use was associated with increased mortality in descriptive crude and age-adjusted analyses. However, after accounting for baseline confounding with IPTW, there was no longer evidence of any significant difference in mortality between participants starting RAL as first INSTI and those starting other INSTIs. Results were consistent when limited to ART-naïve participants.

Compared to a recent analysis in a similar cohort collaboration,[17] this analysis included additional important mortality risk factors at baseline, e.g., ESRD, dyslipidemia, use of chemotherapy, and smoking history. These additional baseline risk factors, along with others, represent important possible confounders in the apparent association between use of RAL and mortality, and likely contribute to the lack of effect shown in this analysis, compared to other findings in the literature.[4,17,19] Though the prevalence of ESRD is relatively low, a clear example of confounding by indication can be found in the strong association between ESRD and starting RAL and the lack of association between RAL and all-cause mortality after accounting for baseline confounding, as RAL can be used for people with HIV with renal impairment without dose adjustments.[7,11,12] Similarly, the association between use of chemotherapy near baseline and starting RAL indicates more confounding by indication, as RAL is also noted for its low potential for drug-drug interactions. The association between initiating RAL and higher levels of HIV-VL at baseline may indicate possible channelling bias, as following the introduction of INSTIs many treatment-experienced people switched to RAL based salvage therapy.[6,10]

The previous evidence in the literature for an association between RAL use and mortality is conflicting. Higher mortality among people with HIV using RAL has been reported in another large international cohort collaboration focussing on first-line ART.[17] Of note, the age-adjusted HR among ART-naïve participants in this current study (starting RAL as first INSTI vs. other INSTI 1.75; 95% CI 1.22, 2.53) was comparable to the multivariable-adjusted hazard ratios reported by Trickey et al. 2022.[17] In a US-based healthcare system cohort, including both first-line ART and ART-experienced participants, an association between RAL use and mortality was reported among the full cohort, but not among solely ART-naïve participants.[4] No difference in mortality between use of RAL-based regimens and EFV-based regimens was shown in a study within the Centers for AIDS Research Network of Integrated Clinical Systems[19] and a meta-analysis of randomised trials found no differences in mortality between INSTI regimens, though there were limited events.[18] In a study focussing on treatment-experienced people with HIV receiving salvage therapy, using another propensity score method to account for baseline confounding, mortality was not associated with use of RAL.[38]

As participant characteristics associated with starting RAL changed over time, RAL use seemed to remain nevertheless associated with mortality risk factors at baseline, shifting from HIV-related mortality risk in the earlier period to non-HIV-specific mortality risk factors in the later period. Associations indicating channelling bias, namely with HIV-VL, were significant over the full period and in the early period, but not in the later period. This reflects well a changing position of RAL in international recommendations for clinical use. At the same time, associations with other mortality risk factors indicating confounding by indication, i.e., ESRD, HCV, and CVD, were all stronger in the later period.

While real world evidence is important for post-registration follow-up of antiretroviral drugs, clinical implementation, and long-term use, the analytical approach remains a challenge. As presented in our work the estimation of average treatment effect using IPTW is still vulnerable to uncontrolled confounding. While covariate balance between RAL and other INSTI groups was very good, not all covariates were balanced. Additionally, as with all observational data, and especially for mortality as an outcome, there may be other unmeasured or unknown confounders that could not be accounted for. While inclusion of many risk factors in the estimation of IPTW is meant to reduce the risk of violating the assumption of no unmeasured confounding, this large number of covariates leads to the likely violation of the positivity assumption, namely that the probability of receiving either treatment must not be 0 or 1 in any given subgroup defined by a combination of covariates. Though the covariate balance between RAL and other INSTI groups was good, likely positivity violation may reduce the accuracy of the estimation of effect.

Calculating IPTW weights based only on baseline risk factors has some limitations, especially comorbidities or drug toxicities that may emerge over the duration of follow-up. However, this approach is similar to other analyses in the literature,[4,17,19,38] allowing for straightforward comparison. This approach could be considered akin to an intent to treat analysis in a randomised controlled trial and has similar limitations

in that we haven't adjusted for any time varying confounding and any effect of RAL on mortality may have been diluted by participants switching to other treatment regimens.

Another limitation of the current analysis is the prevalence of baseline covariates with unknown values. This reduces the ability to draw conclusions about the association between some baseline covariates and starting RAL as first INSTI. This was mostly limited to clinical conditions that may not be tested for without some indication, and no HIV-specific clinical measurements of HIV-VL or CD4 count were missing, as these were necessary inclusion criteria. Inclusion criteria allowed HIV-VL and CD4 measurements within one year prior and three months post RAL or first INSTI initiation to be considered baseline measurements. These post-baseline measurements could potentially lead to immortal time bias, though the proportion of these measurements is low: 1.8% of CD4 measurements and 1.6% of HIV-VL measurements were collected after baseline. Such low prevalence of post-baseline measurements is unlikely to bias the estimate of effect. Unknown baseline covariates may also be interpretable in capturing important indirect information about a participant. For example, unknown laboratory measurements in this cohort often indicate sub-optimal access to care. The generalisability of these findings is limited, as RAL is no longer included among recommended initial regimens for ART-naïve adults in European guidelines.[7] However, RAL is nevertheless included as an alternative initial regimen among ART-naïve adults, and perhaps more crucially, an important option among highly comorbid people with HIV, given the low potential for drug-drug interaction, and usefulness among people with renal failure.[7,11,12]

Strengths of this analysis include the long follow-up time, geographical heterogeneity, large size and wide variety of baseline covariates available for estimating propensity score, and especially the baseline covariates available in this cohort that are not included in other similar investigations. Clinical events in the RESPOND cohort are centrally validated (see Supplemental Text for details), increasing the validity of estimates for those covariates.

In conclusion, in this large and well-characterised cohort we found no significant association between all-cause mortality and use of RAL compared to other INSTIs after accounting for confounding at the time of starting the INSTI. Our findings suggest that prior reports of such an association could have been confounded by indication and channelling bias, most prominently by HCV positive status, chemotherapy near baseline, CVD, and ESRD. While, a large number of potential confounders were accounted for, the results presented are an estimation of average treatment effect using IPTW which is still vulnerable to uncontrolled confounding.

Contributors

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. JB, AC, OD, AG, HG, CH, NJ, JK, KK, CMussini, CMartin, JJV, FW, EW, and RZ were involved in data collection. JR and ET have accessed and verified the data. LP, JR, LR, and ET conceptualised the analyses. HG, NJ, JL, LP, and LR were involved in project administration and steering committees. ET wrote the original draft of the manuscript and all authors contributed to review and editing. The full study group can be found in Supplemental Materials.

Data sharing statement

The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts (please see https://chip.dk/Research/Studies/RESPOND/Study-documents) should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk). The secretariat will direct the proposal to the relevant scientific interest group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definition can be found in the latest version of Standard Operating Procedure for data transfer in RESPOND, EuroSIDA, MISTRAL, and CARE, which is publicly available at https://chip.dk/Research/Studies/RESPOND/Study-documents. For any enquiries regarding data sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk) and Dorthe Raben, Director of Research Coordination (dorthe.raben@regionh.dk).

Declaration of interests

Authors ET, LR, OD, RZ, JK, KK, NJ, JL, LP, and JR have no conflicts of interest to declare. Author CH has received institutional grants, honoraria for lectures, support for travel, and participated on an advisory board for Gilead sciences, Janssen-Cilag, MSD, and ViiV Healthcare. Author HG has participated on an advisory board for Gilead, ViiV, and Merck. Author FW has participated on a data safety monitory board or advisory board for ViiV Healthcare. Author CMussini has received institutional grants from Gilead, honoraria for lectures from ViiV, Filead, Johnson and Johnson, and MSD, support for attending meetings from Gilead, and participated on a data safety monitoring board or advisory board for ViiV, Gilead, and MSD. Author AC has received consulting fees, honoraria for lectures, support for travel, and participated on a data safety monitory board or advisory board for MSD, Gilead Sciences, Jannsen Cilag, and ViiV Healthcare. Author CMartin has received support for attending meetings from MSD Belgium. Author AG has received consulting fees and honoraria for lectures from ViiV, Gilead, Janssen, and MSD, payment for expert testimony from ViiV and Gilead, and support for attending meetings from Gilead. Author JJV has received grants from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), German Federal Ministry of Education and Research (BMBF), Deutsches Zentrum für Luft-und Raumfahrt (DLR), University of Bristol, Rigshospitalet Copenhagen, German Network University Medicine, German Cancer Consortium (DKTK), German Federal Ministry of Health (BMG), and European Union, honoraria for lectures or manuscript writing from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), University Hospital Freiburg/Congress and Communication, Academy for Infectious Medicine, University Manchester, German Society for Infectious Diseases (DGI), Ärztekammer Nordrhein, Ärztekammer Hessen, University Hospital Aachen, Back Bay Strategies, German Society for Internal Medicine (DGIM), Shionogi, Molecular Health, Netzwerk Universitätsmedizin, Janssen, NordForsk, Biontech, APOGEPHA, German Cancer Consortium (DKTK), and University Hospital Oldenburg, support for attending meetings and/or travel from German Centre for Infection Research (DZIF), University Manchester, German Society for Infectious Diseases (DGI), University Hospital Aachen, German Society for Internal Medicine (DGIM), Netzwerk Universitätsmedizin, German Cancer Consortium (DKTK), and participated on a data safety monitoring board or advisory board for Merck/

MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), Academy for Infectious Medicine, University Manchester, German Society for Infectious Diseases (DGI), German Society for Internal Medicine (DGIM), Netzwerk Universitätsmedizin, Janssen, and Biontech. Author JB has received honoraria for lectures from MSD, Gilead, and ViiV and support for travel from MSD and Gilead. Author VV is an employee of ViiV healthcare and owns GSK stock. Author JR is an employee of, and owns stock in, Gilead Sciences. Author SM is an employee of MSD and owns MSD stock. Author JT has participated on the community advisory board for the RBDCOV Project. Author EW has received travel and education arrangements from Gilead, Merck, and ViiV/FSK, consulting fees from ViiV/GSK, honoraria from ViiV/GSK for lectures and from Merck for manuscript writing, support for attending meetings from Gilead, Merck, and ViiV/GSK, and participated on a data safety monitoring board or advisory board for ViiV/GSK.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103521.

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