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Mortality using raltegravir versus other integrase inhibitors in people with HIV in Europe and Australia

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Background

- Integrase inhibitors (INSTI) are widely recommended including for in first-line antiretroviral therapy (ART)
- Raltegravir (RAL) was the first INSTI and is well tolerated, has a low potential drug-drug interactions, and can be used in renal failure.
- RAL is recommended for specific populations of people with HIV, namely those with an intolerance to other non-INSTI antiretrovirals, and as salvage therapy for those failing other drug classes without INSTI resistance
- A prior study among ART-naïve people with HIV (1) found higher all-cause mortality for RAL-based first-line ART compared with other regimens, including dolutegravir (adjusted hazard ratios (aHR) 1.49) and cobicistat boosted elvitegravir (aHR 1.86)
- We investigated all-cause mortality between RAL-based ART vs. other INSTI-based ART in the RESPOND cohort consortium among both ART-naïve and treatment experienced individuals

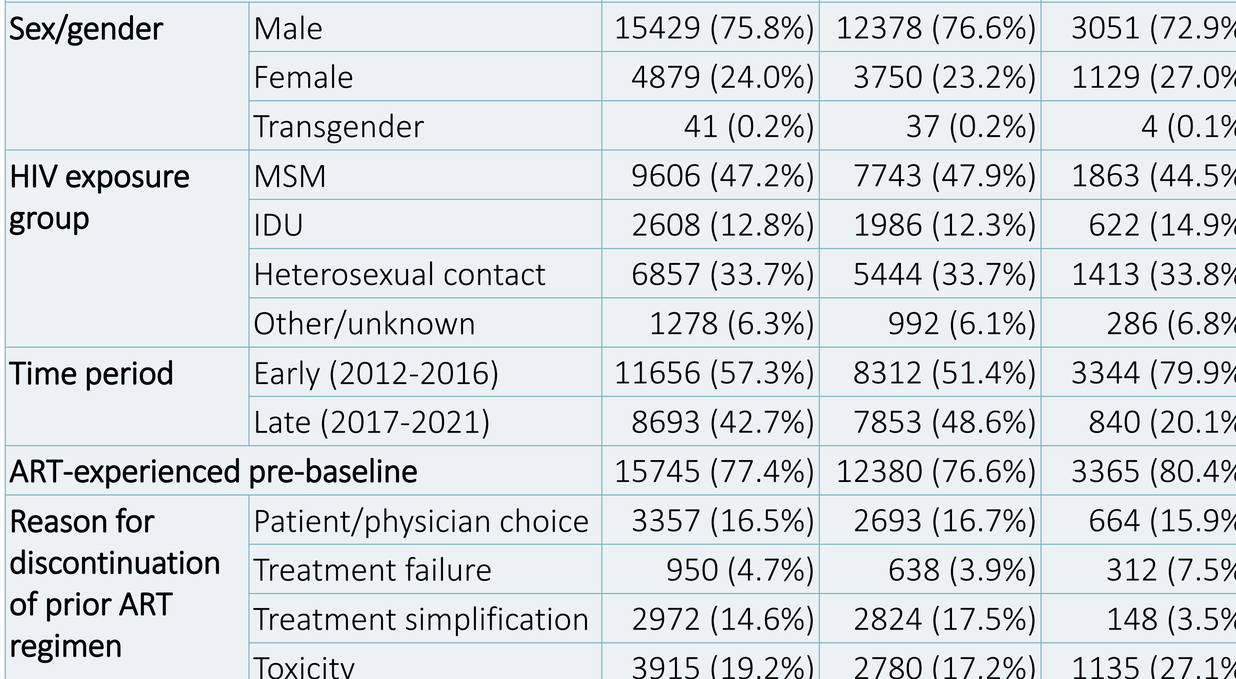
Methods

- Participants in the RESPOND cohort who started their first INSTI between 2012 and 2021 were followed until earliest of death, dropout, loss to follow-up, or administrative censoring (2021-12-31)
- Survival was compared between those starting RAL as their first INSTI vs. any other INSTI using Cox proportional hazards regressions:
  - Adjusting for age
  - Estimating average treatment effect weighted by inverse propensity of treatment weights (IPTW), estimated by covariate balancing propensity score regression
- Participants remained in the same group until end of follow-up
- Predictors of starting RAL were estimated by multivariable logistic regression after feature selection by LASSO penalized regression

Table 1: Baseline characteristics

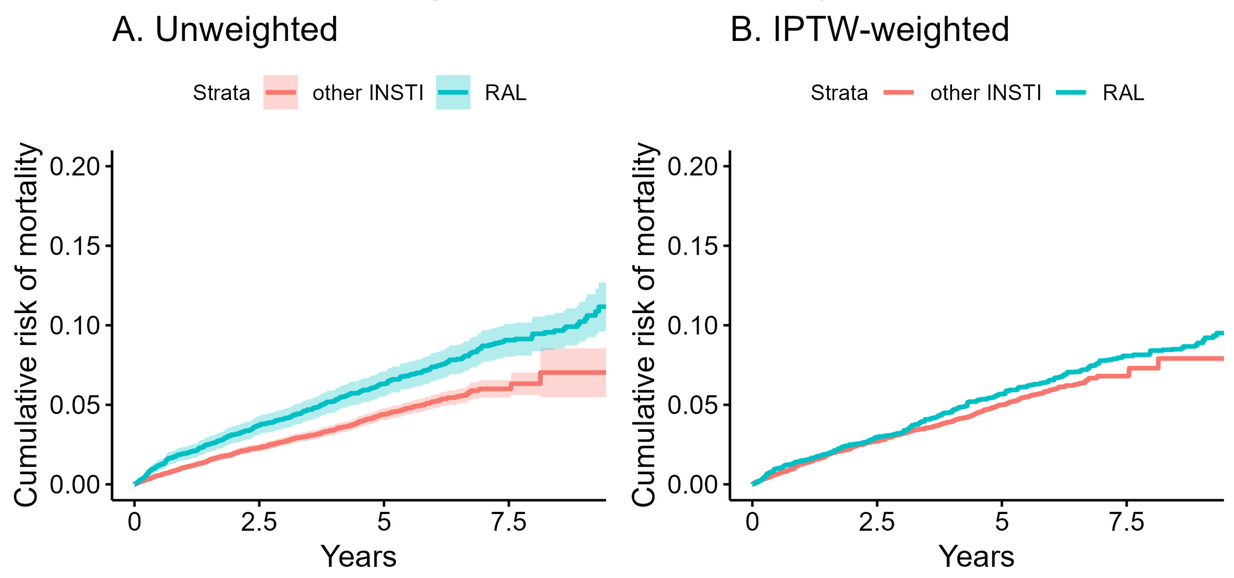
		All Participants N: 20,349	Other INSTI group n: 16,165	RAL group n: 4,184
Age in years (median (IQR))		47 (38, 54)	47 (38, 55)	48 (39, 54)
Sex/gender	Male	15429 (75.8%)	12378 (76.6%)	3051 (72.9%)
	Female	4879 (24.0%)	3750 (23.2%)	1129 (27.0%)
	Transgender	41 (0.2%)	37 (0.2%)	4 (0.1%)
HIV exposure group	MSM	9606 (47.2%)	7743 (47.9%)	1863 (44.5%)
	IDU	2608 (12.8%)	1986 (12.3%)	622 (14.9%)
	Heterosexual contact	6857 (33.7%)	5444 (33.7%)	1413 (33.8%)
	Other/unknown	1278 (6.3%)	992 (6.1%)	286 (6.8%)
Time period	Early (2012-2016)	11656 (57.3%)	8312 (51.4%)	3344 (79.9%)
	Late (2017-2021)	8693 (42.7%)	7853 (48.6%)	840 (20.1%)
ART-experienced pre-baseline		15745 (77.4%)	12380 (76.6%)	3365 (80.4%)
Reason for discontinuation of prior ART regimen	Patient/physician choice	3357 (16.5%)	2693 (16.7%)	664 (15.9%)
	Treatment failure	950 (4.7%)	638 (3.9%)	312 (7.5%)
	Treatment simplification	2972 (14.6%)	2824 (17.5%)	148 (3.5%)
	Toxicity	3915 (19.2%)	2780 (17.2%)	1135 (27.1%)
	Unknown	1960 (9.6%)	1376 (8.5%)	584 (14.0%)
	Other	3455 (17.0%)	2751 (17.0%)	704 (16.8%)
First INSTI	Bictegravir	1768 (8.7%)	1768 (10.9%)	0 (0.0%)
	Cabotegravir	25 (0.1%)	25 (0.2%)	0 (0.0%)
	Dolutegravir	10962 (53.9%)	10962 (67.8%)	0 (0.0%)
	Elvitegravir	3410 (16.8%)	3410 (21.1%)	0 (0.0%)
	Raltegravir	4184 (20.6%)	0 (0.0%)	4184 (100.0%)

Figure 1: Proportion of cumulative exposure per calendar year of follow-up



References: 1. Trickey A et al. Associations of modern initial antiretroviral drug regimens with all-cause mortality in adults with HIV in Europe and North America: a cohort study. The Lancet HIV. 2022;9(6):e404-e13.

Figure 2: Cumulative risk of mortality



Covariate balancing propensity score covariates: age, sex/gender, geographic region, race/ethnicity, HIV exposure group, time period (2012-2016 vs. 2017-2021), indication of pregnancy at baseline, CD4 cell count, CD4 nadir, HIV viral load, prior AIDS diagnosis, AIDS-defining malignancy, Non-AIDS-defining malignancy, use of chemotherapy near baseline, TB history, number of prescribed medications, liver fibrosis score, hepatitis C status, end-stage liver disease, end-stage renal disease, hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, ART-naïve status at baseline, number of previously exposed antiretrovirals, and each individual reason for discontinuation of prior ART regimen: patient/physician choice, treatment failure, treatment simplification, toxicity, unknown, and other (not including pregnancy-related).
Covariates excluded from multivariable logistic regression: history of TB, ART-naïve, and unknown reason for discontinuation of pre-baseline ART regimen

Results

- See table 1 for baseline characteristics and figure 1 for the proportion of cumulative exposure per calendar year to RAL-based ART, other-INSTI-based ART, and non-INSTI based ART
- See table 2 for deaths, follow-up time, and mortality rates in the full time period, early (2012-2016) and late (2017-2021)
- Survival analysis: mortality after starting RAL vs. other INSTI
  - Starting RAL as first INSTI was associated with increased mortality when controlling for age: **aHR 1.43; 95%CI 1.25, 1.65** (figure 2A)
  - After applying IPTW, there was no difference in mortality between starting RAL and other INSTIs: **HR 1.13; 95%CI 0.93, 1.34** (figure 2B)
    - Among ART-naïve: HR 1.20; 95%CI 0.67, 2.03
- Multivariable logistic regression: predictors of starting RAL
  - CD4 nadir (≤200 cells/mm^3 vs. >500 aOR 1.41; 95%CI 1.04, 1.90)
  - HIV viral load (>100,000 copies/mL vs. ≤50 aOR 1.3; 95%CI 1.10, 1.55)
  - End-stage renal disease (requiring dialysis for >3 months and/or kidney transplantation) (aOR 2.58; 95% CI 1.58, 4.20)
  - Cardiovascular disease (aOR 1.57; 95%CI 1.30, 1.90)
  - Hepatitis C (HCV) antibody and/or RNA positive status (vs. anti-HCV negative aOR 2.07; 95%CI 1.81, 2.36)

Table 2: Person-years of follow-up (PYFU) and age-standardized mortality rate per 1,000 PYFU per time period

Time Period	First INSTI	Deaths	PYFU	PYFU Median (IQR)	Age-standardized mortality rate (95%CI)
Full (2012-2021)	All	938	94,677	4.8 (2.9, 6.4)	10.1 (9.4, 10.7)
	RAL	312	24,480	4.6 (2.7, 6.1)	12.7 (11.3, 14.1)
	Other INSTI	626	70,197	6.2 (3.7, 8.1)	9.1 (8.4, 9.9)
Early (2012-2016)	All	229	19,875	1.5 (0.8, 2.4)	11.8 (10.3, 13.4)
	RAL	139	8,844	2.7 (1.5, 3.8)	15.6 (13.1, 18.5)
	Other INSTI	90	11,031	1.3 (0.7, 1.9)	8.6 (6.9, 10.5)
Late (2017-2021)	All	709	74,802	4.5 (2.7, 5.0)	9.6 (8.9, 10.3)
	RAL	173	15,636	4.7 (3.4, 5.0)	11.0 (9.4, 12.8)
	Other INSTI	536	59,166	4.5 (2.6, 5.0)	9.2 (8.5, 10.0)

Limitations

Estimation of average treatment effect (IPTW-weighted Cox regression) is still vulnerable to uncontrolled confounding

- While covariate balance between RAL and other INSTI groups was very good, not all covariates were balanced
- There may be other unmeasured or unknown confounders that could not be accounted for, e.g. socioeconomic status and current drug or alcohol abuse

Conclusions

While there was an age-adjusted association between starting RAL and mortality, this was no longer the case after accounting for confounding at baseline using IPTW

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RESPOND Scientific Interest Groups https://chip.dk/Research/Studies/RESPOND/SIGs
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