ASSOCIATIONS OF MODERN INITIAL ANTIRETROVIRAL DRUG REGIMENS WITH ALL-CAUSE MORTALITY

00764

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BACKGROUND

- Regimens including integrase strand inhibitors (INSTIs) are now the most commonly used for persons with HIV (PWH) starting antiretroviral therapy (ART)
- Trials and observational studies have compared virological failure among individuals receiving INSTI-based or other regimens
- However, few data are available on mortality among PWH treated with INSTIs in routine care
- **AIM: To compare prognosis for virological failure and all-cause mortality between different INSTI-based and non-INSTI-based ART regimens, using recent multi-country cohort data**

METHODS

- Eligible PWH started ART in Europe and North America between 2013 and 2018.
- We used data from 20 HIV cohort studies (the Antiretroviral Therapy Cohort Collaboration (ART-CC) and UK Collaborative HIV Cohort)
- We studied the most-used third (additional to nucleoside reverse transcriptase inhibitor) antiretroviral drugs during 2013-18: rilpivirine, darunavir, raltegravir, elvitegravir, dolutegravir, and efavirenz
- Virologic failure was defined as the first occurrence of a viral load ≥400 copies/ml at least 6 months after ART initiation
- Adjusted hazard ratios (aHRs) were estimated using Cox models stratified by ART start year and cohort
- **Variables included** were CD4 count, viral load, sex, age, AIDS event status, mode of HIV acquisition, CD8 count, alanine aminotransferase, aspartate aminotransferase, haemoglobin, creatinine, hepatitis C virus infection, hepatitis B virus infection, prior non-AIDS defining malignancy, prior cardiovascular conditions, and ethnicity/origin.
- Regimen switching was not accounted for, but Kaplan-Meier curves displaying the cumulative incidence of switching from initial ART regimen up to 3 years after starting ART were plotted
- For the outcome of mortality, sensitivity analyses were performed:
  - Adjusting for potentially informative loss to follow-up (LTFU) by weighting the analysis by the inverse probability of LTFU over time
  - Looking at the outcomes across the separate time periods (2013-15 and 2016-18)

TABLE: Hazard ratios (95% CIs) for mortality for each 3rd drug comparison, using multiple imputation to account for missing data.

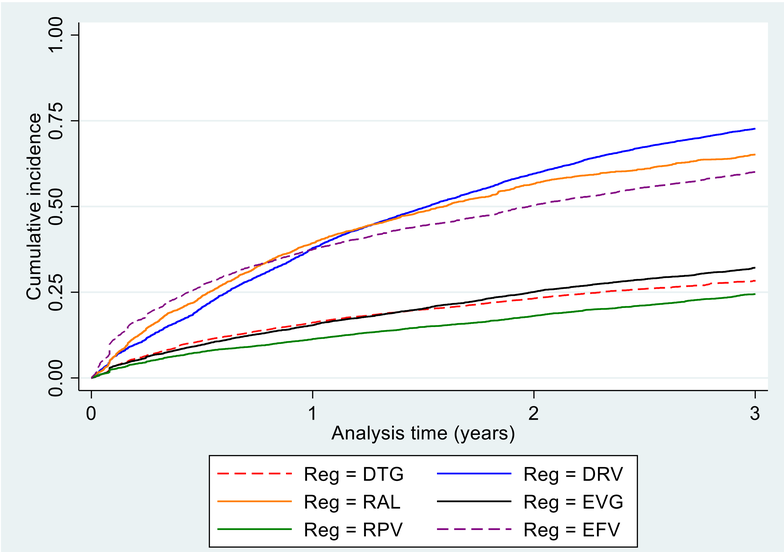
Analysis	Mortality	Virologic failure
RPV vs DTG	0.78 (0.55-1.10)	1.31 (1.16-1.48)
DRV vs DTG	0.98 (0.77-1.25)	1.50 (1.35-1.66)
RAL vs DTG	1.49 (1.15-1.94)	1.60 (1.41-1.81)
EVG vs DTG	0.79 (0.60-1.05)	1.39 (1.23-1.56)
EFV vs DTG	0.75 (0.53-1.07)	1.56 (1.38-1.75)
RPV vs EVG	0.93 (0.68-1.28)	0.94 (0.85-1.05)
DRV vs EVG	1.17 (0.92-1.50)	1.08 (0.99-1.19)
RAL vs EVG	1.86 (1.43-2.42)	1.15 (1.02-1.30)
EFV vs EVG	0.87 (0.64-1.18)	1.12 (1.01-1.25)
DRV vs RPV	1.19 (0.91-1.57)	1.15 (1.04-1.27)
RAL vs RPV	1.99 (1.49-2.66)	1.22 (1.08-1.38)
EFV vs RPV	0.93 (0.68-1.27)	1.19 (1.07-1.33)
RAL vs DRV	1.62 (1.33-1.98)	1.06 (0.96-1.18)
EFV vs DRV	0.82 (0.63-1.07)	1.04 (0.94-1.14)
RAL vs EFV	2.12 (1.60-2.81)	1.03 (0.91-1.15)

Rilpivirine (RPV), Darunavir (DRV), Raltegravir (RAL), Elvitegravir (EVG), Dolutegravir (DTG), Efavirenz (EFV).

RESULTS

- 50,722 ART-naïve PWH were included (21% female; median age 38)
- 1,081 (2.1%) died during 151,651 person-years follow-up (median 3.0 years)
- **There was little evidence that mortality rates differed between PHW starting ART on regimens containing dolutegravir, elvitegravir, rilpivirine, darunavir, or efavirenz as the third drug (see table)**
- **However, mortality was higher for PWH on raltegravir-containing regimens compared with dolutegravir (aHR 1.49 [95%CI: 1.15-1.94]), elvitegravir (1.86 [1.43-2.42]), rilpivirine (1.99 [1.49-2.66]), darunavir (1.62 [1.33-1.98]), and efavirenz- (2.12 [1.60-2.81]) containing regimens.**
- Results were similar for analyses with mortality as the outcome in which different assumptions were made about missing data, when inverse weighting was used for the probability of LTFU and findings were consistent across the time periods 2013-15 and 2016-18
- Rates of virological failure were lower among PWH starting ART on dolutegravir than those starting on other third drugs, whilst rates were lower on elvitegravir than raltegravir and efavirenz, and on rilpivirine compared to darunavir, raltegravir, and efavirenz.
- Cumulative proportions of switching 3 years after starting ART were highest for PWH starting on efavirenz, raltegravir, and darunavir, and were lowest for PWH starting ART on dolutegravir, elvitegravir, and rilpivirine (see figure)

FIGURE: Kaplan-Meier estimates of the cumulative incidence of switching from starting ART regimen within the first 3 years of starting ART, stratified by regimen



CONCLUSIONS

- This large study of PWH starting ART since the introduction of INSTIs found little evidence that mortality rates differed between most first-line ART regimens.
- However, starting on raltegravir-based regimen was associated with higher mortality.
- The results were consistent across various sensitivity analyses
- While unmeasured confounding cannot be excluded as an explanation for our findings, virological benefits of first-line INSTI-based ART may not translate to differences in mortality.

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