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Contributions: JACS and AT conceived and designed the study. AT, LZ, and SI combined, checked, and cleaned the datasets (including dataset verification). Individual cohort representatives (MJG, FB, GB, AC, MC, PC, HC, PD, SG, JG, NO, MP, MR, PR, CR, MR, GS, MJS, CS, MS, TRS, and CAS) contributed to derivation, cleaning, and provision of cohort data, and confirmed the associations of ART regimens within individual cohorts. AT conducted all statistical analyses. AT and JACS drafted the manuscript. All authors contributed to the interpretation of data and critical revisions of the manuscript for important intellectual content. At least two named authors have accessed and verified the data (AT, LZ, and SI).

Summary

Background

Over the last decade regimens including integrase strand inhibitors (INSTIs) have become the most commonly used for persons with HIV (PWH) starting antiretroviral therapy (ART). While trials and observational studies have compared virological failure on INSTI-based with other regimens, few data are available on mortality among PWH treated with INSTIs in routine care. Therefore, we compared all-cause mortality between different INSTI- and non-INSTI-based regimens among adult PWH starting ART from 2013-18.

Methods

Analyses used data on PWH in Europe and North America from the Antiretroviral Therapy Cohort Collaboration (ART-CC) and UK Collaborative HIV Cohort (UK CHIC). We studied the most-used third (additional to nucleoside reverse transcriptase inhibitor) antiretroviral drugs during 2013-18: rilpivirine, darunavir, raltegravir, elvitegravir, dolutegravir, efavirenz, and others. Adjusted (for clinical and demographic characteristics, co-morbid conditions, and other drugs in the regimen) hazard ratios (aHRs) for mortality were estimated using Cox models stratified by ART start year and cohort, with multiple imputation of missing data.

Findings

Of 62,500 ART-naïve PWH starting ART (20% female; median age 38), 1,243 (2.0%) died during 188,952 person-years of follow-up (median 3.0 years). There was little evidence that mortality rates differed between regimens with dolutegravir, elvitegravir, rilpivirine, darunavir, or efavirenz as the third drugs. However, mortality was higher for raltegravir 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]) regimens. Results were similar for analyses making different assumptions about missing data and consistent across the time periods 2013-15 and 2016-18. Rates of virological suppression were higher for dolutegravir than other third drugs.

Interpretation

This large study of patients starting ART since the introduction of integrase strand inhibitors found little evidence that mortality rates differed between most first-line ART regimens, however, raltegravir-based regimens were associated with higher mortality. While unmeasured confounding cannot be excluded as an explanation for our findings, virological benefits of first-line integrase strand inhibitors-based ART may not translate to differences in mortality.

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Research in context

Evidence before this study

We identified papers that studied associations with mortality among persons with HIV (PWH) starting different antiretroviral therapy (ART) regimens by searching PubMed for "mortality HIV regimen integrase" up to 24th of July 2021. Randomised controlled trials (RCTs) have found strong evidence that integrase strand inhibitor (INSTI)-based regimens (raltegravir, elvitegravir, and dolutegravir) were non-inferior or superior in terms of virological failure compared with various non-nucleotide reverse-transcriptase inhibitor (NNRTI) and protease inhibitor (PI)-based regimens. An observational study by the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort found that fewer PWH starting antiretroviral therapy (ART) on dolutegravir-based regimens had virological failure than those starting on other INSTI-based regimens, or non-INSTI-based regimens. The UK Collaborative HIV Cohort (UK CHIC) Study found that virological failure was more common among PWH starting on modern PI-based regimens compared with modern NNRTI-based regimens. However, there has been limited research on associations of modern regimens with mortality. A 2007-2013 study by the Kaiser Permanente cohort observed higher mortality for PWH on raltegravir than on other regimens. A 2007-2015 study by CNICS found similar rates of AIDS-defining illness or death among PWH starting ART on raltegravir- and efavirenz-based regimens. A meta-analysis of randomized trials by Kanters et al. reported that low event rates limited the quality of evidence about mortality, but found differences in rates of virological failure, with raltegravir having higher rates than most other regimens.

Added value of this study

Our study included 62,500 ART-naïve PWH who started ART from 2013-2018 in 21 cohorts spanning 12 countries in Europe and North America. In analyses adjusting for clinical and demographic characteristics (including co-morbid conditions) and other drugs in the regimen, all-cause mortality rates among PWH starting ART were similar for most third drugs. However, there was higher mortality among PWH starting ART on raltegravir-based regimens compared with dolutegravir- (adjusted Hazard Ratio: 1.49 [95% confidence interval: 1.15-1.94]), elvitegravir- (1.86 [95%CI: 1.43-2.42]), rilpivirine- (1.99 [95%CI: 1.49-2.66]), darunavir- (1.62 [95%CI: 1.33-1.98]), and efavirenz- (2.12 [95%CI: 1.60-2.81])-based regimens.

Implications of all the available evidence

Among PWH starting ART between 2013 and 2018, starting ART on raltegravir-based regimens was associated with higher mortality compared with other regimens, consistent with the Kaiser Permanente study, but not the CNICS study, which did not find higher mortality for PWH on raltegravir-based regimens. More rapid virological suppression on dolutegravir and other integrase inhibitors may not translate into mortality benefits. However, confounding by indication cannot be excluded, although we controlled for a wide range of prognostic factors likely to influence regimen choice.

Introduction

The prognosis of persons with HIV (PWH) treated with highly active antiretroviral therapy (ART) has improved since ART was first introduced in the mid-1990s(1, 2). Improvements have been attributed to a range of factors including the availability of improved drug regimens that are easier to take, are less toxic, have fewer side effects, have less potential for drug-drug interactions, and are less susceptible to resistance. These all contribute to the better adherence to, potency, and durability of more modern compared with older ART regimens.

The introduction of integrase strand inhibitors (INSTIs) in 2007 was an important milestone in the history of ART(3). Most patients now start ART on INSTI-based regimens(4, 5), following positive results from randomised controlled trials (RCTs)(6-17). These demonstrated superiority or non-inferiority of INSTI-based regimens for virological failure compared with other regimens such those containing efavirenz (a non-nucleoside reverse transcriptase inhibitor [NNRTI]), atazanavir or darunavir (both protease inhibitors [PIs])(6-17).The most commonly used INSTIs over the last decade have been raltegravir, elvitegravir, and dolutegravir, which became available in that order across North America and Europe.

Whilst there has been research into the incidence of virological failure on INSTI-based regimens(18, 19), there have been few reports to date on mortality among PWH receiving treatment with INSTIs in routine clinical care. Choice of regimen by clinicians and patients will be due to factors including patients' perceived likely adherence, comorbidities, regimen tolerability, pill burden, and toxicity. Therefore, virological failure outcomes observed in RCTs may not be reflected in longer-term mortality patterns observed in the wider clinical population.

The aim of this study is to compare the prognosis on different INSTI-based and non-INSTI-based ART regimens, using recent (2013 onwards) multi-country cohort data and adjusting for potential confounding variables.

Methods

Study design and population

Data were combined from 21 European and North American HIV cohort studies of PWH from the Antiretroviral Therapy Cohort Collaboration (ART-CC))(20) and the UK Collaborative HIV Cohort (UK CHIC)(21). The included cohorts are listed on the first page of the supplementary materials. Analyses were restricted to ART-naïve PWH starting ART regimens containing at least three drugs during or after 01/01/2013, when integrase inhibitor regimens became widely available, and up to 2018 (to ensure up to three years potential subsequent follow up). Eligible participants were aged ≥16 years old when starting ART and had no prior exposure to ART medications. Included participants had a CD4 count and HIV-1 RNA viral load measurement within a window of one month before and one week after starting ART. We excluded PWH who started ART with an HIV-1 RNA viral load value of ≤50, because they may not have been ART-naïve.

Data sources

Ethics committees or institutional review boards approved the individual cohorts, which used standardised data collection methods, and regularly followed-up patients. Cohorts gathered information on mortality through linkage with vital statistics agencies and hospitals or physician report, and the active follow-up of participants.

We studied the most frequently used third (additional to nucleoside reverse transcriptase inhibitors [NRTIs]) antiretroviral drugs during 2013-18: rilpivirine, darunavir, raltegravir, elvitegravir, dolutegravir, efavirenz, and others. The NRTI drug pairs were stratified as: emtricitabine and tenofovir disproxil fumarate (FTC/TDF), lamivudine and abacavir (3TC/ABC), emtricitabine and tenofovir alafenamide (FTC/TAF), and others.

The demographic and biomarker variables at ART start considered in analyses were: CD4 cell count (cells/μL), HIV-1 RNA viral load (copies/mL), sex, age (years), HIV acquisition risk group, CD8 cell count (cells/μL), alanine aminotransferase (ALT, u/L), aspartate aminotransferase (AST, u/L), haemoglobin (g/dL), creatinine (mg/dL), hepatitis C virus (HCV) RNA positive, hepatitis B surface antigen (HbSAg) positive), AIDS event status (no AIDS events, had an AIDS event ever, had a tuberculosis or other mycobacterial infection in the last year, had an AIDS-defining malignancy [ADM] in the last year), prior non-AIDS defining malignancy (NADM), prior cardiovascular events (acute myocardial infarctions and invasive cardiovascular procedures), and ethnicity/geographic origin amalgamated into one ethnicity variable (described on the first page of the supplementary materials). The AIDS event status variable was created as discussions with clinicians indicated that recent mycobacterium, tuberculosis, or ADMs might affect clinician prescribing.

HIV acquisition risk activity was categorised as men who have sex with men (MSM), injection drug use (IDU), heterosexual intercourse, and other. Ethnicity/geographic origin was categorised as white, black, Hispanic, Asian, other, and unknown. Variables at regimen start included: viral load categorised as 0-9999, 10000-99999, and ≥100000 copies/mL, age as 16-29, 30-39, 40-49, 50-59, and ≥60 years, CD4 cell count as 0-49, 50-99, 100-199, 200-349, 350-499, and ≥500 cells/μL, CD8 cell count as 0-399, 400-799, 800-1199, ≥1200 cells/μL, and missing, ALT as 0-9, 10-29, 30-49, ≥50 u/L, and missing, AST as 0-19, 20-39, ≥40 u/L, and missing, haemoglobin as 0-9, 10-14, 15-19, ≥20 g/dL, and missing, creatinine as 0-0.4, 0.5-0.74, 0.75-0.99, ≥1 mg/dL, and missing. The categories for CD8, ALT, AST, haemoglobin, and creatinine were chosen through examination of the distribution of the data, whilst viral load and CD4 were categorised as in previous ART-CC analyses. The other variables were binary variables, with an extra category for missing data where necessary.

As the availability of demographic and biomarker variables varied across these clinical cohorts, they were grouped as either i) "main" variables that were available for all patients from all cohorts: CD4, viral load, sex, age, and AIDS event status; or ii) "additional" variables: transmission group, CD8, ALT, AST, haemoglobin, creatinine, HCV, HBV, prior NADM, prior cardiovascular conditions, ethnicity/origin. Five cohorts were excluded from analyses including additional variables because their data were more than 70% unavailable for at least one additional variable.

Statistical analysis

Hazard ratios for all-cause mortality comparing different initial ART regimens were estimated using Cox models stratified by year of ART start and cohort and using the following analyses:

1) Unadjusted models.
2) Adjusted for the main variables, including all cohorts.
3) Adjusted for the main variables, restricted to cohorts providing additional variables.
4) Adjusted for main and additional variables, restricted to cohorts providing additional variables.

As predictors of ART regimen choice evolved rapidly between 2013 and 2018, we conducted further analyses in which the association of confounders with mortality was modelled separately in two time periods:

5) As in analysis 4, separately for ART start years 2013-15 and 2016-2018.
6) Inverse-variance weighted meta-analyses of hazard ratios for 2013-15 and 2016-18 from analysis 5.

For analyses 4-6 multiple imputation was performed on the variables with missing data (25 imputed datasets). The following variables required imputation: CD8, ALT, AST, haemoglobin, creatinine, transmission mode, HCV, HBV, cardiovascular events, and ethnicity/origin. The continuous variables were log transformed before imputation, and quadratic terms of the log-transformed variables were included in the imputations. Imputation was done via linear regression for numerical variables, logistic regression for binary variables and multinomial regression for categorical variables. The variables included in each imputation regression were those included in the main and additional variable-sets, as well as ART start year (but not the regimen), death, cohort, and the Nelson-Aalen estimate of the cumulative hazard function. After imputation, the continuous variables were exponentiated and categorised as before (e.g., CD8 count: 0-399, 400-799, 800-1199, ≥1200 cells/μL). Results from imputed datasets were combined using Rubin's rules(22). In sensitivity analyses, we performed analyses 4-6 but with a dummy variable for missing data instead of using multiple imputation. In a sensitivity analysis, we adjusted for potentially informative loss to follow up (LTFU) by weighting the analysis by the inverse probability of LTFU over time. The weights were derived by splitting the data by month of follow up and using a pooled logistic regression model with LTFU as the outcome, adjusting for the main and additional variables, as well as cohort, year of ART start, and months after ART start (using cubic splines with 3 knots).

In the analyses with mortality as the outcome, only the initial regimen was considered, and subsequent regimen switching was not accounted for in the models.

We plotted Kaplan-Meier curves showing the incidence of LTFU on each regimen.

In a sensitivity analysis, we investigated differences in mortality rates between starting regimens for those not presenting late for ART initiation (defined as CD4≥350, no prior AIDS, and HIV-1 RNA viral load<100,00) and those presenting late for ART initiation. This analysis adjusted for "main" and "additional" variables, restricted to cohorts providing additional variables, and used multiple imputation.

Kaplan-Meier curves were used to display the cumulative incidence of switching from the initial ART regimen up to 3 years after starting ART according to regimen. This analysis did not include UK CHIC as data on ART switches had not been requested. Censoring was at the earliest of first regimen switch, loss to follow-up, administrative censoring, or three years after starting ART, or death. PWH did not have to be on a regimen for a minimum length of time to be included.

Using Fine and Gray's competing risks regression models adjusting for time to death, we investigated the time to first viral suppression after ART initiation, comparing rates between ART regimens containing different drugs. This endpoint was chosen for comparability with RCTs comparing initial ART regimens. Viral suppression was defined as an HIV-1 RNA viral load ≤50 copies/mL. The analysis adjusted for the "main" and "additional" variables and was restricted to cohorts providing additional variables, whilst using dummy variables for missingness. We also conducted a sensitivity analysis examining time to first virological failure, defined as the occurrence of an HIV-1 RNA viral load ≥400 copies/mL at least 6 months after ART initiation.

Analyses were performed using Stata version 16.1.

Role of the funding source

The funders had no role in the collection, analysis or interpretation of data, report writing, or the decision to submit this study for publication.

Results

In total, 62,500 PWH were included in the analyses, with characteristics at ART start shown in table 1 and supplementary table 1, stratified by the third drug of the ART regimen. A fifth (12,422; 20%) of the included PWH were female and the median age at the start of ART was 38 (interquartile range: 30-48) years. Only 162 (2%) of PWH starting on dolutegravir-containing regimens had a CD4 count <100, which was lower than for all other regimens. Similarly, 3072 (34%) of PWH starting on dolutegravir had viral loads <10000 (copies/mL), which was higher than for the other regimens. 158 (3%) of PWH starting on raltegravir had previously had an NADM and 243 (5%) had recently had TB, both higher than for other regimens.

Table 2 shows the numbers of PWH starting ART with each third ART drug regimen stratified by ART start period (supplementary table 2 gives this information by ART start year). 9120 (15%) of PWH started ART with rilpivirine as their third ART drug, 11,322 (18%) with darunavir, 5,261 (8%) with raltegravir, 10,673 (17%) with elvitegravir, 13,249 (21%) with dolutegravir, 6,752 (11%) with efavirenz, and 6,123 (10%) with others. The percentage of PWH starting ART with each of these third drugs increased between 2013 and 2018 for elvitegravir (from 5038, 13%, in 2013-15 to 5635, 23%, in 2016-18) and dolutegravir (from 3876, 10%, in 2013-15 to 9373, 39% in 2016-18) and decreased for rilpivirine (6988, 18%, in 2013-15 to 2132, 9%, in 2016-18), efavirenz (6081, 16%, in 2013-15 to 671, 3%, in 2016-18), and other regimens (5107, 13%, in 2013-15 to 1016, 4%, in 2016-18). Most regimens (29,925; 78%) started during 2013-15 had FTC/TDF as the other components, but this dropped to 12,046 (50%) between 2016-2018 (supplementary table 2). FTC/TAF were the additional regimen components for just 1,200 (3%) of PWH between 2013-15, increasing to 5,251 (22%) between 2016-18. 5567 (15%) regimens started between 2013-15 included 3TC/ABC, rising to 6,284 (26%) between 2016-18.

The cumulative proportions of switching from the initial ART regimen within the first 3 years of starting ART are shown in figure 1. The cumulative proportions of switching by 3 years after starting ART were highest for PWH starting ART on efavirenz, raltegravir, and darunavir (all with <50% remaining on the regimens), and were lowest for PWH starting ART on dolutegravir, elvitegravir, and rilpivirine (all with approximately 75% remaining on the regimens).

Overall, 1,243 of the participants died during follow-up (table 2) of 188,952 person-years (median follow-up: 3.0 years), giving a mortality rate per 1000 person-years of 6.6 (95%CI: 6.2-7.0). The median follow-up time varied from 1.9 years for dolutegravir to 4.2 years for elvitegravir. The mortality rates per 1000 person-years were 15.0 (95% CI: 13.2-17.1) for raltegravir, 7.7 (6.9-8.6) for darunavir, 7.7 (6.7-8.8) for dolutegravir, 6.9 (5.9-8.1) for other regimens, 5.0 (4.2-6.0) for efavirenz, 4.8 (4.0-5.6) for elvitegravir, and 2.9 (2.4-3.5) for rilpivirine. Supplementary figure 1 shows the cumulative incidence of LTFU for the different regimens. LTFU was lowest among those on efavirenz-based regimens, and otherwise broadly similar across the regimens.

Table 3 shows associations between ART regimen and all-cause mortality. Adjusted hazard ratios (aHRs) were generally substantially attenuated towards the null compared with crude hazard ratios. Estimated hazard ratios did not change substantially after further restriction to the cohorts providing additional variables, when additionally adjusting for the additional variables, or when meta-analysing the analyses across time periods. Results were also similar in sensitivity analyses using dummy variables where data were missing, instead of multiple imputation (supplementary table 3). In analyses weighted by the inverse probability of loss to follow up, the association of raltegravir-based regimens with higher mortality compared to other regimens remained, while most odds ratios comparing other pairs of regimens were attenuated towards 1 (supplementary table 4).

In the meta-analyses across time periods (the most completely adjusted analyses), there was little evidence of lower mortality when starting rilpivirine- compared with dolutegravir-containing ART (aHR 0.78; 95%CI: 0.55-1.10). Mortality was similar comparing darunavir to dolutegravir (aHR 0.98; 0.77-1.25). There was little evidence of differences in mortality comparing rilpivirine- with elvitegravir-containing ART (aHR 0.93; 0.68-1.20]), or efavirenz with elvitegravir (aHR 0.87; 0.64-1.18). Adjusted hazard ratios comparing elvitegravir with dolutegravir, efavirenz with dolutegravir, darunavir with elvitegravir, and darunavir with rilpivirine, efavirenz with rilpivirine and efavirenz with darunavir were all in the range 0.75 to 1.19.

Mortality was higher when starting raltegravir- compared with dolutegravir-containing ART (aHR 1.49; 95%CI: 1.15-1.94) and elvitegravir-containing ART (aHR 1.86; 1.43-2.42). Mortality was also higher when starting raltegravir- compared with rilpivirine-, efavirenz-, and darunavir-containing ART: aHRs 2.00 (95%CI: 1.50-2.67), 2.12 (1.60-2.81), and 1.62 (1.33-1.98), respectively.

Among PWH in cohorts that provided both main and additional variables, 24,690 (49.2%) presented late for treatment. For patients who did and did not present late, hazard ratios were generally attenuated after adjusting for patient characteristics (main and additional variables) at the time of starting ART (supplementary table 5). Adjusted mortality hazard ratios comparing raltegravir-containing ART with other regimens were consistently higher in patients who did not present late (ranging from 2.74 (95%CI: 1.62-4.64) compared with darunavir to 3.24 (1.91-5.48) compared to rilpivirine) than those in patients who presented late (ranging from 1.49 (95%CI: 1.14-1.94) for dolutegravir to 1.97 (1.46-2.67) for efavirenz). aHRs for comparisons between other third drugs were similar in patients who did and did not present late.

Of the 50,722 PWH included in the cohorts providing both main and additional variables, 45,037 reached viral suppression, and 1,081 died before reaching viral suppression. Rates of viral suppression were lower (longer time to viral suppression) for all third drugs compared to dolutegravir, and rates of viral suppression were lower (longer time to suppression) for all regimens except dolutegravir compared to elvitegravir (supplementary table 6). PWH on raltegravir- and efavirenz-containing regimens had faster time to viral suppression than those on rilpivirine- and darunavir-containing regimens, and PWH on raltegravir had faster time to suppression than those on efavirenz. Rates of suppression were similar for PWH on rilpivirine and darunavir. Among 51,837 PWH who survived to 6 months after starting ART, virological failure was recorded in 6,106. 383 died before 6 months. PWH who started ART on dolutegravir-containing regimens had lower rates of virological failure compared to all other regimens, whilst PWH on raltegravir-containing and efavirenz-containing regimens had higher rates compared to PWH on elvitegravir-containing and rilpivirine-containing regimens (Supplementary table 7). PWH on darunavir-containing regimens had higher rates of virologic failure compared with PWH on rilpivirine-containing regimens.

Discussion

In analyses adjusting for a wide-range of variables at baseline, there was no strong evidence of differences in rates of all-cause mortality between PWH starting ART, since the introduction of integrase strand inhibitors, on regimens including dolutegravir, elvitegravir, darunavir, and efavirenz as third drugs. However, starting ART on raltegravir-based regimens was associated with higher mortality than starting on dolutegravir-, elvitegravir-, rilpivirine-, darunavir-, and efavirenz-based regimens. The proportions switching from their initial ART regimen within 3 years were highest for PWH starting ART on efavirenz, raltegravir, and darunavir, and were lowest for dolutegravir, elvitegravir, and rilpivirine. Rates of viral suppression were highest for dolutegravir- and elvitegravir-based regimens, and higher for raltegravir-based regimens than for rilpivirine-, darunavir-, and efavirenz-based regimens. Only 2% of PWH starting on dolutegravir-containing regimens had a CD4 count <100, compared with 20% for raltegravir-containing regimens and between 10% and 24% for other regimens.

To our knowledge, this is the first multi-country study in Europe or North America to examine associations between starting ART regimen type and mortality among PWH in the era of integrase strand inhibitor regimens. A 2007-2013 study from Kaiser Permanente also found that raltegravir-based regimens were associated with higher mortality (aHR: 1.53 [95%CI: 1.02-2.31]) than other regimens, although this analysis included PWH receiving raltegravir as a second- or third-line regimen(23). When restricting to initial ART regimens, the aHR was 1.63 (95%CI: 0.82-3.24). That paper also found higher incidence of AIDS-defining malignancies, non-AIDS defining malignancies, and lipodystrophy among PWH receiving raltegravir. A study by the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort found similar rates of AIDS-defining illness or death comparing raltegravir-based regimens with efavirenz-based regimens(24). A meta-analysis of randomized trials comparing first-line ART regimens found differing rates of viral suppression, including lower rates for raltegravir-based regimens than others, but low event rates limited the quality of evidence for between-regimen differences in mortality(25). A study by NA-ACCORD found that the risk of a composite endpoint of AIDS, acute myocardial infarction, stroke, end-stage renal disease, end-stage liver disease, or death was similar for participants whose first ART regimen was integrase strand inhibitor-based and efavirenz-based(26). That study included raltegravir among the integrase strand inhibitors, but did not compare them separately with efavirenz-based regimens.

There is substantial evidence on associations between initial ART regimen and virological outcomes. An intention-to-treat analysis from a 2012-2017 report from the UK CHIC study found adjusted risk ratios for virological failure of 1.18 (95%CI: 0.98-1.42) for PWH starting ART on INSTI-based regimens compared with NNRTI-based regimens, and 1.83 (95%CI: 1.61-2.08) for PI-based regimens compared with NNRTI-based regimens(18). A 2013-2017 study by the CNICS cohort also found that rates of virologic failure were lower among PWH starting ART on dolutegravir-based compared with other INSTI-based, and darunavir-based, regimens (7%, 12%, 28%, respectively)(19). We also found in this study that PWH on dolutegravir-containing regimens had lower rates of virologic failure compared to other regimens, while PWH on raltegravir-containing and efavirenz-containing regimens had higher rates of virological failure compared elvitegravir-containing and rilpivirine-containing regimens.

This study uses data on 62,500 PWH who started ART between 2013 and 2018 in 12 countries spanning Europe and North America, so should be generalisable to outcomes among adult PWH starting ART in high-income countries. Most (80%) of our study population were men, and data on pregnancy in women were not available. We adjusted for 19 potentially confounding variables that could have influenced clinician decision-making, and dealt with missing data in these variables by restricting analyses and the use of multiple imputation. However, our results may have been

affected by residual or unmeasured confounding. Decisions about the use of specific ART regimens were made by clinicians and patients, and could have been based on factors beyond those adjusted for in these analyses, such as perceived propensity to adhere to the prescribed regimen. Differing drug half-lives may influence regimens prescribing to patients for whom clinicians doubt their ability to adhere to ART, such as those with a history of substance use. Further, several potentially confounding variables were not routinely collected in many of the included cohorts, including: cholesterol, thrombocytes/platelets, prior end-stage renal disease, chronic obstructive pulmonary disease, recent hospitalisations, recent smoking, alcohol consumption, recent IDU, and recent non-injecting drug use. It is possible that PWH with worse prognosis, beyond the factors adjusted for in our study, were more likely to start ART on raltegravir. For example, a higher percentage of those who started on raltegravir previously had NADMs, HCV, and tuberculosis, possibly due to worries about drug-drug interactions(27). Because raltegravir was the first drug in its class, there was substantial research into its interactions with other drugs, and clinicians may have been more likely to choose it for PWH who have comorbidities, compared with other regimens. Conversely, elvitegravir combined with cobicistat is contraindicated for PWH taking many medications, so may have been prescribed less among those with comorbid conditions(28).

Because there may have been differences in prescribing, reporting of outcomes, and healthcare practices across cohorts, countries, and regions(29), we stratified analyses by both cohort and ART start year. Over half the ART-CC cohorts perform linkage with national death registries, and several further cohorts link to local death registries(29) in order to ascertain deaths in patients otherwise lost to follow-up. Several further cohorts have procedures in place to contact and track patients that have been lost to follow-up. We did not have enough information available to include bictegravir in these analyses(30). We chose to not censor at regimen change, so that estimated associations correspond to 'intention-to-treat' estimates from clinical trials. Rates of regimen switching within 3-years of ART start varied between regimens, with switching more common for older ART regimens such as raltegravir, darunavir, and efavirenz. We do not have information on the reasons for these switches, so are unable to comment on whether patients had to change regimen due to adverse events such as immune reconstitution inflammatory syndrome (IRIS), a phenomenon related to morbidity and mortality(31), or whether the reasons for these switches differed between regimens. Finally, this study uses data on adult PWH, so its findings may not be generalisable to children.

We found little evidence for differences in rates of mortality between most first-line ART regimens in the era of integrase strand inhibitors. However, starting ART on raltegravir-based regimens was associated with higher mortality than on other regimens, although this could be due to unmeasured confounding. The percentage of PWH starting ART on raltegravir remained low between the two ART start periods studied (9% during 2013-2015 to 8% during 2016-2018), but these results may imply that other regimens are preferred unless there are clear reasons to choose raltegrevir. The overall trend was of an increased use of INSTI-based regimens, particularly dolutegravir (10% during 2013-2015 to 39% during 2016-2018) and elvitegravir (13% to 23%), with another integrase inhibitor, bictegravir, coming into use at the end of this period(30). Our study suggests that virological advantages of these regimens do not necessarily translate to lower mortality.

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Data sharing statement: Due to the data sharing agreements between individual cohorts and ART-CC, the data collected for this study cannot be shared. Data are owned by the individual cohorts and those wishing to access these data should contact the individual cohorts, details of which are given in the supplementary materials.

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Transparency declarations:

MJG has received honoraria in the last 3 years from ad hoc membership of national HIV advisory boards, Merck, Gilead, and ViiV. MP has received honoraria from national HIV advisory boards, Merck, Gilead and ViiV and research grant from Gilead. FB has received travel grants and honoraria from ViiV Healthcare, Gilead, BMS and MSD. FB's institution has received research grants from Gilead and ViiV Healthcare. Through PR's institution, PR has received independent scientific grant support from Gilead Sciences, Merck & Co and ViiV Healthcare, and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, and Merck & Co, for which honoraria were all paid to his institution - none related to the content of this manuscript. GS received funding from Gilead Sciences and speaker fees from ViiV Healthcare, Bristol Meyer Squibb, MSD and Hormosan for participation in Advisory Boards, Data Safety and Monitoring Boards and for preparation of educational materials and lecturing fees. MR received funds from Gilead science. MJS has received research grant funding from Gilead Sciences, Inc. MC has received research and travel grants for his institution from ViiV and Gilead, and other payments for expert opinion from AbbVie, Gilead, MSD, ViiV, and Sandoz. GB has received a Bristol Myers-Squibb training grant. HC has received research

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Table 1: Patient characteristics at the time of starting antiretroviral therapy (ART), according to the third drug in the initial regimen. Percentages are column percentages within variable categories, except for row percentages corresponding to the totals on each third drug.

Variable		DTG	DRV	RAL	EVG	RPV	EFV	OTH	Total
Other drugs in ART regimen*	FTC/TDF	7940 (87%)	9440 (83%)	3808 (72%)	6419 (60%)	4022 (30%)	6039 (89%)	4303 (70%)	41971 (67%)
	3TC/ABC	257 (3%)	1358 (12%)	783 (15%)	10 (0%)	7865 (59%)	486 (7%)	1092 (18%)	11851 (19%)
	FTC/TAF	874 (10%)	266 (2%)	300 (6%)	3722 (35%)	1112 (8%)	15 (0%)	162 (3%)	6451 (10%)
	Other	49 (1%)	258 (2%)	370 (7%)	522 (5%)	250 (2%)	212 (3%)	566 (9%)	2227 (4%)
Sex	Male	7344 (81%)	8347 (74%)	4122 (78%)	9163 (86%)	11102 (84%)	5908 (88%)	4092 (67%)	50078 (80%)
	Female	1776 (19%)	2975 (26%)	1139 (22%)	1510 (14%)	2147 (16%)	844 (13%)	2031 (33%)	12422 (20%)
Age (years)	16-29	2272 (25%)	2583 (23%)	1085 (21%)	2769 (26%)	3143 (24%)	1559 (23%)	1600 (26%)	15011 (24%)
	30-39	2997 (33%)	3504 (31%)	1511 (29%)	3199 (30%)	3714 (28%)	2112 (31%)	2108 (34%)	19145 (31%)
	40-49	2292 (25%)	2894 (26%)	1369 (26%)	2550 (24%)	3226 (24%)	1681 (25%)	1442 (24%)	15454 (25%)
	50-59	1163 (13%)	1620 (14%)	839 (16%)	1559 (15%)	2197 (17%)	974 (14%)	720 (12%)	9072 (15%)
	≥60	396 (4%)	721 (6%)	457 (9%)	596 (6%)	969 (7%)	426 (6%)	253 (4%)	3818 (6%)
HIV risk activity	Sex between men	5208 (57%)	4819 (43%)	2607 (50%)	6185 (58%)	7486 (57%)	3702 (55%)	2657 (43%)	32664 (52%)
	Injecting drug use	343 (4%)	411 (4%)	196 (4%)	268 (3%)	411 (3%)	166 (2%)	266 (4%)	2061 (3%)
	Heterosexual sex	2789 (31%)	4994 (44%)	1785 (34%)	2803 (26%)	3758 (28%)	1697 (25%)	2534 (41%)	20360 (33%)
	Other	780 (9%)	1098 (10%)	673 (13%)	1417 (13%)	1594 (12%)	1187 (18%)	666 (11%)	7415 (12%)
CD4 count (cells/µL)	0-49	70 (1%)	1654 (15%)	641 (12%)	616 (6%)	1231 (9%)	483 (7%)	641 (10%)	5336 (9%)
	50-99	92 (1%)	980 (9%)	436 (8%)	435 (4%)	764 (6%)	314 (5%)	377 (6%)	3398 (5%)
	100-199	434 (5%)	1681 (15%)	683 (13%)	1019 (10%)	1345 (10%)	730 (11%)	815 (13%)	6707 (11%)
	200-349	1936 (21%)	2593 (23%)	1071 (20%)	2266 (21%)	2741 (21%)	1658 (25%)	1473 (24%)	13738 (22%)
	350-499	2864 (31%)	2171 (19%)	1063 (20%)	2724 (26%)	2964 (22%)	1773 (26%)	1407 (23%)	14966 (24%)
	≥500	3724 (41%)	2243 (20%)	1367 (26%)	3613 (34%)	4204 (32%)	1794 (27%)	1410 (23%)	18355 (29%)
HIV-1 RNA viral load (copies/mL)	0-9999	3072 (34%)	1516 (13%)	853 (16%)	2081 (19%)	2317 (17%)	1158 (17%)	1365 (22%)	12362 (20%)
	10000-99999	5559 (61%)	3891 (34%)	1860 (35%)	4654 (44%)	5263 (40%)	2784 (41%)	2450 (40%)	26461 (42%)
	≥100000	489 (5%)	5915 (52%)	2548 (48%)	3938 (37%)	5669 (43%)	2810 (42%)	2308 (38%)	23677 (38%)
Presenting late**		8288 (63%)	8618 (76%)	3771 (72%)	6109 (57%)	2926 (32%)	4477 (66%)	4104 (67%)	38293 (61%)
Total		**9120 (15%)**	**11322 (18%)**	**5261 (8%)**	**10673 (17%)**	**13249 (21%)**	**6752 (11%)**	**6123 (10%)**	**62500 (100%)**

*Emtricitabine and Tenofovir disoproxil (FTC/TDF), Lamivudine and Abacavir (3TC/ABC), Emtricitabine and Tenofovir alafenamide (FTC/TAF), and others.

**Not presenting late was defined as starting ART with CD4≥350 cells/mm^3, no prior AIDS, and viral load<100,000 copies/mL.

Table 2: Number of people starting on each regimen, rates of deaths, and numbers of deaths by ART start regimen type for all cohorts, by ART start period.

Third drug in regimen		ART start 2013-2018	ART start 2013-2015	ART start 2016-2018	Median (IQR) follow-up (years)
Dolutegravir (DTG)	N starting (% of total)	13249 (21%)	3876 (10%)	9373 (39%)	1.9 (1.1-2.9)
	Deaths (% of those starting on regimen)	208 (1.6%)	88 (2.3%)	120 (1.3%)	
	Mortality rate per 1000 years (95%CI)	7.7 (6.7-8.8)	7.2 (5.9-8.9)	8.0 (6.7-9.6)	
Darunavir (DRV)	N starting (% of total)	11322 (18%)	7840 (20%)	3482 (14%)	3.6 (1.9-4.9)
	Deaths (% of those on regimen)	294 (2.6%)	237 (3.0%)	57 (1.6%)	
	Mortality rate per 1000 years (95%CI)	7.7 (6.9-8.6)	7.3 (6.4-8.3)	10.0 (7.7-13.0)	
Raltegravir (RAL)	N starting (% of total)	5261 (8%)	3355 (9%)	1906 (8%)	2.8 (1.5-4.4)
	Deaths (% of those on regimen)	232 (4.4%)	189 (5.6%)	43 (2.3%)	
	Mortality rate per 1000 years (95%CI)	15.0 (13.2-17.1)	15.0 (13.0-17.3)	15.0 (11.1-20.2)	
Elvitegravir (EVG)	N starting (% of total)	10673 (17%)	5038 (13%)	5635 (23%)	2.4 (1.4-3.7)
	Deaths (% of those on regimen)	129 (1.2%)	91 (1.8%)	38 (0.7%)	
	Mortality rate per 1000 years (95%CI)	4.8 (4.0-5.6)	5.1 (4.2-6.3)	4.1 (3.0-5.6)	
Rilpivirine (RPV)	N starting (% of total)	9120 (15%)	6988 (18%)	2132 (9%)	3.9 (2.2-5.0)
	Deaths (% of those on regimen)	95 (1.0%)	89 (1.3%)	6 (0.3%)	
	Mortality rate per 1000 years (95%CI)	2.9 (2.4-3.5)	3.1 (2.5-3.8)	1.7 (0.7-3.7)	
Efavirenz (EFV)	N starting (% of total)	6752 (11%)	6081 (16%)	671 (3%)	4.2 (2.8-5.1)
	Deaths (% of those on regimen)	131 (1.9%)	128 (2.1%)	3 (0.5%)	
	Mortality rate per 1000 years (95%CI)	5.0 (4.2-6.0)	5.1 (4.3-6.1)	2.8 (0.9-8.7)	
Others	N starting (% of total)	6123 (10%)	5107 (13%)	1016 (4%)	3.9 (2.2-5.0)
	Deaths (% of those on regimen)	154 (2.5%)	139 (2.7%)	15 (1.5%)	
	Mortality rate per 1000 years (95%CI)	6.9 (5.9-8.1)	6.7 (5.7-8.0)	9.7 (5.8-16.1)	
Total	**N starting (% of total)**	**62500 (100%)**	**38285 (100%)**	**24215 (100%)**	**3.0 (1.6-4.4)**
	Deaths (% of those on regimen)	**1243 (2.0%)**	**961 (2.5%)**	**282 (1.2%)**	
	Mortality rate per 1000 years (95%CI)	**6.6 (6.2-7.0)**	**6.4 (6.0-6.8)**	**7.2 (6.4-8.1)**	

95%CI: 95% confidence interval. ART: Antiretroviral therapy. IQR: Interquartile range

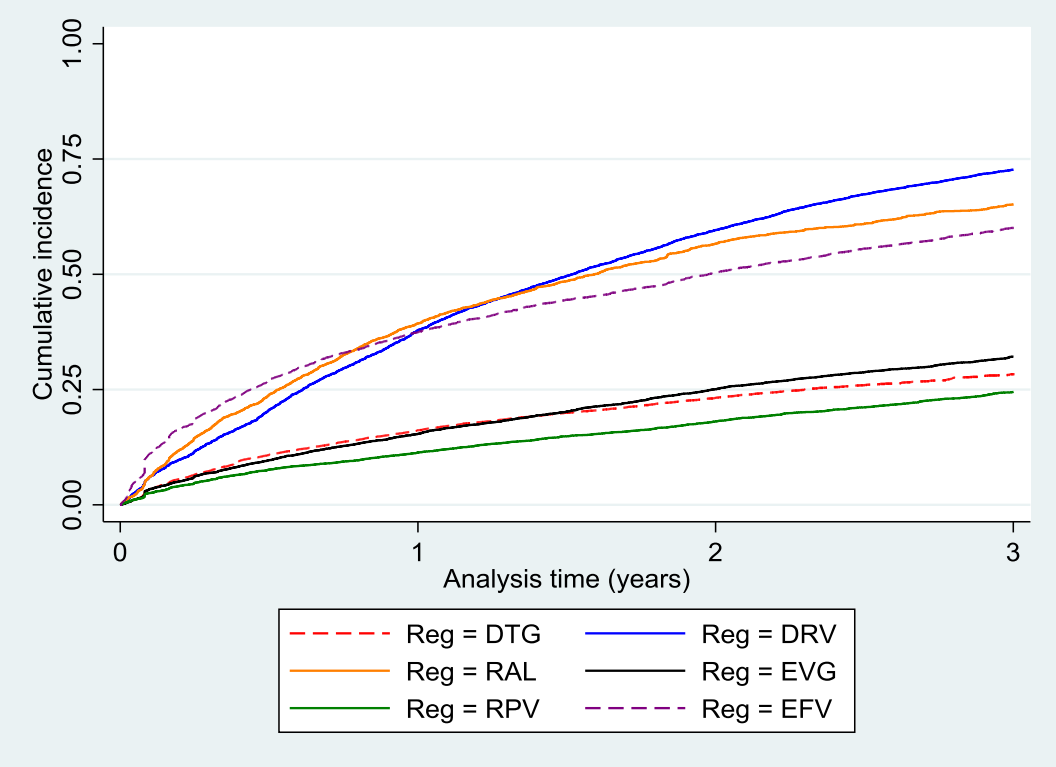
Table 3: Hazard ratios (95% confidence intervals) for mortality for each 3rd drug comparison, using multiple imputation to account for missing data among the "Additional" variables.

Cohorts included	All (N=62,500)		Those providing additional variables (N=50,722)			Those providing additional variables		
Analysis	**A) Crude**	**B) Adjusted**	**C) Adjusted**	**D) Adjusted**	**E) Meta-analysed across time periods**	**F1) Adjusted (2013-2015) N=29,989**	**F2) Adjusted (2016-2018) N=20,733**	**P-value 2013-2015 vs 2016-2018**
Variables adjusted for	**None**	**Main**	**Main**	**Additional**	**Additional**	**Additional**	**Additional**	
RPV vs DTG	0.45 (0.34-0.58)	0.77 (0.57-1.02)	0.74 (0.54-1.01)	0.83 (0.61-1.13)	0.78 (0.55-1.10)	0.82 (0.57-1.20)	0.58 (0.24-1.37)	0.474
DRV vs DTG	1.19 (0.97-1.47)	0.96 (0.77-1.20)	0.92 (0.73-1.15)	0.96 (0.76-1.21)	0.98 (0.77-1.25)	0.94 (0.69-1.27)	1.05 (0.71-1.55)	0.666
RAL vs DTG	2.32 (1.87-2.88)	1.79 (1.42-2.26)	1.73 (1.35-2.21)	1.60 (1.26-2.05)	1.49 (1.15-1.94)	1.62 (1.18-2.23)	1.27 (0.81-1.99)	0.386
EVG vs DTG	0.57 (0.45-0.72)	0.80 (0.62-1.03)	0.74 (0.57-0.96)	0.84 (0.65-1.10)	0.79 (0.60-1.05)	0.88 (0.62-1.25)	0.66 (0.41-1.05)	0.336
EFV vs DTG	0.62 (0.48-0.81)	0.68 (0.52-0.90)	0.70 (0.52-0.94)	0.78 (0.58-1.04)	0.75 (0.53-1.07)	0.78 (0.55-1.12)	0.19 (0.02-1.46)	0.203
RPV vs EVG	0.78 (0.60-1.03)	0.96 (0.72-1.27)	1.00 (0.74-1.35)	0.99 (0.73-1.33)	0.93 (0.68-1.28)	0.94 (0.67-1.31)	0.88 (0.36-2.17)	0.893
DRV vs EVG	2.09 (1.67-2.60)	1.20 (0.96-1.51)	1.24 (0.98-1.58)	1.14 (0.90-1.45)	1.17 (0.92-1.50)	1.06 (0.80-1.41)	1.60 (0.97-2.64)	0.161
RAL vs EVG	4.06 (3.23-5.09)	2.24 (1.77-2.83)	2.35 (1.83-3.01)	1.91 (1.48-2.46)	1.86 (1.43-2.42)	1.84 (1.37-2.49)	1.94 (1.12-3.37)	0.869
EFV vs EVG	1.09 (0.84-1.42)	0.86 (0.65-1.12)	0.95 (0.71-1.27)	0.92 (0.69-1.23)	0.87 (0.64-1.18)	0.89 (0.65-1.21)	0.29 (0.04-2.29)	0.283
DRV vs RPV	1.91 (1.53-2.39)	1.26 (0.98-1.62)	1.24 (0.95-1.62)	1.16 (0.89-1.52)	1.19 (0.91-1.57)	1.14 (0.85-1.51)	1.83 (0.76-4.40)	0.315
RAL vs RPV	5.17 (4.06-6.58)	2.34 (1.81-3.04)	2.34 (1.77-3.10)	1.93 (1.46-2.57)	1.99 (1.49-2.66)	1.97 (1.45-2.67)	2.21 (0.89-5.25)	0.810
EFV vs RPV	1.39 (1.06-1.83)	0.89 (0.67-1.19)	0.94 (0.69-1.28)	0.94 (0.69-1.27)	0.93 (0.68-1.27)	0.95 (0.69-1.30)	0.33 (0.04-2.93)	0.340
RAL vs DRV	1.95 (1.62-2.33)	1.86 (1.55-2.24)	1.89 (1.55-2.30)	1.67 (1.37-2.04)	1.62 (1.33-1.98)	1.73 (1.39-2.16)	1.21 (0.76-1.94)	0.176
EFV vs DRV	0.52 (0.42-0.65)	0.71 (0.56-0.89)	0.76 (0.59-0.98)	0.81 (0.63-1.04)	0.82 (0.63-1.07)	0.84 (0.64-1.09)	0.18 (0.02-1.39)	0.158
RAL vs EFV	3.72 (2.98-4.65)	2.62 (2.07-3.32)	2.48 (1.91-3.23)	2.09 (1.60-2.73)	2.12 (1.60-2.81)	2.07 (1.56-2.76)	6.67 (0.86-42.2)	0.244

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

Analyses: A) Unadjusted models. B) Adjusted for the main variables, including all cohorts. C) Adjusted for the main variables, restricted to cohorts providing additional variables. D) Adjusted for main and additional variables, restricted to cohorts providing additional variables. E) Inverse-variance weighted meta-analyses of adjusted hazard ratios for 2013-15 (F1) and 2016-18 (F2).

Figure 1: Kaplan-Meier estimates of the cumulative incidence of switching from starting ART regimen within the first 3 years of starting ART, stratified by regimen



Number at risk	ART initiation	1 year	2 years	3 years
DTG	12563	8269	4855	2303
DRV	11322	6096	3438	1922
RAL	3729	1905	1119	720
EVG	10431	7378	4759	2791
RPV	8433	6686	5470	4269
EFV	4702	2724	2019	1480

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

References

1. Trickey A, May MT, Vehreschild JJ, Obel N, Gill MJ, Crane HM, et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet Hiv. 2017;4(8):E349-E56.
2. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada. Plos One. 2013;8(12).
3. Brooks KM, Sherman EM, Egelund EF, Brotherton A, Durham S, Badowski ME, et al. Integrase Inhibitors: After 10 Years of Experience, Is the Best Yet to Come? Pharmacotherapy. 2019;39(5):576-98.
4. Ryom L, Cotter A, De Miguel R, Beguelin C, Podlekareva D, Arribas JR, et al. 2019 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 10.0. Hiv Med. 2020;21(10):617-24.
5. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults 2020 Recommendations of the International Antiviral Society-USA Panel. Jama-J Am Med Assoc. 2020;324(16):1651-69.
6. Clarke A, Wohl D, Oka S, Clumeck N, Brinson C, Tashima K, et al. A randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat and emtricitabine (E/C/F) for initial HIV-1 treatment: week 96 results. Hiv Med. 2016;17:14-.
7. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014;383(9936):2222-31.
8. Kouanfack C, Sanchez TT, Wandji ML, Mpoudi-Etame M, Bassega PO, Perrineau S, et al. Dolutegravir- versus low-dose Efavirenz-based regimen for the initial treatment of HIV-1 infection in Cameroon: Week 96 Results of the ANRS 12313-NAMSAL trial. J Int Aids Soc. 2020;23:17-8.
9. Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1. A randomized, controlled equivalence trial (vol 161, pg 461, 2014). Ann Intern Med. 2014;161(9):680-.
10. Orrell C, Hagins DP, Belonosova E, Porteiro N, Walmsley S, Falco V, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet Hiv. 2017;4(12):E536-E46.
11. Squires K, Kityo C, Hodder S, Johnson M, Voronin E, Hagins D, et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. Lancet Hiv. 2016;3(9):E410-E20.
12. Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. Aids. 2013;27(11):1771-8.
13. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. New Engl J Med. 2019;381(9):803-15.
14. Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-Josses MA, et al. Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. Jaids-J Acq Imm Def. 2015;70(5):515-9.

15. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus Abacavir-Lamivudine for the Treatment of HIV-1 Infection. New Engl J Med. 2013;369(19):1807-18.
16. Zolopa A, Sax PE, DeJesus E, Mills A, Cohen C, Wohl D, et al. A Randomized Double-Blind Comparison of Coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results. Jaids-J Acq Imm Def. 2013;63(1):96-100.
17. Lennox JL, DeJesus E, Berger DS, Lazzarin A, Pollard RB, Madruga JVR, et al. Raltegravir Versus Efavirenz Regimens in Treatment-Naive HIV-1-Infected Patients: 96-Week Efficacy, Durability, Subgroup, Safety, and Metabolic Analyses. Jaids-J Acq Imm Def. 2010;55(1):39-48.
18. El Bouzidi K, Jose S, Phillips AN, Pozniak A, Ustianowski A, Gompels M, et al. First-line HIV treatment outcomes following the introduction of integrase inhibitors in UK guidelines. Aids. 2020;34(12):1823-31.
19. Nance RM, Vannappagari V, Smith K, Johannes CB, Calingaert B, Saltus CW, et al. Virologic Failure Among People Living With HIV Initiating Dolutegravir-Based Versus Other Recommended Regimens in Real-World Clinical Care Settings. Jaids-J Acq Imm Def. 2019;81(5):572-7.
20. May MT, Ingle SM, Costagliola D, Justice AC, de Wolf F, Cavassini M, et al. Cohort Profile: Antiretroviral Therapy Cohort Collaboration (ART-CC). Int J Epidemiol. 2014;43(3):691-702.
21. Sabin C, Babiker A, Dunn D, Easterbrook P, Fisher M, Gilson R, et al. The creation of a large UK-based multicentre cohort of HIV-infected individuals: The UK Collaborative HIV Cohort (UK CHIC) Study. Hiv Med. 2004;5(2):115-24.
22. Rubin D. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons; 1987.
23. Horberg MA, Oakes AH, Hurley LB, Towner WJ, Chao CR, Silverberg MJ, et al. Association of raltegravir use with long-term health outcomes in HIV-infected patients: an observational post-licensure safety study in a large integrated healthcare system. Hiv Clin Trials. 2018;19(5):177-87.
24. Cole SR, Edwards JK, Hall HI, Brookhart MA, Mathews WC, Moore RD, et al. Incident AIDS or Death After Initiation of Human Immunodeficiency Virus Treatment Regimens Including Raltegravir or Efavirenz Among Adults in the United States. Clin Infect Dis. 2017;64(11):1591-6.
25. Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet Hiv. 2016;3(11):E510-E20.
26. Lu H, Cole SR, Westreich D, Hudgens MG, Adimora AA, Althoff KN, et al. Clinical Effectiveness of Integrase Strand Transfer Inhibitor-Based Antiretroviral Regimens Among Adults With Human Immunodeficiency Virus: A Collaboration of Cohort Studies in the United States and Canada. Clin Infect Dis. 2021;73(7):e1408-e14.
27. Kolakowska A, Maresca AF, Collins IJ, Cailhol J. Update on Adverse Effects of HIV Integrase Inhibitors (vol 11, pg 372, 2019). Curr Treat Opt Infec. 2021;13(1):32-3.
28. Nguyen T, McNicholl I, Custodio JM, Szwarcberg J, Piontkowsky D. Drug Interactions with Cobicistat- or Ritonavir-Boosted Elvitegravir. Aids Rev. 2016;18(2):101-11.
29. May MT, Hogg RS, Justice AC, Shepherd BE, Costagliola D, Ledergerber B, et al. Heterogeneity in outcomes of treated HIV-positive patients in Europe and North America: relation with patient and cohort characteristics. Int J Epidemiol. 2012;41(6):1807-20.
30. Zeuli J, Rizza S, Bhatia R, Temesgen Z. Bictegravir, a novel integrase inhibitor for the treatment of HIV infection. Drug Today. 2019;55(11):669-82.
31. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(4):251-61.