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ORIGINAL ARTICLE

Effectiveness and safety of two-drug regimens containing an integrase inhibitor and reverse transcriptase inhibitor in a cohort of virologically suppressed people with HIV: Data from the COMBINE-2 study

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Abstract

Objectives: This study assessed real-world effectiveness and safety of switching to dual therapy regimens consisting of an integrase inhibitor

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(INSTI), and reverse transcriptase inhibitor (RTI), among suppressed people living with HIV in Europe.

Methods: This observational cohort enrolled adults with HIV from 28 sites across Europe who were switching to a two-drug regimen of an INSTI plus a nucleoside reverse transcriptase inhibitor or non-nucleoside reverse transcriptase inhibitor while suppressed [viral load (VL) <50 copies/mL]. Participants were followed from regimen start date (baseline) until the earliest of 96 weeks, regimen discontinuation, loss to follow-up, or death. The primary endpoints were suppression, low-level viraemia (VL ≥50 to <200 copies/mL), and high-level viraemia (VL ≥200 copies/mL) at 24-, 48- and 96-weeks post-baseline, and virologic failure (VF) within 96 weeks (2 consecutive VLs ≥50 copies/mL or 1 VL ≥50 copies/mL followed by regimen discontinuation). Adverse events and discontinuations were also described.

Results: 737 individuals switched to DTG + 3TC (536, 72.7%), DTG + RPV (186, 25.2%) and other INSTI+RTI regimens (15, 2.0%). At 24-,48-, and 96 weeks of follow up, >98% of individuals with VL data maintained suppression; among VLs ≥50 copies/mL, most (19/23; 82.6%) were low-level viraemia. Five individuals (<1%, DTG + 3TC:2; DTG + RPV:3) experienced VF. Forty-seven non-serious drug-related AEs were reported by 38 participants (5.4%); 2 people experienced serious AEs (0.3%). Regimen discontinuations were infrequent ($n = 39$, 5.3%) and most commonly attributed to tolerability issues ($n = 17$).

Conclusions: Among suppressed people living with HIV in a real-world setting, INSTI+RTI two-drug regimens were highly effective and well tolerated over 96 weeks of follow-up.

KEYWORDS
dolutegravir/lamivudine, dolutegravir/rilpivirine, integrase inhibitors, two-drug regimens

OBJECTIVES

Two-drug antiretroviral regimens for the treatment of HIV may decrease the risk of drug–drug interactions, toxicities, and costs when compared to combination antiretroviral therapy (ART) regimens containing three or more antiretrovirals (ARVs) [1, 2]. High levels of clinical efficacy and genetic barriers, as well as good tolerability, make second-generation integrase strand transfer inhibitors (INSTIs) optimal core agents for two-drug regimens. HIV treatment guidelines now include recommendations for the use of oral two-drug regimens containing dolutegravir [DTG; DTG+ rilpivirine (RPV) and DTG+ lamivudine (3TC)], as switch strategies for virologically suppressed people living with HIV [3, 4].

These guideline recommendations are supported by findings from randomized clinical trials, as well as a growing body of real-world evidence. The SWORD, TANGO and SALSA trials showed non-inferiority of two-drug regimens compared to standard-of-care three-drug regimens in maintaining viral suppression among adults living with HIV who suppressed switch to DTG/RPV or DTG/3TC [5–8]. A meta-analysis evaluating the real-world effectiveness and discontinuations among people with HIV switching to DTG + 3TC or DTG + RPV found low rates of virologic failure and discontinuation, as well as high rates of viral suppression among people living with HIV in diverse settings [9].

The goal of this study was to assess the uptake of two-drug regimens containing an INSTI and a reverse transcriptase inhibitor (RTI) in a multicentre European cohort, and to evaluate the effectiveness, tolerability and durability of these regimens in a real-world clinical setting.

METHODS

Study design and population

The Real-World Evidence for Effectiveness of Two-Drug Regimen, Antiretroviral Therapy with Integrase Inhibitors

Plus a Reverse Transcriptase Inhibitor (COMBINE-2) Study was an observational cohort study conducted at sites across Europe. Both retrospective and prospective data collection were utilized by including individuals who initiated an oral two-drug regimen of an INSTI and an RTI for the treatment of HIV either prior to or after the study start date (June 2018). It was anticipated that most of the captured regimens would be DTG + 3TC or DTG + RPV. Additional inclusion criteria were age ≥ 18 years, suppressed viral load (HIV-RNA <50 copies/mL) when switching to an INSTI + RTI oral two-drug regimen in the year 2014 or later, and informed consent for data collection.

A minimum enrolment target of 320 participants was set prior to study initiation. The expected virologic failure rate for a standard 3-drug regimen by 48 weeks was estimated at 4%, with a non-inferiority margin of 4%. Therefore, a two-drug regimen was considered acceptable if the percentage of individuals with virologic failure by 48 weeks of follow up was less than 8%. Including 320 individuals gives a 95% probability of correctly concluding that the two-drug regimen is not non-inferior if its true failure rate is 8% or higher.

Data were collected from electronic medical records at 28 hospital sites across 6 countries (United Kingdom, Spain, France, Belgium, Italy and Portugal). Participating sites were part of the European treatment network for HIV, hepatitis and global infectious diseases (NEAT ID). Data reflect routine clinical care, with no additional follow up required for study participation.

Included individuals were followed from initiation of an eligible two-drug regimen (baseline). Follow up was censored at Week 96, or at the earliest of: date of last study contact, INSTI+RTI dual therapy modification or discontinuation, loss to follow up, or death. Switching from the baseline therapy to another INSTI+RTI dual therapy was not considered a modification, except when switching to a long-acting regimen. Data were extracted from medical records at baseline, as well as every 6 months thereafter through 96 weeks post-baseline. The last participant reached 96 weeks of follow up in November 2023.

Outcomes and covariates

The primary objective for this analysis was to assess the effectiveness of INSTI+RTI two-drug regimens during the first 96 weeks after regimen initiation. Virologic outcomes were assessed at 24-, 48- and 96 weeks post-baseline, and included the proportion of participants maintaining suppression (a viral load <50 copies/mL), experiencing low-level viremia (viral load ≥50 and < 200 copies/mL), and high-level viraemia (viral load ≥200 copies/mL) at each time point, as well as protocol-defined virological failure during the 96-week follow-up.

Virologic failure was defined as 2 consecutive plasma HIV RNA viral loads ≥50 copies/mL, or 1 viral load ≥50 copies/mL followed by INSTI+RTI dual therapy modification or discontinuation. The proportion of participants with a single viral load ≥50 copies/mL and no additional viral load lab data was also assessed, as it was unknown if these individuals resuppressed or went on to experience treatment failure. A sensitivity analysis applied a threshold of ≥200 copies/mL for the definition of virologic failure.

Immunologic response to treatment was assessed as the mean changes in CD4 and CD8 cell counts (difference in cells/mm^3) and CD4:CD8 ratio between baseline measurements and 96 weeks.

ART-related adverse events (all grades), ART-related serious adverse events (SAEs), and deaths that occurred at any point during follow up were described. Modification or discontinuation of the INSTI+RTI dual therapy was assessed, and where information was provided in the medical record, reasons for discontinuation were also described.

Baseline demographic and clinical characteristics, including resistance profiles, were captured. Missing values at the time of initiation used the last reported value prior to baseline when possible.

Statistical Analysis

Descriptive statistics were used to describe the overall study population. Baseline characteristics were stratified by two-drug regimen (DTG + 3TC, DTG + RPV, and other INSTI + RTI).

The observed proportion and 95% confidence interval (CI) of participants with protocol defined virological failure were calculated with the Kaplan–Meier method, censoring at Week 96 or last follow-up date if missing HIV RNA viral load values at Week 96, or upon discontinuation of INSTI+RTI dual therapy, whichever occurred first. The proportion of participants experiencing specified virologic outcomes at Weeks 24, 48 and 96 was calculated using a denominator of participants with virological data available at each time point. To account for variability in timing of clinic visits in a real-world setting, viral load assessments taken within a window of ±6 weeks of 24-, 48- and 96 weeks of follow up were included. For each time point, participants without viral load lab data within the specified window were excluded.

Classification of virologic status was based on a single viral load measure within each window; if multiple measures were available, the result with the highest value was used.

Change from baseline to Week 96 in CD4 count, CD8 count and CD4:CD8 ratio were compared using a mixed model with a random intercept and spatial power covariance structure. Time was modelled as a categorical variable.

The proportion of INSTI+RTI dual therapy discontinuation was calculated by dividing the number of discontinuations by the full analysis population. The 95% CI of the observed proportion was calculated using the exact Clopper-Pearson method.

Predictors of time to loss of suppression (first viral load ≥50 copies/mL) were identified using Cox regression analysis. Variables showing a significant association (p-value <0.2) with the outcome in the univariate analysis were then evaluated in multivariate models. Covariates retained in the final multivariable Cox model were determined by a stepwise backward variable selection process. For multivariable analysis, missing values for CD4 count and CD4 nadir were imputed with the mean value.

RESULTS

Study Population

Seven hundred and thirty-seven people with HIV met the inclusion criteria and were enrolled, including 536 (72.7%) switching to DTG + 3TC, 186 (25.2%) switching to DTG + RPV, and 15 (2.0%) switching to another INSTI + RTI regimen [raltegravir (RAL) + etravirine (ETR): $n = 10$; RAL + nevirapine (NVP): $n = 1$; RAL + RPV ($n = 1$); DTG + tenofovir disoproxil (TDF): $n = 1$; DTG + efavirenz (EFV): $n = 1$; DTG + ETR: $n = 1$].

Regimens immediately prior to switching to a two-drug regimen were varied, but all consisted of 3 or more daily oral ARVs. The most common regimens were DTG + 3TC + abacavir (18.2%), DTG + tenofovir alafenamide (TAF) + emtricitabine (FTC; 6.8%), DTG + TDF + FTC (5.8%), EFV + TDF + FTC (4.9%), and elvitegravir/cobicistat + FTC (4.2%).

Across regimens, participants were predominantly male ($n = 556$; 75.5%) and White ($n = 492$; 66.8%), with a median age of 54 (IQR: 47–59) years. Median time on ART prior to baseline was longer for those switching to DTG + RPV [14.5 (6.1–21.3) years] compared to DTG + 3TC [9.1 (4.6–16.9) years] or other INSTI + RTI regimens [7.9 (1.9–16.3) years]. Median baseline CD4 count was similar between the DTG + RPV [678 (543–906) cells/mm^3] and DTG + 3TC [690 (534–924) cells/mm^3]. Full population characteristics are summarized in Table 1.

Overall, 61.7% of individuals had at least 1 resistance test documented at any point prior to baseline [66.1% (123/186) in DTG + RPV group; 59.7% (320/536) in DTG + 3TC group]. Median time since most recent resistance test prior to baseline was 105 (36–167) months for those on DTG + RPV, 86 (42–130) months for those on DTG + 3TC, and 44 (3–86) months for those on other INSTI +RTI regimens.

Among those tested, a history of documented resistance mutations was common, although seen least frequently in the DTG + 3TC group (42.5%) compared to DTG + RPV group (67.5%) and the other INSTI + RT group (75.0%). No one had previously documented mutations associated with resistance to dolutegravir, and 1 individual switching to DTG + RPV had a history of a major mutation (F121Y) associated with resistance to a first-generation INSTI (RAL). Among those taking DTG + 3TC, 5.6% ($n = 18/320$) had a documented history of M184V/I, the major mutation associated with resistance to 3TC. History of major mutations associated with reduced susceptibility to RPV was documented for three individuals (K101E, E138A, and Y181C documented for 1 person each) taking DTG + RPV.

Virologic Outcomes

At 24, 48 and 96 weeks of follow up, 598/605 (98.8%), 579/588 (98.5%) and 578/585 (98.8%) of individuals who switched to a two-drug INSTI+RTI regimen and who had viral load measurements were still suppressed, respectively. (Table 2) Most individuals who did not maintain suppression had low-level viraemia, with 6 of the 7 VLs ≥50 copies/mL at Week 24, 8 of 9 VLs ≥50 copies/mL at Week 48, and 5 of 7 VLs ≥50 copies/mL at week 96 measuring between 50 and 200 copies/mL.

During the 96-week follow-up period, 5 individuals experienced protocol-defined virologic failure, including one person taking DTG + 3TC who had 2 consecutive viral loads ≥50 copies/mL [K-M estimate: 0.1% (95% CI: 0.0–1.0%)], and 4 people (1 on DTG + 3TC and 3 on DTG + RPV) who experienced a single VL≥50 copies/mL followed by regimen discontinuation [K-M estimate: 0.6% (95% CI: 0.2–1.6%)].

Using a threshold of 200 copies/mL to define virologic failure, there were 2 events: 1 person experiencing 2 consecutive VLs ≥200 copies/mL [K-M estimate: 0.2% (95% CI: 0.0–1.0%)] while taking DTG + 3TC and 1 person on DTG + RPV experiencing a VL ≥200 copies/mL followed by regimen discontinuation [K-M estimate: 0.2% (95% CI: 0.0–1.0%)].

Additionally, 6 people [K-M estimate: 1.0 (0.5–2.3%)] had a VL≥50 copies/mL without additional viral load

TABLE 1 Demographic and clinical characteristics at initiation of two-drug regimen, by regimen.

	DTG + RPV *N* = 186	DTG + 3TC *N* = 536	Other INSTI + RTI[a] *N* = 15	Overall *N* = 737
Demographic characteristics				
Age	56 (51–60)	53 (44–59)	61 (59–68)	54 (47–59)
Gender				
Male	135 (72.6)	411 (76.7)	10 (66.7)	556 (75.5)
Female	50 (26.9)	123 (22.9)	5 (33.3)	178 (24.2)
Transgender women	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Transgender unknown sex	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Unknown	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Ethnicity				
White	130 (69.9)	352 (65.7)	10 (66.7)	492 (66.8)
Black	27 (14.5)	108 (20.1)	5 (33.3)	140 (19)
Asian	2 (1.1)	6 (1.1)	0 (0)	8 (1.1)
Other	27 (14.5)	70 (13.1)	0 (0)	97 (13.2)
Clinical characteristics				
Duration of ART, years, median (IQR)	14.5 (6.1–21.3)	9.1 (4.6–16.9)	7.9 (1.9–16.3)	10.1 (4.7–18.8)
CD4 baseline, median (IQR)	*N* = 146 678 (543–906)	*N* = 355 690 (534–924)	*N* = 9 554 (443–648)	*N* = 510 684 (532–920)
CD4 nadir, median (IQR)	*N* = 183 210 (120–313)	*N* = 528 260 (144–385)	*N* = 14 182 (90–234)	*N* = 725 251 (134–366)
Resistance				
Resistance test occurred at baseline (±1 week from baseline)				
No	183 (98.4)	531 (99.1)	14 (93.3)	728 (98.8)
Yes	3 (1.6)	5 (0.9)	1 (6.7)	9 (1.2)
≥1 resistance test documented prior to baseline				
No	63 (33.9)	216 (40.3)	3 (20)	282 (38.3)
Yes	123 (66.1)	320 (59.7)	12 (80)	455 (61.7)
History of any resistance mutations	83/123 (67.5)	136/320 (42.5)	9/12 (75)	228/455 (50.1)
Single class resistance				
NRTI only	19 (15.4)	10 (3.1)	1 (8.3)	30 (6.6)
NNRTI only	3 (2.4)	22 (6.9)	0 (0)	25 (5.5)
PI only	13 (10.6)	56 (17.5)	1 (8.3)	70 (15.4)
INSTI only	0 (0)	2 (0.6)	1 (8.3)	3 (0.7)
Two class resistance				
NRTI + NNRTI	7 (5.7)	9 (2.8)	3 (25)	19 (4.2)
NRTI + PI	24 (19.5)	7 (2.2)	0 (0)	31 (6.8)
NRTI + INSTI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NNRTI + PI	2 (1.6)	22 (6.9)	1 (8.3)	25 (5.5)
NNRTI + INSTI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PI + INSTI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Three class resistance				
NRTI + NNRTI + PI	11 (8.9)	6 (1.9)	2 (16.7)	19 (4.2)
NRTI + NNRTI + INSTI	2 (1.6)	1 (0.3)	0 (0)	3 (0.7)

(Continues)

TABLE 1 (Continued)

	DTG + RPV N = 186	DTG + 3TC N = 536	Other INSTI + RTI[a] N = 15	Overall N = 737
NRTI + PI + INSTI	2 (1.6)	1 (0.3)	0 (0)	3 (0.7)
NNRTI + PI + INSTI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Four class resistance				
NRTI + NNRTI + PI + INSTI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Characteristics are summarized as *n* (%) or median [IQR].
Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; DTG, dolutegravir; HIV, human immunodeficiency virus; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RPV, rilpivirine; RTI, reverse transcriptase inhibitor (NNRTI or NRTI).
[a]Other regimens: raltegravir+ etravirine ($n = 10$), raltegravir+ nevirapine ($n = 1$); raltegravir +rilpivirine ($n = 1$); dolutegravir +tenofovir disoproxil ($n = 1$); dolutegravir + efavirenz ($n = 1$); dolutegravir + etravirine ($n = 1$).

assessments. Each of these events occurred at the 96-week time point, after which follow up was censored, and 4 of the 6 had low-level viraemia. In all 6 cases, the VL ≥50 copies/mL at 96 weeks was the first documented loss of suppression experienced during follow up.

Among those on DTG + 3TC who lost suppression at any point during follow up ($n = 15$), none had a documented history of mutations associated with resistance to DTG or 3TC. Among those on DTG + RPV with any loss of suppression ($n = 12$), one person had a history of a major mutation associated with RPV resistance (K101E). There were no events of loss of suppression among those on other INSTI + RTI two-drug regimens. No one had a documented resistance test to evaluate treatment-emergent mutations following a protocol-defined virologic failure event.

Immunologic Response

The mean change in CD4 count/mm^3 between baseline and 96 weeks among the 510/737 who had CD4 lab values was an increase of 7 cells/mm^3 (95% CI: −11 to 24), which was not statistically significant ($p = 0.460$). Mean change in CD8 count/mm^3 over 96 weeks among those with data (487/737) was statistically significant ($p = 0.002$), with a mean decrease of −38 cells/mm^3 (95% CI: −64 to −14). The CD4:CD8 ratio change over the study period also showed a statistically significant change of +0.05 (0.01 to 0.09, $p = 0.016$).

Safety

Overall, there were a total of 47 non-serious (grade 1 or 2) drug-related adverse events among 38/737 (5.2%) individuals in the analysis population; 28 of these events occurred among 25/536 (4.7%) individuals taking DTG + 3TC and 19 events occurred among 13/186 (7.0%) of individuals taking DTG + RPV.

TABLE 2 Virologic response to treatment with a two-drug INSTI+RTI regimen at weeks 24, 48 and 96.

	Events	
	N	% (95% CI)
Suppressed (VL < 50 copies/mL)		
24 weeks <50 copies/mL	598/605	98.8 (97.6–99.5)
48 weeks <50 copies/mL	579/588	98.5 (97.1–99.3)
96 weeks <50 copies/mL	578/585	98.8 (97.6–99.5)
Low-level viraemia (VL ≥ 50 and < 200 copies/mL)		
24 weeks ≥50 and < 200 copies/mL	6/605	1.0 (0.4–2.1)
48 weeks ≥50 and < 200 copies/mL	8/588	1.4 (0.6–2.7)
96 weeks ≥50 and < 200 copies/mL	5/585	0.9 (0.3–2.0)
Viral load ≥ 200 copies/mL		
24 weeks ≥200 copies/mL	1/605	0.2 (0.0–0.9)
48 weeks ≥200 copies/mL	1/588	0.2 (0.0–0.9)
96 weeks ≥200 copies/mL	2/585	0.3 (0.0–1.2)

Note: Proportions were estimated by dividing the number of participants with the event by the total number of participants in the ITT population at each time point (ITT as observed). Participants with missing values (no viral load data) at each time point were excluded. Windows for data collection at each time points were 24 weeks: 18–30 weeks, 48 weeks: 42–54 weeks; 96 weeks: 90–102 weeks. Data were censored at the time of baseline regimen discontinuation.

The most common non-serious drug-related adverse event was weight gain, which occurred in 8 people (1.1%); this includes 7 events on DTG + 3TC and 1 event on DTG + RPV. Diarrhoea, sleep disorders, pruritus and rash all occurred in a small number of individuals (3, 3, 2, and 2 respectively). All other non-serious drug-related AEs occurred in one person.

There were 2 drug-related SAEs occurring in 2 people (0.3%) over 96 weeks. This includes an event of low

TABLE 3 Regimen modification or discontinuation, stratified by baseline two-drug INSTI+RTI regimen.

	Overall Total $N = 737$		DTG + 3TC $N = 536$		DTG + RPV $N = 186$		Other INSTI + RTI $N = 15$	
	N	% (95% CI)	*N*	% (95% CI)	*N*	% (95% CI)	*N*	% (95% CI)
Total discontinuation	39	5.3 (3.8–7.2)	25	4.7 (3.0–6.8)	13	7.0 (3.8–11.7)	1	6.7 (0.2–31.9)
Switch for simplification (switch to long acting)	2	0.3 (0–1.0)	2	0.4 (0.0–1.3)	0	0.0 (0–2.0)	0	0.0 (0–21.8)
Switch for virologic failure	4	0.5 (0.1–1.4)	2	0.4 (0.0–1.3)	2	1.1 (0.1–3.8)	0	0.0 (0–21.8)
Switch for tolerability	17	2.3 (1.3–3.7)	12	2.2 (1.2–3.9)	5	2.7 (0.9–6.2)	0	0.0 (0–21.8)
Switch for toxicity	6	0.7 (0.2–1.6)	3	0.6 (0.1–1.6)	3	1.6 (0.3–4.6)	0	0.0 (0–21.8)
Switch for other reasons	10	1.5 (0.7–2.7)	6	1.1 (0.4–2.4)	3	1.6 (0.3–4.6)	1	6.7 (0.2–31.9)

Note: Regimen discontinuation defined by last prescription in medical record; reason for discontinuation reported as documented by treating clinician.
Abbreviations: DTG, dolutegravir; 3TC, lamivudine; RPV, rilpivirine; INSTI, integrase strand transfer inhibitor; RTI, reverse transcriptase inhibitor; CI, confidence interval.

mood, documented in one person (0.2%) on DTG + 3TC and an event of anxiety and depression that occurred in one person (0.5%) on DTG + RPV.

No deaths were reported.

Regimen discontinuations

By 96 weeks of follow up, 39/737 individuals 5.3% (95% CI: 3.8–7.2%) had discontinued their baseline two-drug regimen (Table 3). This included 25/536 DTG + 3TC discontinuations [4.7% (95% CI: 3.0–6.8%)], 13/186 DTG + RPV discontinuations [7.0% (95% CI: 3.8–11.7%)], and 1/15 discontinuation of another INSTI+RTI combination [6.7% (95% CI: 0.2–31.9%)]. Among the 25 participants who discontinued DTG + 3TC, 8 discontinuations occurred between 0 and 24 weeks after initiation, 5 between 25 and 48 weeks and 12 between 49 and 96 weeks. Among the 13 participants who discontinued DTG + RPV, 6 discontinuations occurred between 0 and 24 weeks, 2 between 25 and 48 weeks and 5 between 49 and 96 weeks.

Four discontinuations were attributed to virologic failure. The most commonly documented reasons for regimen discontinuation were switch for tolerability [$n = 17$; 2.3% (95% CI: 1.3–3.7%)] and switch due to toxicity [$n = 6$; 0.7% (95% CI: 0.2–1.6%)]. Two individuals switched from DTG + 3TC to a long-acting injectable two-drug regimen [cabotegravir (CAB) + RPV].

Predictors of loss of suppression

Baseline factors associated with risk of a viral load ≥50 copies/mL during 96 weeks of follow up are shown in Table 4. In multivariate analyses, Black participants had an increased risk of loss of viral suppression [adjusted HR (aHR): 3.30, 95% CI: 1.42, 7.67]. Compared to participants taking DTG + RPV, individuals on DTG + 3TC or another INSTI+RTI regimen had a lower risk of loss of suppression (aHR: 0.38, 95% CI: 0.18, 0.81).

DISCUSSION

The results of this real-world observational, multicentre study support the use of oral two-drug INSTI+RTI regimens, particularly the combinations of DTG + 3TC and DTG + RPV, as effective switch regimens for virologically suppressed, treatment-experienced people with HIV. Low rates of virologic failure and high estimated proportion of participants maintaining virologic suppression were observed through 96 weeks of follow-up across treatment groups. Of 737 individuals included in the analysis, 5 (<1%) experienced protocol-defined virologic failure (2 on DTG + 3TC and 3 on DTG + RPV) within 2 years, and the proportion of participants maintaining suppression was greater than 98% at each evaluated time point (24-, 48- and 96 weeks). Further, most events of loss of suppression were low-level viraemia (19/23 viral loads ≥50 copies/mL were ≤200 copies/mL), with the majority being blips (resuppression observed).

There were 6 events of a single viral load ≥50 copies/mL observed at 96 weeks, which were classified as potential failure events given the inability to observe the true outcome, but with 4 of the 6 events measured as low-level viraemia, and most people with low-level viraemia at earlier timepoints resuppressing, this may be an overestimation of potential failures.

Several other real-world studies have reported similarly high degrees of effectiveness to our analysis, with

TABLE 4 Baseline factors associated with the risk of plasma viral load ≥50 copies/mL during the 96 weeks of follow-up.

Characteristics	Total *N*	Events *n* (%) or median (IQR) <50 copies/mL *N* = 710	Events *n* (%) or median (IQR) ≥50 copies/mL *N* = 27	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value
Age, years	737	54 (47–59)	54 (49–59)	1.00 (0.96–1.03)	0.896		
Gender							
Male or Transgender	558	537 (96.2)	21 (3.8)	1			
Female	178	172 (96.6)	6 (3.4)	0.9 (0.36–2.23)	0.816		
Ethnicity					**0.033**		**0.020**
White	492	480 (97.6)	12 (2.4)	1		1	
Black	140	130 (92.9)	10 (7.1)	3.01 (1.3–6.97)	**0.010**	3.30 (1.42–7.67)	**0.006**
Asian or other	105	100 (95.2)	5 (4.8)	2.04 (0.72–5.79)	**0.181**	2.04 (0.72–5.8)	0.179
Duration of antiretroviral treatment (years)	737	10.3 (4.9–18.8)	7.3 (3.6–16.2)	0.96 (0.92–1.02)	**0.165**		
CD4 count nadir (cells/mm^3)[a]	725	252 (136–374)	181 (97–313)	0.83 (0.62–1.11)	0.202		
CD4 count (cells/mm^3)[a]	510	689 (540–924)	553 (392–758)	0.51 (0.25–1.05)	**0.067**		
CD8 count (cells/mm^3)[a]	487	795 (580–1043)	893 (635–1078)	1.06 (0.35–3.2)	0.912		
CD4/CD8 ratio	487	0.9 (0.6–1.2)	0.6 (0.4–1.1)	0.86 (0.33–2.21)	0.747		
Baseline regimen[b]							
DTG + RPV	186	174 (93.5)	12 (6.5)	1		1	
DTG + 3TC or Other INSTI+RTI	551	536 (97.3)	15 (2.7)	0.41 (0.19–0.88)	**0.023**	0.38 (0.18–0.81)	**0.013**
Hypertension							
No	559	541 (96.8)	18 (3.2)	1			
Yes	178	169 (94.9)	9 (5.1)	1.59 (0.71–3.53)	0.259		
Hyperlipidaemia							
No	545	528 (96.9)	17 (3.1)	1			
Yes	192	182 (94.8)	10 (5.2)	1.66 (0.76–3.62)	0.206		
Renal disorder							
No	635	613 (96.5)	22 (3.5)	1			
Yes	102	97 (95.1)	5 (4.9)	1.43 (0.54–3.77)	0.473		
Liver disorder							
No	677	653 (96.5)	24 (3.5)	1			
Yes	60	57 (95)	3 (5)	1.45 (0.44–4.81)	0.546		
Diabetes							
No	690	665 (96.4)	25 (3.6)	1			
Yes	47	45 (95.7)	2 (4.3)	1.15 (0.27–4.85)	0.850		
Any resistance mutations					0.445		
No	227	217 (95.6)	10 (4.4)	1			
Yes	228	218 (95.6)	10 (4.4)	0.99 (0.41–2.38)	0.983		
No genotype	282	275 (97.5)	7 (2.5)	0.57 (0.22–1.5)	0.253		
NRTI mutations					0.436		
No	350	335 (95.7)	15 (4.3)	1			
Yes	105	100 (95.2)	5 (4.8)	1.1 (0.4–3.03)	0.850		
No genotype	282	275 (97.5)	7 (2.5)	0.59 (0.24–1.44)	0.242		

TABLE 4 (Continued)

Characteristics	Total *N*	Events *n* (%) or median (IQR) <50 copies/mL *N* = 710	Events *n* (%) or median (IQR) ≥50 copies/mL *N* = 27	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value
NNRTI mutations					0.443		
No	364	348 (95.6)	16 (4.4)	1			
Yes	91	87 (95.6)	4 (4.4)	0.95 (0.32–2.84)	0.926		
No genotype	282	275 (97.5)	7 (2.5)	0.57 (0.23–1.38)	0.209		
PI mutations					0.328		
No	307	292 (95.1)	15 (4.9)	1			
Yes	148	143 (96.6)	5 (3.4)	0.69 (0.25–1.89)	0.468		
No genotype	282	275 (97.5)	7 (2.5)	0.51 (0.21–1.26)	**0.145**		
INI mutations					0.260		
No	446	427 (95.7)	19 (4.3)	1			
Yes	9	8 (88.9)	1 (11.1)	2.75 (0.37–20.51)	0.325		
No genotype	282	275 (97.5)	7 (2.5)	0.59 (0.25–1.41)	0.234		
Mutation K103N/S					**0.054**		
No	420	404 (96.2)	16 (3.8)	1			
Yes	35	31 (88.6)	4 (11.4)	2.96 (0.99–8.84)	**0.053**		
No genotype	282	275 (97.5)	7 (2.5)	0.66 (0.27–1.6)	0.358		
Mutation M184V/I					0.444		
No	387	370 (95.6)	17 (4.4)	1			
Yes	68	65 (95.6)	3 (4.4)	0.96 (0.28–3.26)	0.942		
No genotype	282	275 (97.5)	7 (2.5)	0.57 (0.24–1.37)	0.208		

Note: Variables with univariable *p*-value <0.20 were retained for the multivariable analysis. Univariable and multivariable Cox proportional hazard models were used. For multivariable analysis, missing values for CD4 count and CD4 nadir were imputed with the mean value. Multivariable stepwise backward technique was used to identify factors independently associated with the risk of viral load ≥50 copies/mL. In the final multivariate model, predictors with a *p*-value of <0.05 were considered statistically significant.

Abbreviations: DTG, dolutegravir; RPV, rilpivirine; 3TC, lamivudine; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; CI, confidence interval; HR: hazard ratio.

[a]Standard logarithm transformation for the model.

[b]For the baseline regimen variable, DTG + 3TC and other INSTI+RTI regimens were combined into a single category due to zero events of VL≥50 copies/mL in the other INSTI + RTI regimens group.

more published data currently available for DTG/3TC regimens than DTG/RPV or other INSTI+RTI regimens. A 2021 systematic review identified 5 cohorts ($n = 2224$) of treatment-experienced, virologically suppressed people with HIV ($n > 100$) who were initiating DTG/3TC and found 97–100% at week 48 and 92–100% at week 96 maintained suppression [10–15]. A more recent (2025) systematic review and meta-analysis pooled data among ART-experienced individuals switching to DTG + 3TC and estimated the proportions virologically suppressed at 48 weeks (from 24 studies with 7130 individuals) as 96.6% [95% CI: 95.0, 98.0] and at 96 weeks (9 studies with 3192 individuals) as 97.1% [95% CI: 94.6–99.0] [16]. The TANDEM study, a chart review study from the US, showed that among virologically suppressed people who switched to a two-drug regimen, 96% of those on DTG/3TC (median 81 weeks follow up) and 93% of those on DTG/RPV (median 143 weeks follow up) maintained suppression [17].

In the assessment of factors associated with loss of suppression, Black ethnicity was identified as a significant predictor of a VL ≥50 copies/mL. This is consistent with findings in other European and US study populations [18–20]. This may be partially attributed to the fact that racial minorities with HIV are more likely to experience social and economic factors impacting access to care, quality of life, and overall physical and mental health, compared to White individuals with HIV [21]. Migration status may also influence viral rebound and other adverse HIV outcomes [22], with Black migrants

from the Africa region having greater barriers to consistent treatment and care, as well as increased HIV-related stigma and discrimination in Europe [22, 23].

INSTI+RTI two-drug regimens were durable and well-tolerated in this population. By 96 weeks, discontinuations of baseline regimens were overall low, but slightly higher in the DTG + RPV group (7.0%, 95% CI: 3.8, 11.1%) compared to the DTG + 3TC group (4.7%, 95% CI: 3.0, 6.8%). Adverse events were also higher among the DTG + RPV group (7.5% vs. 4.9% for DTG + 3TC), which may have contributed to the discontinuation rate.

The most frequent ($n = 8$, 1.1%) individual adverse event was weight gain, but only 3 regimen discontinuations were attributed to weight changes. Weight-related endpoints were not included as part of the per-protocol analysis, so the extent of the weight changes cannot be evaluated. Weight gain on DTG regimens has been documented in the literature, particularly when switching from regimens containing EFV or TDF, which may have a suppressive effect on weight [24–28]. The fact that weight gain was only significant enough to be documented as an adverse event in a small proportion of the study population reflects that most participants were switching to an INSTI + RTI two-drug regimen from a DTG-based three-drug regimen.

In this setting, proviral DNA testing capable of evaluating resistance in suppressed individuals, including archived drug resistance mutations, was not commonly available as part of routine care. Overall, 61.7% had at least one resistance test documented in their medical record that occurred at any point prior to baseline, and history of any resistance mutations was documented in 50% of those tested (67.5% DTG + RPV; 42.5% DTG + 3TC). However, many of the documented mutations may no longer be present in replicating virus given the duration of time between prior testing and current INSTI+RTI exposures. Of the 18/536 (3.6%) of individuals on DTG/3TC with documented history of M184V/I resistance mutations, none experienced loss of virologic suppression during 96 weeks of follow up. Similarly high levels of suppression among individuals taking DTG + 3TC with prior documented M184V/I mutations have been reported in both clinical trials and observational settings [7, 17]. One individual on DTG + RPV and experiencing a single viral load ≥50 copies/mL at 96 weeks had a K101E resistance mutation, which confers low level reduced susceptibility to RPV. No other individuals with loss of suppression of DTG + RPV had documented history of mutations associated with reduced susceptibility to DTG or RPV.

Lack of resistance data prior to initiating a DTG-based two-drug regimen is a risk for functional monotherapy should pretreatment resistance mutations to NRTIs or NNRTI components go undetected. While the lack of resistance testing at the time of suppressed switch is expected in a setting where proviral DNA analysis is not routinely available, close to 40% of the population had no documentation of prior resistance assessments to inform regimen selection. It is, therefore, reassuring that in this study population neither the lack of resistance history nor the common occurrence of mutations among those tested appears to have impacted the effectiveness of DTG-based two-drug regimens given the very low virologic failure rate.

The CD4+ cell count and CD4/CD8 ratio are important indicators of immune function and prognosis in people with HIV who are receiving ART. DTG-based regimens have been shown to support immune recovery by increasing both markers among treatment-naïve individuals initiating treatment [29–31]. In this study population, however, individuals were stable on effective treatment when switching to INSTI+RTI dual therapy. Baseline mean CD4+ cell counts were high across regimens [733 (IQR:708–757)] cells/mm^3), as was the mean CD4:CD8 ratio of 1.00 (IQR:0.95–1.05). Over 96 weeks, small and non-statistically significant increases in CD4 cell counts [mean change of +7 cells/mm^3 (95% CI: −11 to 24), $p = 0.46$] and small statistically significant increases in the CD4:CD8 ratio [+0.05 (0.01 to 0.09), $p = 0.016$] were documented. These small increases likely had limited clinical impact and are consistent with what has been seen in other switch cohorts. This suggests that immune recovery had already occurred in these treatment-experienced individuals, and that effective new regimens sustain, rather than continue to improve immune function after switch [7, 32, 33].

This analysis has limitations, including possible selection bias introduced by inclusion of sites or participants different in characteristics or health status compared to the general population of people living with HIV in Europe. This is not strictly a limitation applicable to non-interventional study designs. More specific to the secondary analysis of medical record data is the potential for incomplete or missing information for key variables, as data are only available if collected as part of routine clinical practice. Additionally, the frequency and timing of follow up between individuals is variable. Participants with missing values were excluded from the snapshot analyses which may have overestimated effectiveness.

Due to the limitations of the available data, we were unable to assess all characteristics which may have influenced effectiveness and safety of oral two-drug regimens, such as adherence and comorbidities, including hepatitis B co-infections. This information may have provided additional insights into the study population and treatment responses; however, none of the 39 two-drug

regimen discontinuations were attributed to reactivation or new onset of co-infections, including hepatitis B, or to adherence challenges. Further, there were no drug-related adverse events or SAEs of reduced liver function or hepatic flares which may occur with uncontrolled hepatitis infection.

As anticipated, the study population was primarily prescribed DTG + 3TC or DTG + RPV. This is reflective of currently approved two-drug oral treatment regimens, but minimal representation of other INSTI + RTI dual therapy regimens limits the generalizability of these results to all oral INSTI + RTI regimens. Given the time period of the study, some individuals initiated DTG + RPV or DTG + 3TC prior to the availability of these regimens in single tablet fixed-dose combination formulations. We did not account for formulation in our analysis, which may have missed differences in outcomes among those with a higher pill burden compared to those taking single-tablet regimens. Generally, single-tablet HIV treatment is associated with increased adherence and improved virologic outcomes [34]. The high rates of suppression across the study population suggest that 2DRs were effective regardless of formulation or other unassessed characteristics like adherence. Finally, COVID-19 may have impacted clinical practices towards the end of the study period, potentially influencing prescribing patterns and frequency of clinical follow up.

In conclusion, the results of this study from a large European multicentre sample reflective of real-world clinical practice show that INSTI+RTI two-drug regimens, specifically DTG + 3TC and DTG + RPV, were effective maintenance therapies for virologically suppressed people with HIV. In addition to high rates of continued suppression, adverse events were few and non-serious, and all-cause discontinuations infrequent over 96 weeks of follow up. These findings support the use of oral two-drug regimens (DTG + 3TC, DTG + RPV) as a treatment switch strategy for people living with HIV who are stable on their current ART regimens.

AUTHOR CONTRIBUTIONS

All authors contributed to the interpretation of the findings and preparation and review of the manuscript. JvW, VV, MA, LA and AP contributed to the design of the study. CH, LR, VV and CF contributed to the study conduct and data management for the study. CH drafted the manuscript. CM, SDW, MJ, EQR, CK, CD, DZ, FP, RM, LC, JF, GL, CM, JE, GT and MD were involved in collection of data for the study.

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CONFLICT OF INTEREST STATEMENT

Cristina Mussini has served on advisory boards for ViiV Healthcare, Gilead Sciences, Merck Sharp & Dohme, and Janssen Pharmaceuticals, and has received a research grant from Gilead Sciences. Eugenia Quiros-Roldan has received speaker honoraria, research grants, and travel support from Gilead Sciences, ViiV Healthcare and Merck Sharp and Dohme. Frank Post has received grants and honoraria from Gilead Sciences, and grants from Immunocore, ViiV Healthcare, and Merck Sharp and Dohme. Laura Comi has received speaker honoraria, research grants, and travel support from Gilead, ViiV, and Merck, Sharp and Dohme. Geoffroy Liegeon has served on advisory boards for ViiV Healthcare. Anton Pozniak has received grants/research support from ViiV Healthcare, Janssen Pharmaceuticals, Gilead Sciences, and Merck Sharp & Dohme; he has received honoraria or consultation fees from ViiV Healthcare, Gilead Sciences, and Merck Sharp and Dohme. Cassidy Henegar, Leigh Ragone, Bryn Jones, Jean van Wyk, Michael Aboud, and Vani Vannappagari are employees of ViiV Healthcare and receive GSK stock through their employment. Lambert Assoumou, Stephane De Wit, Margaret Johnson, Chris Kenyon, Colin Deschanvres, David Zucman, Roya Movahedi, Julie Fox, Geoffrey Liegeon, Charlotte Martin, Jonathan Edwards, Giorgio Tiecco, Marc Delforge and Carl Fletcher have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets used in this study are not publicly available due to privacy concerns and the proprietary nature of the database but can be accessed upon reasonable request through the corresponding author.

ETHICS STATEMENT

Informed consent procedures were undertaken as required by country-specific regulations and local procedures for the collection of retrospective and/or prospective data. Individuals included in the analysis population did not need to attend any additional visits or undergo any procedures above their routine standard of care. Ethics Committees (EC) in each of the relevant countries approved the study protocol and any accompanying materials prior to the beginning of any study activities. Any subsequent amendments requiring review by EC were not implemented until the EC granted a favourable opinion for the study which was disseminated to the investigator and sites.

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