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Virologically suppressed switch to Dolutegravir/Lamivudine 2-Drug regimen versus switch to commonly prescribed 3-Drug regimens in the United States

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Abstract

Background Two-drug regimens (2DRs) have been introduced in recent years to potentially reduce antiretroviral therapy (ART) toxicities and drug-drug interactions while demonstrating comparable efficacy to three-drug regimens (3DRs) for people with HIV (PWH). The objective of this study was to compare the real-world effectiveness and durability of a single-tablet 2DR of dolutegravir/lamivudine (DTG/3TC) with that of commonly prescribed 3DRs in ART-experienced, virologically suppressed PWH during the first 24 months of DTG/3TC availability in the United States.

Methods Virologically suppressed (viral load [VL] < 200 copies/mL) adult PWH initiating DTG/3TC 2DR, bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF), or a DTG-based 3DR between 01MAY2019 and 31OCT2020 were identified in the OPERA® cohort and followed through 30APR2021. Univariate Poisson regression (incidence rates) and marginal structural Cox proportional hazards models with inverse probability of treatment weights (hazard ratios) were used to quantify relationships between regimen type and confirmed virologic failure (2 consecutive VLs ≥ 200 copies/mL) or regimen discontinuation. Reasons for discontinuation were examined.

Results A total of 8,037 ART-experienced, virologically suppressed PWH met the inclusion criteria and switched to DTG/3TC ($n = 1,450$), BIC/FTC/TAF ($n = 5,691$), or a DTG-based 3DR ($n = 896$). Incidence rates of confirmed virologic failure were low for all groups, at 0.66 (DTG/3TC), 0.84 (BIC/FTC/TAF), and 1.78 (DTG 3DR) per 100 person-years (py). Compared to DTG/3TC, only the DTG 3DRs were associated with a statistically significant increased hazard of confirmed virologic failure (hazard ratio: 5.21, 95% confidence interval: 1.85, 14.67). Discontinuation rates per 100 py were highest in the DTG 3DR group (24.90), followed by the DTG/3TC group (17.69) and the BIC/FTC/TAF group (8.30). Regardless of regimen, discontinuations were infrequently attributed to effectiveness (VL ≥ 200 copies/mL; 4%) or tolerability (adverse diagnoses, side effects, or lab abnormalities; 6%).

Conclusions Among virologically suppressed PWH initiating a new regimen, few individuals experienced virologic failure in real-world clinical care. While rates of regimen discontinuation were high, most discontinuations could not

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be attributed to a lack of virologic control or poor tolerability. These findings suggest that DTG/3TC is an effective option for ART-experienced, virologically suppressed PWH.

Keywords 2-drug regimen, 3-drug regimen, Antiretroviral therapy, Cohort, HIV, Effectiveness, Dolutegravir, Dolutegravir/lamivudine, Bictegravir/emtricitabine/tenofovir alafenamide

Background

The use of three-drug regimens (3DRs), most frequently consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent from either the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase strand transfer inhibitor (INSTI) class, has long been the standard of care for HIV treatment. Since their approval, INSTI-based 3DRs have been among the preferred regimens, especially those containing dolutegravir (US Food and Drug Administration [FDA] approval in August 2013) and bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF; FDA approval in February 2018) [1, 2].

As effective ART has increased life expectancy for people with HIV (PWH) [3, 4], concerns about long-term ART toxicities, polypharmacy and drug-drug interaction have been raised [5, 6]. Two-drug regimens (2DRs) have been introduced in recent years to address these concerns [7, 8]. In late 2017, dolutegravir/rilpivirine (DTG/RPV) was the first single-tablet 2DR to be approved in the US for the treatment of ART-experienced, virologically suppressed adult PWH [9]. Dolutegravir/lamivudine (DTG/3TC) was the first once-daily single-tablet 2DR without a food requirement; it was approved for ART-naïve PWH in April 2019 and for ART-experienced, virologically suppressed PWH in August 2020 [10].

Clinical trials have established the efficacy, safety, and tolerability of DTG/3TC [11–15]. Real-world evidence on DTG 2DRs has been promising but often limited by relatively small sample sizes or the use of retrospectively collected data [16–20]. Notably, real-world evidence in North American settings is particularly sparse but has been generally favorable [9, 21]. Given the potential value of single-tablet 2DRs, the objectives of this study were to evaluate the effectiveness and durability of DTG/3TC 2DR compared to other commonly prescribed 3DRs in ART-experienced, virologically suppressed PWH during the first 24 months of DTG/3TC availability in a large clinical cohort in the US.

Methods

Study design and population

This study used prospectively collected electronic health record (EHR) data from the Observational Pharmacoepidemiology Research and Analysis (OPERA®) cohort. OPERA includes data from rural clinics, wellness centers, sexual health clinics, health departments, federally qualified health centers, and large metropolitan multidisciplinary health centers across 19 US states and Puerto Rico. At the time of the study, PWH in OPERA represented approximately 12% of all PWH linked to care in the US [22]. The OPERA cohort obtains annual institutional review board (IRB) approval from Advarra IRB, including a waiver of informed consent and authorization for the use of protected health information. OPERA complies with all HIPAA and HITECH requirements.

Individuals who switched to the single-tablet formulation of DTG/3TC, BIC/FTC/TAF, or a DTG 3DR (i.e., dolutegravir/abacavir/lamivudine [DTG/ABC/3TC], dolutegravir+tenofovir disoproxil fumarate/emtricitabine [DTG+TDF/FTC], or dolutegravir+tenofovir alafenamide/emtricitabine [DTG+TAF/FTC]) were eligible for the study. Of note, twice daily DTG was allowed in the DTG 3DR group and any formulation of these DTG 3DRs was included. The study population included ART-experienced people with HIV-1 infection who were aged 18 years or older and were virologically suppressed (last HIV RNA viral load [VL]<200 copies/mL within 12 months before/at regimen initiation). The window of eligibility was from 01MAY2019 to 31OCT2020. PWH with any prior exposure to the ART regimens of interest were excluded. Included individuals contributed person-time from initiation of the regimen of interest until the first occurrence of the outcome of interest (virologic failure or regimen discontinuation) or one of the following censoring events: (a) loss to follow-up (i.e., 12 months of follow-up with no contact), (b) death, (c) study end (30APR2021), or (d) regimen discontinuation (analyses of virologic failure only).

Measurements

Demographic and clinical characteristics were described for each group. Confirmed virologic failure was defined as two consecutive VLs≥200 copies/mL. Regimen discontinuation occurred when any component of the ART regimen was changed (i.e., adding and/or removing any ARV agent). Switching from a DTG/3TC single-tablet 2DR to a multi-tablet DTG+3TC regimen was considered as a discontinuation in this analysis.

Reasons for discontinuation were identified from provider notes, lab results, and diagnoses. These reasons were categorized as treatment-related, non-treatment related, or no reason identified. Treatment-related reasons included last VL≥200 copies/mL, adverse diagnosis/side effect (i.e., new mental health, liver, renal, or bone comorbidity diagnosed within 21 days before

discontinuation), or lab abnormality (i.e., alkaline phosphatase [ALP]; alanine transaminase [ALT]; aspartate transaminase [AST]; or bilirubin > 3 times the upper limits of normal within 21 days of discontinuation). Non-treatment-related reasons included regimen simplification, access issues, non-adherence, treatment gaps, or patient/provider choice.

Statistical analyses

Baseline was defined as the initiation date of the ART regimen of interest. Descriptive statistics for baseline demographic and clinical characteristics consisted of medians with interquartile range (IQR) for continuous variables and absolute and relative frequencies for categorical variables. Incidence rates and 95% confidence intervals (CI) for the first occurrence of confirmed virologic failure or regimen discontinuation were estimated using univariable Poisson regression.

Marginal structural Cox proportional hazards models with stabilized inverse probability of treatment weights (IPTW) were used to evaluate the association between ART regimen and time to virologic failure or regimen discontinuation. IPTWs were constructed with multinomial logistic regression including potential confounders identified a priori based on the literature. These were measured at baseline and included age (linear and quadratic terms), number of ART classes experienced prior to initiation of the regimen of interest (linear and quadratic terms), female sex, Black race, Hispanic ethnicity, receiving care in the Southern US, core agent class of regimen immediately prior to initiation of the regimen of interest (INSTI, NNRTI, PI, other/unknown), CD4 cell count (linear and quadratic terms) at baseline, and an interaction term between sex and region of care.

Sensitivity analyses

The study period included both time before (01MAY2019–29FEB2020) and during (01MAR2020–30APR2021) the COVID-19 pandemic, an era during which provider-patient interactions, prescribing practices (of all medicines, including ART), and lab testing (e.g., viral load monitoring) were impacted [23–25]. Sensitivity analyses explored its potential impact by assessing incidence rates of visits with healthcare providers (in-person and telehealth), viral load measurements, regimen discontinuations, and virologic failures both before and during the COVID-19 pandemic.

Results

Study Population

A total of 8,037 ART-experienced, virologically suppressed PWH met the inclusion criteria and switched to DTG/3TC (n = 1,450), BIC/FTC/TAF (n = 5,691), or a DTG 3DR (n = 896). Baseline demographic and clinical characteristics varied across groups (Table 1). Individuals who switched to DTG/3TC were slightly older, less likely to be Black or to receive care in the US South, and more likely to have comorbid conditions than individuals initiating BIC/FTC/TAF or a DTG 3DR. PWH initiating a DTG 3DR were most likely to be new to an OPERA provider and therefore, to be missing information about their prior ART experiences (Table 1). There were 13 PWH taking a DTG 3DR that were prescribed DTG twice daily, suggesting that they were heavily treatment experienced.

Effectiveness: confirmed Virologic failure

Overall, only 88 PWH (1%) experienced virologic failure over a total of 9,696 py. Incidence rates for confirmed virologic failure were < 2 per 100 py in each of the three ART regimen groups. After adjustment for confounding, those in the DTG 3DR group were over five times more likely to experience virologic failure compared to the DTG/3TC group (Fig. 1). There was no statistically significant difference in incidence rate of virologic failure between the DTG/3TC and BIC/FTC/TAF groups.

Durability: Follow-Up and Regimen Discontinuation

The median duration of follow-up on the regimen of interest exceeded a year in all groups; PWH on BIC/FTC/TAF were followed the longest (Table 2). The incidence rates for regimen discontinuation varied considerably across groups (11–27%) and confidence intervals did not overlap. In adjusted analyses, compared to DTG/3TC, those on BIC/FTC/TAF were half as likely to discontinue the regimen than those on DTG/3TC. Individuals on DTG 3DRs had a 69% higher hazard of regimen discontinuation than those on DTG/3TC.

While the reasons for regimen discontinuation were often unknown, only 7 to 11% of discontinuations were related to the effectiveness (VL ≥ 200 copies/mL) or tolerability (adverse diagnoses, side effects or lab abnormalities) of the ART regimen (Fig. 2). Notably, regardless of regimen, nearly all PWH who discontinued their regimen were suppressed (VL < 200 copies/mL) at the time of discontinuation (DTG/3TC: 97%; BIC/FTC/TAF: 94%; DTG 3DR: 93%). The most common non-treatment related reasons for discontinuation included provider choice (all groups), access issues related to cost, formulary, or availability (DTG/3TC), and a reduction of pill count (DTG 3DR).

Sensitivity analyses: impact of the COVID-19 pandemic

The median follow-up time in this study was considerably longer during the COVID-19 pandemic (14.0 months; IQR: 9.4, 14.0) than before it (4.9 months; IQR: 2.4, 7.4). Overall, the incidence rate of in-person visits with healthcare providers decreased from 7.55 per py (95% CI: 7.44, 7.66) before COVID-19 to 5.04 per py (95% CI: 4.99, 5.09)

Table 1 Baseline demographic and clinical characteristics of ART-experienced, virologically suppressed PWH switching to DTG/3TC, BIC/FTC/TAF, or a DTG 3DR between 01MAY2019 and 31OCT2020 (*N* = 8,037)

	DTG/3TC[a] (*N* = 1,450)	BIC/FTC/TAF[b] (*N* = 5,691)	DTG 3DR[c] (*N* = 896)
Age, Median (IQR)	45 (34, 55)	43 (32, 54)	43 (32, 53)
Sex, n (%)			
Female	271 (19)	909 (16)	163 (18)
Race, n (%)			
Asian	36 (3)	100 (2)	11 (1)
Black	508 (35)	2,456 (43)	438 (49)
White	802 (55)	2,752 (48)	376 (42)
Mixed race or other race	52 (4)	196 (3)	40 (5)
Unknown	52 (4)	187 (3)	31 (4)
Ethnicity, n (%)			
Hispanic	376 (26)	1,368 (24)	148 (17)
Not Hispanic	1,014 (70)	4,138 (73)	723 (81)
Unknown	60 (4)	185 (3)	25 (3)
Geographic Region, n (%)			
US Midwest	25 (2)	259 (5)	35 (4)
US Northeast	91 (6)	602 (11)	116 (13)
US South	778 (54)	3,901 (69)	665 (74)
US West	555 (38)	892 (16)	74 (8)
US Territories	≤ 5[d]	37 (1)	6 (1)
Payer, n (%)			
Medicare	154 (11)	441 (8)	90 (10)
Medicaid	355 (25)	1,242 (22)	161 (18)
Commercial Insurance	761 (53)	2,685 (47)	384 (43)
Ryan White / ADAP	469 (32)	1,879 (33)	304 (34)
Cash	11 (1)	66 (1)	≤ 5[d]
No payer data available	87 (6)	501 (9)	109 (12)
Core agent class of regimen immediately prior to baseline, n (%)			
INSTI	1,062 (73)	2,522 (44)	117 (13)
NNRTI	127 (9)	823 (15)	52 (6)
PI	57 (4)	421 (7)	57 (6)
Entry inhibitor	≤ 5[d]	≤ 5[d]	0 (0)
Unknown	99 (7)	1,718 (30)	635 (71)
> 1 core agent	104 (7)	203 (4)	35 (4)
CD4 cell count (cells/μL)			
CD4 count test result available	1,442 (99)	5,603 (99)	878 (98)
Median cells/μL (IQR)	730 (550, 944)	675 (484, 892)	678 (471, 861)
Any comorbidities[e], n (%)	1,126 (78)	4,054 (71)	548 (61)

3DR, 3-drug regimen; 3TC, lamivudine; ART, antiretroviral therapy; BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; IQR, interquartile range; INSTI, Integrase strand transfer inhibitor; N, number; NNRTI, Non-nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; PWH, people with HIV; TAF, tenofovir alafenamide; μL, microliter; US, United States

[a] DTG/3TC: dolutegravir/lamivudine single-tablet 2-drug regimen

[b] BIC/FTC/TAF; bictegravir/emtricitabine/tenofovir alafenamide

[c] DTG 3DR: dolutegravir/abacavir/lamivudine, dolutegravir + tenofovir disoproxil/emtricitabine, or dolutegravir + tenofovir alafenamide/emtricitabine 3-drug regimen

[d] HIPAA privacy requirements preclude the reporting of 5 or fewer observations in any cell

[e] Any diagnosis at or prior to baseline of autoimmune disease, cardiovascular disease, invasive cancers, endocrine disorders, mental health disorders, liver disease, bone disorders, peripheral neuropathy, renal disease, hypertension, or substance abuse

during COVID-19, while incidence rates of telehealth visits increased from 0.21 per py (95% CI: 0.19, 0.23) to 1.65 per py (95% CI: 1.62, 1.68). There was also a small decrease in both viral load measurements (2.94 to 2.17 per py) and regimen discontinuations (0.15 to 0.10 per py). Virologic failures were infrequent in both periods. Results were mostly consistent across the three regimen groups. However, individuals on DTG/3TC experienced an increase in visits during COVID-19, driven by a much larger increase in telehealth visits and a smaller reduction

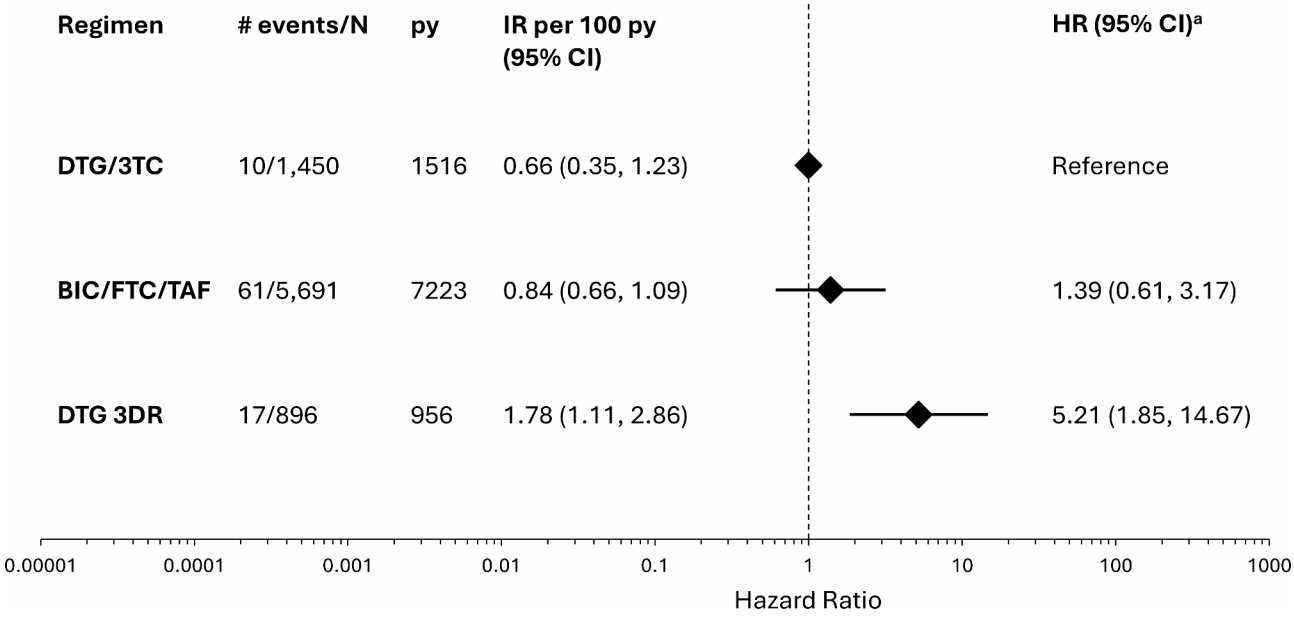

Fig. 1 Incidence rates of confirmed virologic failure and association between ART regimen and confirmed virologic failure, by ART regimen (DTG/3TC, BIC/FTC/TAF, DTG 3DR) 3DR, 3-drug regimen; 3TC, lamivudine; ART, antiretroviral therapy; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; FTC, emtricitabine; HR, hazard ratio; IR, incidence rate; py, person-years; TAF, tenofovir alafenamide. [a] Marginal structural Cox proportional hazards models with stabilized inverse probability of treatment weights controlling for baseline age (linear & quadratic), number of ART classes (linear & quadratic), female, Black race, Hispanic ethnicity, Southern US, core agent class of prior regimen, CD4 cell count (linear & quadratic)

Table 2 Duration of follow up and regimen discontinuation among virologically suppressed PWH switching to DTG/3TC, BIC/FTC/TAF, or a DTG 3DR between 01MAY2019 and 31OCT2020 (*N* = 8,037)

	DTG/3TC[a] (*N* = 1,450)	BIC/FTC/TAF[b] (*N* = 5,691)	DTG 3DR[c] (*N* = 896)
Months of follow-up on the regimen, Median (IQR)	13.6 (7.3, 18.3)	15.8 (11.6, 19.8)	13.4 (7.9, 18.2)
Regimen discontinuation[d]			
n (%)	269 (19)	602 (11)	240 (27)
IR per 100 py (95% CI)	17.69 (15.70, 19.94)	8.30 (7.66, 8.99)	24.90 (21.94, 28.26)
Unadjusted HR (95% CI)	Reference	0.48 (0.42, 0.56)	1.40 (1.18, 1.67)
Adjusted HR[e] (95% CI)	Reference	0.51 (0.42, 0.62)	1.69 (1.30, 2.19)

3DR, 3-drug regimen; 3TC, lamivudine; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; FTC, emtricitabine; HR, hazard ratio; IQR, interquartile range; IR, incidence rate; N, number; PWH, people with HIV; py, person-year; TAF, tenofovir alafenamide;

[a] DTG/3TC: dolutegravir/lamivudine single-tablet 2-drug regimen

[b] BIC/FTC/TAF; bictegravir/emtricitabine/tenofovir alafenamide

[c] DTG 3DR: dolutegravir/abacavir/lamivudine, dolutegravir + tenofovir disoproxil/emtricitabine, or dolutegravir + tenofovir alafenamide/emtricitabine 3-drug regimen

[d] Regimen discontinuation: adding and/or removing any antiretroviral agent

[e] Marginal structural Cox proportional hazards models with stabilized inverse probability of treatment weights controlling for baseline age (linear & quadratic); number of ART classes (linear & quadratic); female; Black race, Hispanic ethnicity; Southern US; core agent class of prior ART regimen; CD4 cell count (linear & quadratic)

in in-person visits than those in either of the 3DR groups (Table 3).

Discussion

In this observational study evaluating the effectiveness and durability of a single-tablet DTG/3TC 2DR compared to commonly prescribed 3DRs among 8,037 ART-experienced, virologically suppressed PWH, rates of virologic failure were low across all regimens. This is noteworthy given that use of a 2DR may alleviate issues relating to tolerance and drug-drug interactions. Rates of discontinuation differed between groups and were high, especially in the DTG/3TC and DTG 3DR groups.

The effectiveness of DTG/3TC is consistent with results from clinical trials and observational studies [11–13]. A meta-analysis of real-world evidence studies reported that only 1% of ART-experienced, suppressed individuals experienced virologic failure defined as two consecutive viral loads ≥ 50 copies/mL or a single viral load > 1000 copies/mL [16]. Incidence rates of virologic failure

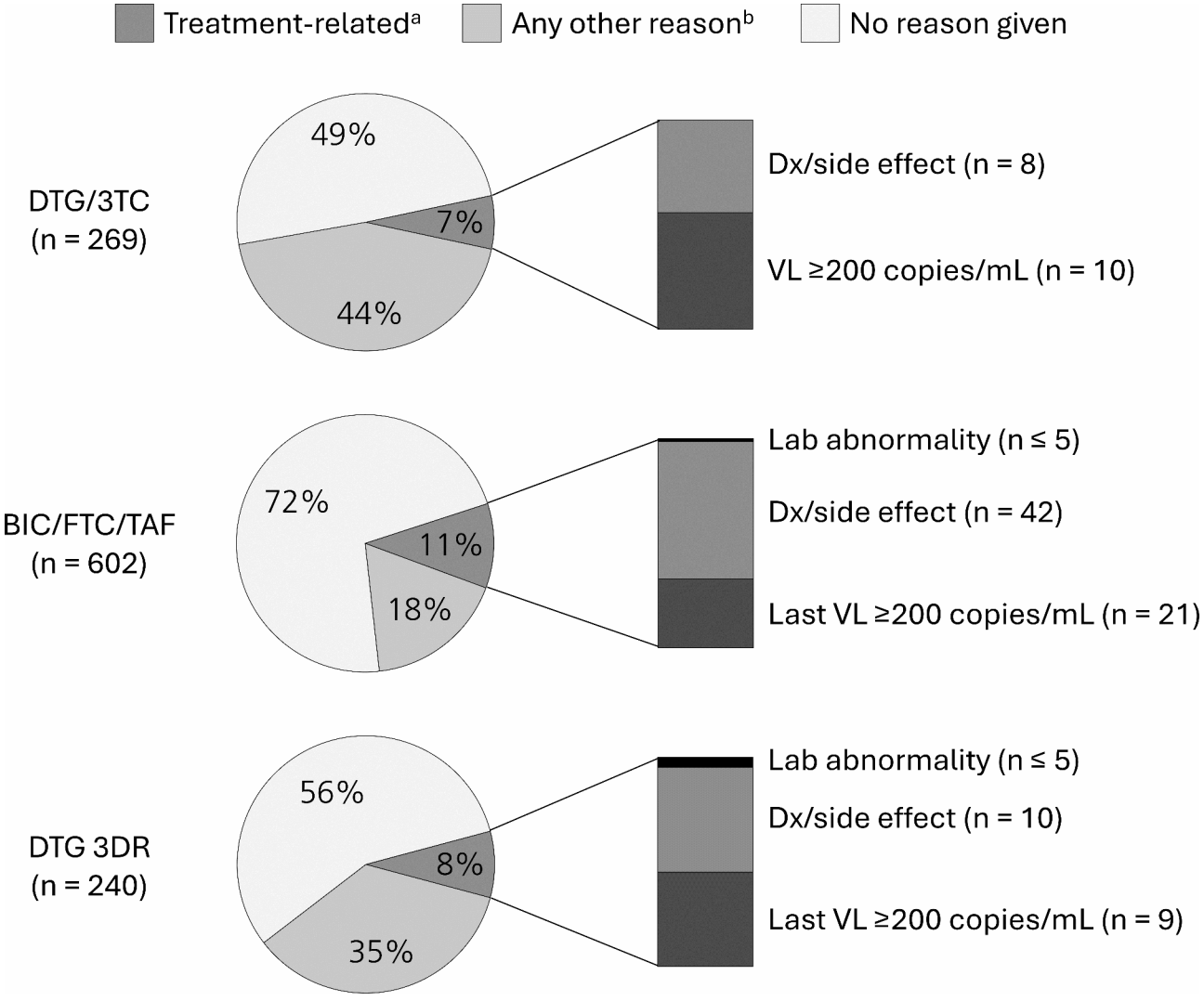

Fig. 2 Reasons for ART regimen discontinuation identified from healthcare provider notes, lab results, and diagnoses, by ART regimen (DTG/3TC, BIC/FTC/TAF, DTG 3DR). 3DR, 3-drug regimen; 3TC, lamivudine; ART, antiretroviral therapy; BIC, bictegravir; DTG, dolutegravir; Dx, diagnosis; FTC, emtricitabine; mL, milliliter; TAF, tenofovir alafenamide; VL, viral load. [a] Last VL > 200 copies/mL, adverse diagnosis/side effect (i.e., new mental health, liver, renal or bone comorbidity diagnosed within 21 days before discontinuation, or as noted), lab abnormality (i.e., alkaline phosphatase [ALP], alanine transaminase [ALT], aspartate transaminase [AST] or bilirubin > 3 times the upper limits of normal within 21 days of discontinuation). [b] Simplification; access issues; non-adherence; treatment gap; patient/provider choice; any other reason noted

ranged from 0.9 per 100 py to 3.3 per 100 py in European observational studies [26–29]. In this study, only DTG 3DRs were significantly associated with virologic failure compared to DTG/3TC (adjusted HR: 5.21; 95% CI: 1.85, 14.67). Notably, none of the 13 PWH prescribed twice-daily DTG as part of a DTG 3DR experienced confirmed virologic failure.

Rates of discontinuation varied across regimens, from 8.3 per 100 py with BIC/FTC/TAF, to 17.7 per 100 py with DTG/3TC, and 24.9 per 100 py with DTG 3DR. These rates are elevated compared to rates of discontinuation reported by other cohorts, which ranged from 4.7 per 100 py to 11.1 per 100 py [28–31]. Compared to DTG/3TC, hazard of regimen discontinuation was lower with BIC/FTC/TAF (adjusted HR: 0.51; 95% CI: 0.42, 0.62), but higher with DTG 3DRs (adjusted HR: 1.69; 95% CI: 1.30, 2.19). Most PWH remained virologically suppressed at discontinuation and only 7 to 11% of discontinuations appeared related to effectiveness or tolerability. This finding is in line with clinical trials and observational studies, which reported between 1% and 8% of discontinuations linked to adverse events, intolerance, or toxicity [11, 30, 32, 33]. Although most discontinuations had no reason listed in the EHR, other discontinuations not associated with elevated VL or toxicity were frequently attributed to provider choice (17–37% of discontinuations).

The higher rates of regimen discontinuation among DTG/3TC and DTG 3DR users may be explained in

Table 3 Clinical follow-up measures before and during the COVID-19 pandemic[a] among virologically suppressed PWH switching to DTG/3TC, BIC/FTC/TAF, or a DTG 3DR between 01MAY2019 and 31OCT2020 (*N* = 8,037)

	DTG/3TC[b]		BIC/FTC/TAF[c]		DTG 3DR[d]	
	Before COVID *N* = 871	**During COVID *N* = 1,348**	**Before COVID *N* = 4,138**	**During COVID *N* = 5,531**	**Before COVID *N* = 624**	**During COVID *N* = 800**
Person-months of follow-up, Median (IQR)	4.0 (1.5, 6.3)	13.8 (7.8, 14.0)	5.1 (2.6, 7.6)	14.0 (10.3, 14.0)	4.8 (2.4, 7.3)	12.7 (7.9, 14.0)
Provider visits, n	2,070	10,296	13,407	35,273	2,276	4,401
Median (IQR)	2 (0, 4)	6 (3, 9)	2 (0, 4)	5 (2, 9)	2 (1, 5)	4 (1, 8)
IR per py (95% CI)						
All visits	6.89 (6.60, 7.19)	8.41 (8.25, 8.58)	7.70 (7.57, 7.83)	6.38 (6.31, 6.45)	9.17 (8.80, 9.55)	6.13 (5.95, 6.31)
In-person visits[e]	6.75 (6.46, 7.05)	6.30 (6.16, 6.44)	7.50 (7.37, 7.63)	4.84 (4.78, 4.89)	8.85 (8.49, 9.23)	4.50 (4.35, 4.66)
Telehealth visits[f]	0.14 (0.10, 0.19)	2.12 (2.04, 2.20)	0.20 (0.18, 0.22)	1.54 (1.51, 1.58)	0.31 (0.25, 0.39)	1.63 (1.54, 1.73)
Viral load measurements, n	899	3,024	4,979	11,739	854	1,464
IR per py (95% CI)	2.99 (2.80, 3.19)	2.47 (2.38, 2.56)	2.86 (2.78, 2.94)	2.12 (2.09, 2.16)	3.44 (3.22, 3.68)	2.04 (1.94, 2.15)
Discontinuations, n (%)	101 (12)	168 (13)	151 (4)	451 (8)	95 (15)	145 (18)
IR per py (95% CI)	0.34 (0.28, 0.41)	0.13 (0.12, 0.16)	0.09 (0.07, 0.10)	0.08 (0.07, 0.09)	0.38 (0.31, 0.47)	0.20 (0.17, 0.24)
Virologic failures, n (%)	≤ 5[g]	9 (1)	7 (< 1)	54 (1)	≤ 5[g]	12 (2)
IR per 100 py (95% CI)	0.33 (0.05, 2.36)	0.74 (0.00, 1.42)	0.40 (0.19, 0.84)	0.98 (1.00, 1.28)	2.02 (0.84, 4.86)	1.68 (1.00, 2.96)

3DR, three-drug regimen; 3TC, lamivudine; ART, antiretroviral therapy; BIC, bictegravir; CI, confidence interval; COVID, coronavirus disease 2019; DTG, dolutegravir; FTC, emtricitabine; HIV, human immunodeficiency virus; IQR, interquartile range; IR, incidence rate; n, number; PWH, people with HIV; py, person-year; TAF, tenofovir alafenamide

[a] The before COVID-19 period was 01MAY2019–29FEB2020; the during COVID-19 period was 01MAR2020–30APR2021

[b] DTG/3TC 2DR: dolutegravir/lamivudine single-tablet 2-drug regimen

[c] BIC/FTC/TAF 3DR; bictegravir/emtricitabine/tenofovir alafenamide 3-drug regimen

[d] DTG 3DR: dolutegravir/abacavir/lamivudine, dolutegravir + tenofovir disoproxil/emtricitabine, or dolutegravir + tenofovir alafenamide/emtricitabine 3-drug regimen

[e] In-person visits with a healthcare provider included any scheduled or walk-in outpatient, inpatients, emergency, or lab visit

[f] Telehealth visits included any phone or video encounters with a healthcare provider

[g] HIPAA privacy requirements preclude the reporting of 5 or fewer observations in any cell

part by the fact that comorbidities were more common in these groups than in BIC/FTC/TAF users, and management of comorbidities could have an impact on HIV treatment decisions. Moreover, high discontinuation rates for DTG 3DRs may be associated to the fact that DTG 3DRs are the oldest ART options in the study. Regimen selection and discontinuation decisions may also have been influenced by the staggered FDA approval for DTG/3TC 2DR in the US (April 2019 for ART-naïve, August 2020 for ART-experienced, suppressed PWH). Most included PWH (79%) switched to DTG/3TC between April 2019 and July 2020, representing off-label prescribing. The remaining 21% of PWH switched to DTG/3TC after FDA approval for ART-experienced, suppressed individuals [10]. In a post-hoc analysis, the proportion of individuals who discontinued their DTG/3TC regimen during follow-up was larger before FDA approval (20%) than after (12%). Surveys of healthcare providers highlight due caution when treating PWH [34], especially when switching to a new treatment paradigm [35]; precautionary decision-making may have been applied to the off-label prescribing of this new 2DR during the study.

The timing of this study may have also contributed to its limitations. Disruptions to HIV care during the beginning of the COVID-19 pandemic impacted the frequency and type of care received, as demonstrated by the sensitivity analysis. During the COVID-19 pandemic, there was a reduction in the rates of overall visits, in-person visits, and viral load monitoring among PWH who switched to BIC/FTC/TAF or a DTG 3DR, compared to rates observed before the pandemic; the increase in telehealth visits did not completely offset the decrease in in-person visits. In the DTG/3TC group, however, there was an overall increase in visits; the decrease in in-person visits was minimal and the increase in telehealth visits was more substantial than in the 3DR groups.

Missing data were also a challenge in this study. DTG 3DRs were more likely to be prescribed to PWH who were new to an OPERA provider and thus had missing or incomplete clinical history, including their prior ART experiences and comorbidities. Missingness was also an issue when considering reasons for regimen discontinuation as they are poorly documented in EHRs. While efforts were made to identify potential reasons by harnessing the richness of EHR data to evaluate not only provider notes but also diagnoses and lab results around the time of discontinuation, no reason could be attributed to 49–72% of discontinuations.

An additional limitation of the study is its short duration of two years, resulting in limited time to observe virologic outcomes and discontinuations. Further, despite the large sample size, the number of virologic failures was small across all three groups, leading to wide confidence intervals for the associated hazard ratios. This limits the ability to determine if clinically and/or statistically significant differences were truly present.

Key strengths of this study included the use of prospectively captured clinical data from the US-based OPERA cohort, representing a diverse group of approximately 12% of PWH in the US at the time of this study (June 2021) [36]. Even after applying the study's inclusion and exclusion criteria, the study sample size was over 8,000 PWH with 1,450 PWH initiating DTG/3TC. One previous study evaluated 966 PWH on DTG/3TC 2DR while all others were much smaller, ranging from 117 to 566 PWH on DTG/3TC in retrospective studies predominantly conducted in European countries [16, 18, 20, 27, 31, 37, 38]. The present study provided an opportunity to compare DTG/3TC 2DR in its first 24 months of availability in the US with commonly prescribed 3DRs in the US and to identify the rare outcome of virologic failure, even during the COVID-19 pandemic. The large sample size and rich EHR data also allowed for the adjustment through IPTWs of several potential confounders identified a priori. Our findings that DTG/3TC is likely an effective and durable treatment option for suppressed PWH were consistent with prior studies based in Europe and elsewhere, despite differences in sample sizes, geographic settings, and methodologic rigor of those studies.

Conclusions

Given the potential value of 2DRs in situations where complex polypharmacy, drug-drug interaction, and long-term ARV toxicity may be of concern, it is notable that virologic failure was rare among ART-experienced, virologically suppressed PWH in the US-based OPERA cohort who newly switched to DTG/3TC, BIC/FTC/TAF, or a DTG 3DR. Though regimen discontinuations were slightly higher than expected, only a small percentage was attributed to effectiveness or tolerability. The findings of this study suggest that DTG/3TC, a single-tablet 2DR, is an effective option for ART-experienced, virologically suppressed PWH. Continued study of 2DRs is needed to evaluate longer-term effectiveness and durability of these ART regimens for PWH.

Abbreviations

2DR	2-drug regimen
3DR	3-drug regimen
3TC	Lamivudine
ABC	Abacavir
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ART	Antiretroviral therapy
AST	Aspartate transaminase
ARV	Antiretroviral
BIC	Bictegravir
CI	Confidence interval
DTG	Dolutegravir
HER	Electronic health record
FDA	Food and Drug Administration
FTC	Emtricitabine
HIV	Human immunodeficiency virus
HR	Hazard ratio
INSTI	Integrase strand transfer inhibitor
IPTW	Inverse probability of treatment weights
IQR	Interquartile range
IRB	Institutional review board
mL	Milliliter
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OPERA®	Observational Pharmaco-Epidemiology Research and Analysis
PI	Protease inhibitor
PWH	People with HIV
Py	Person-years
RPV	Rilpivirine
STR	Single-tablet regimen
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
US	United States
VL	Viral load

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Author contributions

GP and JSF share the responsibility for the design of this study and protocol development. GP, JSF, MBW, and GPF contributed to the acquisition of data. JSF and LB are responsible for all analyses which were conducted according to the protocol. GP, JSF, LB, MBW, and GPF contributed to the interpretation of results. JSF and LB drafted the manuscript. All authors have critically reviewed and approved the manuscript and have participated sufficiently in the work to take public responsibility for its content. It is Epividian's policy to publish the results of all studies, regardless of the results, for full transparency; the sponsor of this study did not direct the study design, analysis, or submission of this manuscript for publication.

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Data availability

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 to the OPERA Epidemiological and Clinical Advisory Board. Access to codes may be granted

upon request with parties agreeing to privacy restrictions and technological specifications and requirements.

Declarations

Ethics approval and consent to participate

Institutional review board (IRB) approval covering patient data contained in the OPERA database was received from Advarra IRB; a waiver of informed consent and authorization for the use of protected health information for patient data was granted (Pro00023648). The study was conducted in accordance with HIPAA and HITECH requirements, which expand upon the ethical principles detailed in the 1964 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

GP, MBW, and AM are members of the Epidemiology and Clinical Advisory Board for Epividian. MBW has participated in post-conference advisory boards for the Conference on Retroviruses and Opportunistic Infections and International AIDS Conference and serves as a principal investigator on ViiV Healthcare clinical trials but does not receive personal compensation for this work, which goes directly to the AIDS Healthcare Foundation. AM receives research funding from Gilead, ViiV, GSK, Abbott, Roche, and Merck. He has attended advisory boards for Gilead, ViiV, and Epividian. JSF, LB, and GPF are employed by Epividian, Inc.; Epividian has had research funded by ViiV Healthcare, Merck & Co., Janssen, Gilead Sciences, Theratechnologies, EMD Serono, and AIDS Healthcare Foundation. VV, SS, CEH, and JvW are employed by ViiV Healthcare and hold stock in GSK as part of their employment.

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References

1. Ballantyne AD, Perry CM. Dolutegravir: first global approval. Drugs. 2013;73(14):1627–37.
2. Markham A. Bictegravir: first global approval. Drugs. 2018;78:601–6.
3. Teeraananchai S, Kerr S, Amin J, Ruxrungtham K, Law M. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. HIV Med. 2017;18(4):256–66.
4. Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr Opin HIV AIDS. 2016;11(5):492–500.
5. Back D, Marzolini C. The challenge of HIV treatment in an era of polypharmacy. J Int AIDS Soc. 2020;23(2):e25449.
6. Krentz HB, Gill MJ. The impact of non-antiretroviral polypharmacy on the continuity of antiretroviral therapy (ART) among HIV patients. AIDS Patient Care STDS. 2016;30(1):11–7.
7. Pérez-González A, Suárez-García I, Ocampo A, Poveda E. Two-drug regimens for HIV - Current evidence, Research Gaps and Future challenges. Microorganisms. 2022;10(2):433.
8. Baril JG, Angel JB, Gill MJ, Gathe J, Cahn P, van Wyk J, et al. Dual therapy treatment strategies for the management of patients infected with HIV: a systematic review of current evidence in ARV-Naive or ARV-Experienced, virologically suppressed patients. PLoS ONE. 2016;11(2):e0148231.
9. Pierone G, Fusco JS, Vannappagari V, Brunet L, Weber RP, Aboud M et al. Dolutegravir/rilpivirine 2-drug regimen comparable to commonly prescribed 3-drug regimens up to 18-months in a real-world setting. Antivir Ther. 2022;27(1).
10. U.S, Food, Drug Administration. &. FDA approved changes to the DOVATO (dolutegravir/lamivudine) product labeling 2020 [updated 08/07/2020. https://www.fda.gov/drugs/human-immunodeficiency-virus-hiv/fda-approved-changes-dovato-dolutegravirlamivudine-product-labeling
11. van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla J et al. Efficacy and safety of switching to Dolutegravir/Lamivudine fixed-dose two-drug Regimen Versus Continuing a Tenofovir Alafenamide-based three- or four-drug regimen for maintenance of Virologic Suppression in adults with HIV-1: phase 3, Randomized, non-inferiority TANGO study. Clin Infect Dis. 2020.
12. Rial-Crestelo D, de Miguel R, Montejano R, Dominguez-Dominguez L, Aranguren-Rivas P, Esteban-Cantos A, et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: Week 96 results of ART-PRO pilot study. J Antimicrob Chemother. 2020;76(3):738–42.
13. Li JZ, Sax PE, Marconi VC, Fajnzylber J, Berzins B, Nyaku AN et al. No significant changes to residual Viremia after switch to Dolutegravir and Lamivudine in a Randomized Trial. Open Forum Infect Dis. 2019;6(3).
14. Cento V, Perno CF. Two-drug regimens with dolutegravir plus rilpivirine or lamivudine in HIV-1 treatment-naïve, virologically-suppressed patients: latest evidence from the literature on their efficacy and safety. J Glob Antimicrob Resist. 2020;20:228–37.
15. Llibre JM, Brites C, Cheng C-Y, Osiyemi O, Galera C, Hocqueloux L, et al. Efficacy and safety of switching to the 2-Drug Regimen Dolutegravir/Lamivudine Versus Continuing a 3- or 4-Drug regimen for maintaining Virologic suppression in adults living with Human Immunodeficiency Virus 1 (HIV-1): Week 48 results from the phase 3, Noninferiority SALSA Randomized Trial. Clin Infect Dis. 2022;76(4):720–9.
16. Punekar YS, Parks D, Joshi M, Kaur S, Evitt L, Chounta V, et al. Effectiveness and safety of dolutegravir two-drug regimens in virologically suppressed people living with HIV: a systematic literature review and meta-analysis of real-world evidence. HIV Med. 2021;22(6):423–33.
17. Lee KH, Kim J, Lee JA, Kim CH, Ahn JY, Jeong SJ, et al. Real-world effectiveness, tolerability, and Safety of Dolutegravir/Lamivudine in Korea. Viruses. 2022;14(11):2558.
18. Mazzitelli M, Sasset L, Gardin S, Leoni D, Trunfio M, Scaglione V, et al. Real-life experience on Dolutegravir and Lamivudine as initial or switch therapy in a Silver Population living with HIV. Viruses. 2023;15(8):1740.
19. Martínez-Serra A, De Lazzari E, Berrocal L, Foncillas A, De La Mora L, Inciarte A, et al. Clinical use and effectiveness of dolutegravir and lamivudine: a long-term, real-world, retrospective study. J Antimicrob Chemother. 2023;78(8):1955–62.
20. Gagliardini R, Lorenzini P, Cozzi-Lepri A, Tavelli A, Borghi V, Galli L, et al. Real world efficacy of dolutegravir plus lamivudine in people living with HIV with undetectable viral load after previous failures. J Global Antimicrob Resist. 2023;32:158–63.
21. Ward D, Scheibel SF, Ramgopal M, Riedel DJ, Garris C, Oglesby A, et al. editors. 2485. Real-world experience with Dolutegravir Plus Rilpivirine two-drug Regimen. Open Forum Infectious Diseases; 2019.
22. Centers for Disease Control and Prevention, Surveillance Report HIV. 2021; vol. 34 2023 [updated 23 May 2023. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-34/index.html
23. Meyer D, Slone SE, Ogungbe O, Duroseau B, Farley JE. Impact of the COVID-19 pandemic on HIV Healthcare Service Engagement, Treatment Adherence, and viral suppression in the United States: a systematic literature review. AIDS Behav. 2022.
24. Budak JZ, Scott JD, Dhanireddy S, Wood BR. The impact of COVID-19 on HIV Care provided via Telemedicine—Past, Present, and Future. Curr HIV/AIDS Rep. 2021;18(2):98–104.
25. Pierone GJ, Fusco JS, Brunet L, Henegar C, van Wyk J, Sarkar S, et al. editors. The Impact of the COVID-19 Pandemic on Clinical Follow-up, Monitoring and Regimen Discontinuation for People Living with HIV in the US. IDWeek; 2021; Virtual Event.
26. Baldin G, Ciccullo A, Borghetti A, Di Giambenedetto S. Virological efficacy of dual therapy with lamivudine and dolutegravir in HIV-1-infected virologically suppressed patients: long-term data from clinical practice. J Antimicrob Chemother. 2019;74(5):1461–3.
27. Galizzi N, Poli A, Galli L, Muccini C, Mastrangelo A, Dell'Acqua R, et al. Retrospective study on the outcome of two-drug regimens based on dolutegravir plus one reverse transcriptase inhibitor in virologically-suppressed HIV-infected patients. Int J Antimicrob Agents. 2020;55(3):105893.
28. Borghetti A, Lombardi F, Gagliardini R, Baldin G, Ciccullo A, Moschese D, et al. Efficacy and tolerability of lamivudine plus dolutegravir compared with lamivudine plus boosted PIs in HIV-1 positive individuals with virologic

suppression: a retrospective study from the clinical practice. BMC Infect Dis. 2019;19(1):59.
29. Ciccullo A, Borghi V, Giacomelli A, Cossu MV, Sterrantino G, Latini A et al. Five years with Dolutegravir Plus Lamivudine as a switch strategy: much more than a positive finding. JAIDS J Acquir Immune Defic Syndr. 2021;88(3).
30. Nasreddine R, Yombi JC, Darcis G, Florence E, Allard SD, De Scheerder MA et al. Efficacy, durability, and tolerability of dolutegravir/lamivudine and dolutegravir/rilpivirine for the treatment of HIV in a real-world setting in Belgium. HIV Med. 2022;n/a(n/a).
31. Baldin G, Ciccullo A, Rusconi S, Capetti A, Sterrantino G, Colafigli M, et al. Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multi-centre cohort of HIV-1-infected, virologically suppressed patients. Int J Antimicrob Agents. 2019;54(6):728–34.
32. Patel R, Evitt L, Mariolis I, Di Giambenedetto S, d'Arminio Monforte A, Casado J, et al. HIV Treatment with the two-drug Regimen Dolutegravir Plus Lamivudine in Real-world clinical practice: a systematic literature review. Infect Dis Ther. 2021;10(4):2051–70.
33. Mendoza I, Lázaro A, Torralba M, Effectiveness. Durability, and Safety of Dolutegravir and Lamivudine Versus Dolutegravir, Lamivudine, and Abacavir in a real-life cohort of HIV-Infected adults. Ann Pharmacother. 2022;56(4):412–21.
34. Schuettfort G, Cabello A, Cotter AG, Leuw PDE, Górgolas M, Hamzah L, et al. Reasons for choice of antiretroviral regimens in HIV patients presenting late for initial treatment in Europe. AIDS Patient Care STDs. 2021;35(4):110–5.
35. Davis W, Mantsios A, Karver T, Murray M, Punekar Y, Ward D, et al. It made me more confident that I have it under control: patient and provider perspectives on moving to a two-drug ART regimen in the United States and Spain. PLoS ONE. 2020;15(5):e0232473.
36. Centers for Disease Control and Prevention. Diagnoses of HIV Infection in the United States and Dependent Areas. 2020. HIV Surveillance Report [Internet]. 2022; 33. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html
37. Hidalgo-Tenorio C, Cortés LL, Gutiérrez A, Santos J, Omar M, Gálvez C, et al. DOLAMA study: effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. Medicine. 2019;98(32):e16813.
38. Borghetti A, Baldin G, Lombardi F, Ciccullo A, Capetti A, Rusconi S et al. Efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of patients with suppressed HIV-1 replication. HIV Med. 2018.

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