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SHORT REPORT

Switching to Dolutegravir/Lamivudine Two-Drug Regimen: Durability and Virologic Outcomes by Age, Sex, and Race in Routine US Clinical Care

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Purpose: Two-drug regimens (2DR) may address drug–drug interactions and toxicity concerns. Dolutegravir/lamivudine (DTG/3TC) 2DR was approved in the US for both treatment-naïve and treatment-experienced individuals with a viral load <50 copies/mL. This study describes real-world DTG/3TC 2DR treatment outcomes among treatment-experienced individuals, stratified by age, sex, and race.

Methods: From the OPERA® cohort, people with HIV with a viral load <50 copies/mL who switched from a commonly used three-drug regimen to DTG/3TC 2DR as per the label between April 8, 2019 and April 30, 2021 were included. Incidence rates (Poisson regression) for loss of virologic control (first viral load ≥50 copies/mL), confirmed virologic failure (2 viral loads ≥200 copies/mL or discontinuation after 1 viral load ≥200 copies/mL), and DTG/3TC 2DR discontinuation were estimated overall and stratified by age, sex, and race.

Results: The 787 individuals included were followed for a median of 13.6 months (IQR: 8.2, 22.3). Confirmed virologic failure occurred in ≤5 individuals. Loss of virologic control occurred at a rate of 14.0 per 100 person-years (95% CI: 11.7, 16.8). DTG/3TC 2DR discontinuation occurred at a rate of 17.5 per 100 person-years (95% CI: 15.0, 20.3); 4% discontinued for treatment-related reasons (viremia, adverse diagnosis, side effect, lab abnormality). For all outcomes, incidence rates were comparable across strata of age, sex, and race.

Conclusion: This descriptive study demonstrates that DTG/3TC 2DR is an effective and well-tolerated treatment option for people with HIV with a viral load <50 copies/mL at switch, regardless of their age, sex, or race.

Keywords: antiretroviral therapy, cohort, electronic health records, suppressed, viral load

Introduction

Two-drug regimens (2DR) may be a valuable antiretroviral therapy (ART) option to alleviate concerns of drug–drug interactions and antiretroviral toxicity.[1–4] Dolutegravir/lamivudine (DTG/3TC) 2DR was approved in the US for ART-naïve (April 2019)[5] and ART-experienced individuals on a stable ART regimen with a viral load (VL) <50 copies/mL, no treatment failure history, and no resistance to DTG or 3TC (August 2020).[6] Its safety, tolerability, non-inferiority to three-drug regimens (3DR), and real-world effectiveness has been established among ART-experienced individuals in clinical trials and real-world observational studies.[7–24] However, very few studies have assessed the effectiveness of DTG/3TC 2DR based on age, sex, or race.[25,26]

We aimed to describe the real-world experience of ART-experienced individuals with a VL <50 copies/mL switching to DTG/3TC 2DR from a commonly prescribed three-drug regimen in the US, including the impact of age, sex, and race on treatment outcomes.

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Methods

This study utilized data from the Observational Pharmaco-Epidemiology Research & Analysis (OPERA®) cohort, which consists of prospectively captured routine clinical data from electronic health records from 84 clinics in 18 US states and territories. This study included all HIV-1 positive individuals aged 13 years or older who switched to DTG/3TC 2DR between April 8, 2019 and April 30, 2021 from either bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC), DTG/abacavir (ABC)/3TC or DTG+TAF/FTC. All had a VL<50 copies/mL at switch and no known history of virologic failure or resistance. All were followed from switch to the first of (a) any antiretroviral change, (b) loss to follow up (ie, 18 months after the last clinical contact), (c) death, or (d) study end (October 31, 2021).

Virologic outcomes were assessed in the subset with ≥1 follow-up VL. Loss of virologic control was defined as the first VL ≥50 copies/mL during follow-up. Confirmed virologic failure was defined as two consecutive VL ≥200 copies/mL, or regimen discontinuation after 1 VL ≥ 200 copies/mL.

Regimen discontinuation was defined as either a switch from DTG/3TC 2DR to any other regimen (stop DTG or 3TC and/or add any other antiretroviral) or ART interruption (>45 days without ART). Treatment gaps of >45 days were classified as discontinuations to account for possible delays between prescription receipt and pharmacy pick-up, as well as potential stockpiling of pills if adherence was incomplete. Reasons for discontinuation were inferred from electronic health records and based on provider notes, diagnoses, and laboratory results. Treatment-related reasons included a VL ≥200 copies/mL within 30 days before discontinuation, an adverse diagnosis or side effect, or a laboratory abnormality (ie, value 3 times the upper limit of normal). Treatment-unrelated reasons for discontinuation included a treatment gap >45 days, switch to a long-acting regimen or a note regarding either access issues, non-adherence, patient preference, provider preference or any other reasons. If both treatment-related and treatment-unrelated reasons were identified, the discontinuation was classified as treatment-related. If neither was identified, the reason for discontinuation remained unknown.

For all outcomes, incidence rates were estimated with univariate Poisson regression to account for differential durations of follow-up. Results were presented overall and stratified by age (<50 vs ≥50 years old), sex (male vs female), and race (Black vs non-Black race). Incidence rate ratios were estimated with univariate Poisson regression to compare the rate of each outcome across strata of age, sex, and race.

Results

A total of 787 individuals with a VL <50 copies/mL switched to DTG/3TC 2DR from DTG/ABC/3TC (n = 421), BIC/TAF/FTC (n = 240), or DTG+TAF/FTC (n = 126). Demographic and clinical characteristics at switch are presented in Table 1.

Table 1 Study Population Characteristics at the Time of Switch to DTG/3TC 2DR in the OPERA Cohort (N = 787)

	n (%) or Median (IQR)
Prior ART regimen	
DTG/ABC/3TC	421 (54)
BIC/TAF/FTC	240 (30)
DTG + TAF/FTC	126 (16)
Age (years)	
<50	490 (62)
≥50 to <65	261 (33)
≥65	36 (5)

(*Continued*)

Table 1 (Continued).

	n (%) or Median (IQR)
Female	128 (16)
Race	
Asian	20 (2)
Black	250 (32)
White	447 (57)
Other	34 (4)
Unknown	36 (5)
CD4 cell count (cells/μL)	738 (569, 932)
History of AIDS	149 (19)
Years since HIV diagnosis	5.8 (2.5, 14.3)
HBV co-infection	19 (2)
Any comorbidity[a] actively managed in past 12 months	422 (54)
Ryan White/ADAP program[b] beneficiary	252 (32)

Notes: [a]Autoimmune disease, cardiovascular disease, invasive cancers, endocrine disorders, mental health disorders, liver disease, bone disorders, peripheral neuropathy, renal disease, hypertension, substance abuse, COVID-19. [b]The Ryan White HIV/AIDS Program helps low-income people with HIV receive medical care, medications and essential support services to help them stay in care. ADAP provides FDA-approved medications to low-income people with HIV who have limited or no health insurance. ADAP funds can also be used to buy health insurance for eligible clients and provide services that improve drug treatments.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ADAP, AIDS Drug Assistance Program; BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; IQR, interquartile range; TAF, tenofovir alafenamide.

During follow-up, a median of 3 VL measurements were available per person (IQR: 2, 5). Overall, 118 individuals (17%) had a VL ≥50 copies/mL documented (median: 80 copies/mL; IQR: 60, 147), for an incidence rate of 14.0 per 100 person-years (95% CI: 11.7, 16.8). Of the 84 individuals with additional VL available after a first VL ≥50 copies/mL, 70 (83%) immediately re-suppressed (ie, blip; single elevated VL followed by a VL <50 copies/mL); similar proportions of blips were observed across strata, ranging from 82 to 86%). Across age, sex, and race strata, incidence rates ranged from 13.0 to 17.7 per 100 person-years, without meaningful variation. No statistically significant difference was observed between groups, with confidence intervals for incidence rate ratios crossing the null for all comparisons (Table 2). Only 30 individuals (4%) had ≥1 VL ≥200 copies/mL during follow-up (median copies/mL: 842; IQR: 260, 3600), for an overall rate of 3.3 per 100 person-years (95% CI: 2.3, 4.7; not shown). Confirmed virologic failure was rare, occurring in ≤5 individuals over follow-up; no statistically significant differences were observed across strata (Table 2).

Over a median follow-up of 13.6 months (IQR: 8.2, 22.3), 170 individuals (22%) discontinued DTG/3TC 2DR. Only six (4%) discontinued for treatment-related reasons: viremia (n ≤ 5), adverse diagnosis or side effect (n ≤ 5). For 37% of discontinuations, treatment-unrelated reasons were identified: provider preference (n = 48), switch to a long-acting regimen (n = 13), therapeutic gap (n = 10), access issues (n = 6), patient preference (n ≤ 5). No reason could be identified for the remaining 59% of discontinuations. Overall, discontinuation occurred at a rate of 17.5 per 100 person-years (95% CI: 15.0, 20.3). Incidence rates were comparable across strata of age, sex, and race, ranging from 15.3 to 18.2 discontinuations per 100 person-years and all incidence rate ratio confidence intervals crossing the null (Table 3).

Table 2 Incidence of Virologic Outcomes Among Individuals Who Switched to DTG/3TC 2DR and Have ≥1 Follow-Up Viral Load, Compared Across Strata of Age, Sex, and Race

	Loss of Virologic Control[a]			Confirmed Virologic Failure[b]		
	n (%)	IR per 100 Person-Years (95% CI)	IRR (95% CI)	n (%)	IR per 100 Person-Years (95% CI)	IRR (95% CI)
Overall, N=696	118 (17)	14.0 (11.7, 16.8)	NA	≤5[c]	0.4 (0.2, 1.1)	NA
Age <50 years, N=432	72 (17)	13.8 (11.0, 17.4)	Reference	≤5[c]	0.5 (0.2, 1.6)	Reference
Age ≥50 years, N=264	46 (17)	14.4 (10.8, 19.2)	1.04 (0.72, 1.51)	≤5[c]	0.3 (0.0, 2.0)	0.55 (0.06, 5.31)
Male sex, N=582	94 (16)	13.3 (10.9, 16.3)	Reference	≤5[c]	0.5 (0.2, 1.4)	Reference
Female sex, N=114	24 (21)	17.7 (11.9, 26.4)	1.33 (0.85, 2.08)	0	0	NA
Non-Black race, N=481	77 (16)	13.0 (10.4, 16.3)	Reference	≤5[c]	0.2 (0.0, 1.1)	Reference
Black race, N=215	41 (19)	16.4 (12.1, 22.3)	1.26 (0.86, 1.84)	≤5[c]	1.1 (0.3, 3.3)	7.00 (0.73, 67.30)

Notes: Incidence rates and incidence rate ratios were estimated using univariate Poisson regression. [a]First viral load ≥50 copies/mL. [b]2 consecutive viral loads ≥200 copies/mL, or regimen discontinuation after 1 VL ≥ 200 copies/mL. [c]HIPAA regulations require the masking of cells with 1 to 5 individuals.
Abbreviations: CI, confidence interval; IQR, interquartile range; IR, incidence rate; IRR, incidence rate ratio; N, number; NA, not applicable.

Table 3 Duration of Follow-Up and Incidence of Regimen Discontinuation Among Individuals Who Switched to DTG/3TC 2DR, Compared Across Strata of Age, Sex, and Race

	Months of Follow-Up	DTG/3TC Discontinuation		
	Median (IQR)	n (%)	IR per 100 Person-Years (95% CI)	IRR (95% CI)
Overall, N=787	13.6 (8.2, 22.3)	170 (22)	17.5 (15.0, 20.3)	NA
Age <50 years, N=490	13.7 (8.8, 22.2)	104 (21)	17.0 (14.0, 20.6)	Reference
Age ≥50 years, N=297	13.5 (7.5, 22.3)	66 (22)	18.2 (14.3, 23.2)	1.07 (0.79, 1.46)
Male sex, N=659	13.6 (8.3, 22.4)	146 (22)	17.9 (15.2, 21.0)	Reference
Female sex, N=128	13.6 (7.6, 21.3)	24 (19)	15.3 (10.2, 22.8)	0.85 (0.55, 1.31)
Non-Black race, N=537	13.3 (7.9, 21.3)	118 (22)	17.4 (14.6, 20.9)	Reference
Black race, N=250	13.3 (7.9, 21.3)	52 (21)	17.5 (13.4, 23.0)	1.00 (0.72, 1.39)

Note: Incidence rates and incidence rate ratios were estimated using univariate Poisson regression.
Abbreviations: 3TC, lamivudine; CI, confidence interval; DTG, dolutegravir; IQR, interquartile range; IR, incidence rate; IRR, incidence rate ratio; N, number; NA, not applicable.

Discussion

In this study of adults with a VL <50 copies/mL in routine clinical care in the US, switching to DTG/3TC 2DR was virologically effective. The consistency of results across strata of age, sex, and race suggests that all groups were able to take DTG/3TC 2DR with comparable success.

Low rates of loss of virologic control (first VL ≥50 copies/mL) and rare virologic failure were observed in this population. This is consistent with results from a meta-analysis of six observational studies, where only 1% of virologically suppressed individuals switching to DTG/3TC 2DR had virologic failure (two consecutive VL ≥50 copies/mL or a single VL >1000 copies/mL) at weeks 48 and 96.[13] In other observational studies of virologically suppressed switch to DTG/3TC 2DR, the incidence rate of virologic failure ranged from 0.9 to 1.2 per 100 person-years or from 0.1% to 3% by 48 weeks,[19–22] with loss of undetectability in only 1–4% of individuals at week 48, 1–5% at week 96, and 7% over five years.[14–18,20,23] The presence of M184V resistance mutations at DTG/3TC 2DR may be associated

with earlier time to, though not with an increased likelihood of, virologic failure.[20,22] Emergence of resistance appears to be rare among individuals experiencing failure on DTG/3TC 2DR.[21,22]

Other studies have reported 2% to 20% of DTG/3TC 2DR discontinuation among ART-naïve and ART-experienced individuals, compared to 22% in OPERA.[12,13,21] However, DTG/3TC 2DR was well tolerated in this study: only 4% of discontinuations were deemed to be treatment-related. Similarly, discontinuation due to adverse events, intolerance, or toxicity were reported in 1% to 8% in trials and observational studies.[11,12,14,21,24] The most common reason for discontinuation was provider preference, which does not provide much context, but has been noted as a common reason for switch in other studies.[27–29] Notably, in a recent survey of 27 US healthcare providers, 89% reported provider-initiated regimen switches, while all reported switch discussions initiated by their patient, driven among other things by their community or commercials.[29] Switch to a long-acting regimen was another documented reason for discontinuation in this study. A large survey of 553 people with HIV and 450 physicians in the US and Canada showed that 59% of people with HIV and 55–66% of physicians would prefer/recommend a long-acting injectable to overcome treatment challenges such as daily pill burden and adherence.[30]

The real-world effectiveness of DTG/3TC 2DR in individuals aged ≥65 years old has been assessed in two recent observational studies. Among 112 individuals ≥65 years of age starting DTG/3TC 2DR in Northern Italy (6 ART-naïve, 106 ART-experienced), 93% had an undetectable viral load at end of follow-up.[25] In another Italian cohort, 72 ART-experienced individuals aged ≥65 years who switched to DTG/3TC 2DR with a viral load <20 copies/mL, 89% had maintained a viral load <20 copies/mL after 12 months.[26] In OPERA, age was stratified at 50 years instead of 65 because only 5% of the population were aged 65 years or older. However, the proportion who maintained virologic control was slightly lower in OPERA (83%) than in the Italian cohort, although no difference by age was observed in OPERA. While loss of virologic control was numerically higher in women than men in OPERA, no statistically significant difference was observed in the incidence rates. A study comparing virologic outcomes of DTG-based regimens (2DR and 3DR combined) between women and men in the ICONA cohort has shown a higher likelihood of treatment failure, but not virologic failure in women compared to men. Treatment failures in women appeared to be driven by discontinuations due to toxicity.[31]

Of note, this study included 19 individuals with HIV-HBV co-infection. The DTG/3TC 2DR label includes a boxed warning stating that additional treatment or alternative regimens should be considered for chronic HBV due to risks of emergent 3TC-resistant HBV variants.[32] This study population was restricted to individuals on a DTG/3TC single-tablet 2DR. Therefore, there was no concurrent prescriptions for any other ARV agents active against both HIV and HBV (tenofovir disoproxil fumarate, tenofovir alafenamide, emtricitabine), although the use of entecavir was not assessed.

A limitation of this study was that the experience of individuals switching to DTG/3TC 2DR from regimens other than DTG/ABC/3TC, BIC/TAF/FTC or DTG+TAF/FTC was not represented. Due to the absence of a comparison group, while we can conclude that DTG/3TC 2DR was associated with favorable outcomes among people with undetectable VL, no inference can be drawn in terms of its effectiveness compared to other regimens. In addition, this is a purely descriptive study, and no statistical adjustments were performed to control potential confounding. The duration of follow-up was relatively short, with close to half of individuals followed for a year or less, thus preventing the assessment of long-term treatment outcomes. Assessment of virologic outcomes were restricted to individuals with at least one follow-up VL. However, confirmed virologic failure required two consecutive VL unless the regimen was discontinued, and all did not have the opportunity for this event to be observed over the study period. The presence of ART resistance following virologic failure could not be assessed: such tests are not done systematically in routine clinical care, and results may be incomplete in the EHR. Adherence information was also unavailable. Since OPERA clinical data are collected for the medical management of patients and reasons for discontinuation are often poorly documented in electronic health records, 59% of discontinuers did not have an identifiable reason for discontinuation despite using diagnoses, laboratory results, and provider notes to determine likely reasons. Moreover, 28% of DTG/3TC 2DR discontinuations were justified as a provider preference, although the reason for such preference was not documented in the EHR. Finally, this study spanned from April 8, 2019 (~11 months COVID-19 pre-pandemic) to October 31, 2021 (~20 months since pandemic onset). The COVID-19 pandemic has disrupted healthcare services, including HIV care.[33] In OPERA, lower rates of clinical visits, VL measurements, and regimen discontinuations were observed between March and October 2020, compared to the

prior eight months.[34] The impact of the pandemic on HIV care and treatment outcomes may have varied over this long study period.

This study also has several strengths. The study population was derived from the OPERA cohort, which includes a diverse population and is representative of routine HIV clinical care in the US. Indeed, the 140,817 people with HIV in the OPERA cohort at the time of this study represented approximately 13% of people with HIV in the US.[35] The 787 individuals who switched to DTG/3TC 2DR within the first 24 months of commercial use were followed for a median of 13.6 months (max 30.7 months) after switch, allowing time to observe the clinical outcomes of interest. Clinical diagnoses, prescriptions, and laboratory results were captured prospectively from electronic health records for all individuals receiving healthcare at participating sites, thus providing complete and accurate clinical information reflecting real-world clinical practices.

Conclusion

In conclusion, this descriptive study demonstrated that a 2DR consisting of DTG/3TC is an effective and well-tolerated treatment option for virologically suppressed people with HIV, regardless of their age, sex, or race.

Ethical Considerations

The OPERA® observational database complies with all HIPAA and HITECH requirements and has received annual institutional review board (IRB) approval by Advarra IRB (Pro00023648), including a waiver of informed consent and authorization for use of protected health information. All data are anonymized to ensure confidentiality of all participants.

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Disclosure

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