Suppressed Switch to DTG/3TC 2-Drug Regimen vs. BIC- or DTG-Based 3-Drug Regimens

Gerald Pierone, Jr[1], Jennifer S Fusco[2], Laurence Brunet[2], Vani Vannappagari[3], Supriya Sarkar[3], Cassidy Henegar[3], Jean van Wyk[3], Andrew Zolopa[3], Gregory P Fusco[2]

[1] Whole Family Health, Vero Beach, FL; [2] Epividian, Durham, NC; [3] ViiV Healthcare, Research Triangle Park, NC

Contact Information:
Jennifer Fusco
302-354-9909
jennifer.fusco@epividian.com

OPERA® The Longitudinal Cohort

Background

- For years, antiretroviral therapy (ART) consisting of three-drug regimens (3DR) were the standard to treat people with HIV (PWH)[1]
- Two-drug regimens (2DR) have been introduced in recent years to potentially reduce ART toxicities and drug-drug interactions for individuals with comorbid conditions[2] while demonstrating comparable efficacy to 3DRs[3]
- Dolutegravir/lamivudine (DTG/3TC) 2DR was approved by the FDA for ART-naïve PWH in April 2019[4] and for ART-experienced PWH in August 2020[5]

Objective

To assess the real-world effectiveness of DTG/3TC 2DR during its first 24 months of availability in the US, compared to common 3DR regimens (i.e., bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) or any DTG-based 3DR) among suppressed ART experienced PWH

Methods

Study Population

- OPERA cohort
  - Prospectively captured, routine clinical data from electronic health records in the US (96 clinics, 22 states, 1 US territory)
  - >133K PWH as of June 2021, representing ~12% of people with diagnosed HIV infection in the US[6]
- Inclusion criteria
  - HIV-1 infection without HIV-2 infection
  - Aged 18+
  - ART-experienced
  - Switched to DTG/3TC 2DR, BIC/TAF/FTC (BIC 3DR) or DTG + 2 NRTIs (DTG 3DR) between 01MAR2019 and 31OCT2020
  - Suppressed to viral load (VL) <200 copies/mL at switch
  - No prior exposure to any regimen of interest
- Censoring events
  - Study end (i.e., 30APR2021)
  - Loss to follow-up (i.e., 12 months after last contact)
  - Death
  - Regimen change

Outcome Definition

- Confirmed virologic failure: 2 consecutive VL ≥200 copies/mL
- Regimen discontinuation: any regimen change (i.e., adding and/or removing any antiretroviral agent)

Analyses

- Incidence rates: univariate Poisson regression
- Association between regimen and confirmed virologic failure or regimen discontinuation:
  - Cox proportional hazards model
  - Inverse probability of treatment weights (IPTW): baseline age (quadratic), number of ART classes (quadratic), female, Black race, Hispanic ethnicity, Southern US, core agent class of prior regimen, CD4 cell count (quadratic)

Results

Table 1. Population characteristics at switch

	DTG/3TC 2DR N = 1450	BIC 3DR N = 5691	DTG 3DR N = 896
Age, median years (IQR)	45 (33, 55)	43 (32, 54)	42 (31, 53)
Female sex, n (%)	271 (19)	909 (16)	163 (18)
Black race, n (%)	508 (35)	2,456 (43)	438 (49)
Hispanic ethnicity, n (%)	376 (26)	1,368 (24)	148 (16)
US region: South, n (%)	778 (54)	3,901 (68)	665 (74)
# of ART classes ever experienced, median (IQR)	2 (2, 3)	2 (0, 2)	0 (0, 2)
Class of core agent in prior regimen, n (%)			
INSTI	1062 (73)	2522 (44)	117 (13)
NNRTI	127 (9)	823 (14)	52 (6)
PI	57 (4)	421 (7)	57 (6)
>1 class	104 (7)	203 (4)	35 (4)
Any other class	≤5	≤5	0 (0)
Unknown	99 (7)	1,718 (30)	635 (71)
CD4 cell count, median cell/μL (IQR)	730 (550, 944)	675 (484, 892)	678 (471, 861)
Any comorbidities[a], n (%)	1126 (78)	4054 (71)	548 (61)

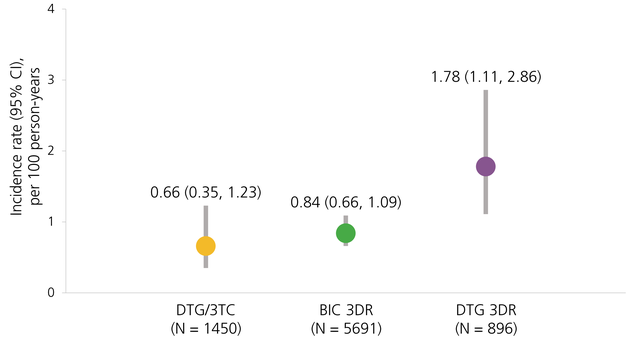
2DR, two-drug regimen; 3DR, three-drug regimen; 3TC, lamivudine; ART, antiretroviral therapy; BIC, bictegravir; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor
[a] Any diagnosis of autoimmune disease, cardiovascular disease, invasive cancers, endocrine disorders, mental health disorders, liver disease, bone disorders, peripheral neuropathy, renal disease, hypertension, or substance abuse

Table 2. Duration of follow-up and regimen discontinuation

	DTG/3TC 2DR N = 1450	BIC 3DR N = 5691	DTG 3DR N = 896
Median months of follow-up (IQR)	13.6 (7.3, 18.3)	15.8 (11.6, 19.8)	13.4 (7.9, 18.2)
Regimen discontinuation			
IR per 100 person-years (95% CI)	17.7 (15.7, 19.9)	8.3 (7.7, 9.0)	24.9 (21.9, 28.3)
HR[a] (95% CI)	Ref.	0.51 (0.42, 0.62)	1.69 (1.30, 2.19)

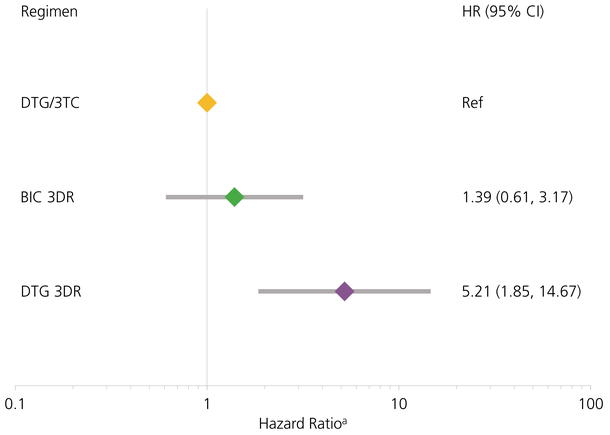
2DR, two-drug regimen; 3DR, three-drug regimen; 3TC, lamivudine; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; HR, hazard ratio; IQR, interquartile range; IR, incidence rate
[a] Cox proportional hazards model with inverse probability of treatment weights (IPTW): baseline age (quadratic), # of ART classes (quadratic), female, Black race, Hispanic ethnicity, Southern US, core agent class of prior regimen, CD4 cell count (quadratic)

Figure 1. Incidence rate of confirmed virologic failure over follow-up



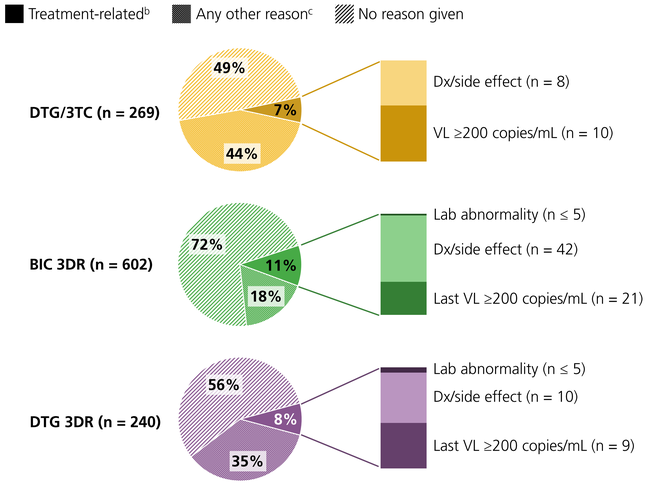
3TC, lamivudine; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; HF, hazard ratio

Figure 2. Association between regimen and confirmed virologic failure



3DR, three-drug regimen; 3TC, lamivudine; BIC, bictegravir; CI, confidence interval; DTG, dolutegravir; HF, hazard ratio
[a] Cox proportional hazards model with inverse probability of treatment weights (IPTW): baseline age (quadratic), # of ART classes (quadratic), female, Black race, Hispanic ethnicity, Southern US, core agent class of prior regimen, CD4 cell count (quadratic)

Figure 3. Reasons for regimen discontinuation,[a] among discontinuers



3DR, three-drug regimen; 3TC, lamivudine; BIC, bictegravir; DTG, dolutegravir; Dx, diagnosis; n, number; VL, viral load
[a] Reasons for discontinuation identified using physician notes, lab results, and diagnoses
[b] 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., ALP, ALT, ASP or bilirubin >3X ULN within 21 days of discontinuation)
[c] Simplification, access issues, non-adherence, treatment gap, patient/provider choice, any other reason noted

Discussion

- This study assessed the effectiveness of DTG/3TC 2DRs over it's first 24 months of use in the US, compared to two commonly prescribed 3DRs
- DTG 3DRs were more likely to be prescribed to PWH who were new to the OPERA provider (more likely to have missing ART history); the geographic, racial and ethnic composition of this group also differed (**Table 1**)
- Rates of confirmed virologic failure were low for all groups (IR: 0.66 to 1.78 per 100 person-years) (**Fig. 1**)
- No difference in risk of confirmed virologic failure was observed between DTG/3TC and BIC 3DR (HR: 1.39; 95% CI: 0.61, 3.17) (**Fig. 2**)
- The similar magnitude of risk for confirmed virologic failure with DTG/3TC and BIC 3DR is not reflected in discontinuation rates (**Table 2**)
- Discontinuations were largely unrelated to the effectiveness or tolerability of the regimen (**Fig. 3**)
  - Only 7 to 11% of discontinuations appeared related to the treatment itself (unsuppressed, adverse diagnosis/side effect, lab abnormality)
  - >95% were virologically suppressed (VL <200 copies/mL) at the time of discontinuation
- The COVID-19 pandemic was ongoing during approximately half of the study period
  - Disruptions to HIV care and retention in care during the COVID period may have impacted regimen selection and discontinuation decisions[7]

Key Findings

Among ART-experienced, virologically suppressed PLWH switching to DTG/3TC 2DR, BIC 3DR or DTG 3DR:

- Confirmed virologic failure was rare
- Across regimens, most discontinuations were not treatment-related, suggesting other reasons for discontinuation despite high levels of suppression and tolerability

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV Department of Health and Human Services.
2. 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.
3. van Wyk, 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
4. U.S. Food & Drug Administration. FDA approves first two-drug complete regimen for HIV-infected patients who have never received antiretroviral treatment. April 08, 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-first-two-drug-complete-regimen-hiv-infected-patients-who-have-never-received.
5. U.S. Food & Drug Administration. FDA approved changes to the DOVATO (dolutegravir/lamivudine) product labeling. August 7, 2020. https://www.fda.gov/drugs/human-immunodeficiency-virus-hiv/fda-approved-changes-dovato-dolutegravirlamivudine-product-labeling.
6. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2014–2018. HIV Surveillance Supplemental Report; 25 (No. 1).
7. 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.

Acknowledgements

This research would not be possible without the generosity of people living with HIV and their OPERA caregivers. Additionally, we are grateful for the following individuals: Lito Torres (SAS programming), Robin Beckerman(QA), Bernie Stooks (Data Management), Lisa Lutzi (Database Architecture), and Judy Johnson (Medical Terminology Classification)

Support

This research was sponsored by ViiV Healthcare

ViiV Healthcare

Epividian®