Virologic Outcomes of Switching to Dolutegravir Functional Monotherapy, or Functional Dual Therapy With Dolutegravir Plus A Non-cytosine Nucleoside Analog: A Retrospective Study of Treatment-Experienced, HIV-1 Infected Patients

Charlotte-Paige Rolle (crolle@oicorlando.com)
Emory University Rollins School of Public Health https://orcid.org/0000-0002-6444-2225
Vu Nguyen
University of Central Florida College of Medicine
Federico Hinestrosa
University of Central Florida College of Medicine
Edwin DeJesus
University of Central Florida College of Medicine

Research

Keywords: dolutegravir, HIV drug resistance, monotherapy, dual therapy

Posted Date: September 15th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-74793/v1

Abstract

Background Dolutegravir (DTG) monotherapy results in unacceptable virologic failure rates and the development of DTG resistance. Here, we evaluated virologic outcomes of patients switched to DTG functional monotherapy, or functional dual therapy with DTG plus a non-cytosine nucleoside analog (NA).

Methods This observational study included treatment-experienced patients switched to regimens containing ≥ 3 antiretrovirals later found to be on DTG functional monotherapy, or functional dual therapy with DTG plus a non-cytosine NA based on historical genotypes. Eligible patients were either suppressed or viremic at baseline and had ≥2 HIV-1 RNA measurements at least four weeks apart following switch. The primary endpoint was the proportion with HIV-1 RNA<50 copies/mL following switch.

Results Thirty-nine patients were included, 19 (49%) were found to be on DTG functional monotherapy and 20 (51%) were found to be on functional dual therapy with DTG plus a non-cytosine NA. The median duration of follow-up was 50 weeks (range 12-244). Following switch, 32/39 (82%) patients achieved or maintained an HIV-1 RNA<50 copies/mL. In 7 (18%) patients with persistent HIV-1 RNA ≥50 copies/mL, there was no evidence of treatment-emergent resistance among those with post-switch genotypes.

Conclusions In this real-world cohort, the majority of whom had virus with the M184V/I and ≥ 1 additional NA mutation, switching to DTG functional monotherapy, or functional dual therapy with DTG plus a non-cytosine NA resulted in persistent HIV-1 RNA≥ 50 copies/mL in 18%. None with post-switch genotypes developed treatment-emergent resistance.

Introduction

Phase 3 clinical trials have demonstrated the efficacy of 2-drug dolutegravir (DTG) containing regimens (DCRs) in treatment-naïve and-experienced adults. In the GEMINI studies, 86% of treatment-naïve adults receiving DTG + lamivudine (3TC) achieved virologic suppression through Week 96 [1]. In treatment-experienced, virologically suppressed adults, 84% switched to DTG + rilpivirine (RPV) maintained virologic suppression through Week 148 [2], and 93% switched to DTG + 3TC maintained suppression through Week 48 [3].

Switch studies of DTG + RPV demonstrated that 6/11 patients experiencing confirmed virologic withdrawal developed resistance to RPV, but not DTG [2]. Other clinical trials of suppressed patients switched to DTG monotherapy revealed that a high proportion of virologic failures (VFs) developed DTG resistance [4–6]. This suggests that these regimens are 'less forgiving' in the setting of imperfect adherence which is more common in real-world scenarios [7]. Data from non-clinical trial settings would be useful to validate the real-world efficacy and barrier to resistance of DTG-based mono-and dual therapy.

Methods

This was a retrospective study to describe virologic outcomes of patients switched to DTG functional monotherapy, or functional dual therapy with DTG plus a non-cytosine nucleoside analog (NA). Eligible patients included all HIV-1 infected patients seen at the Orlando Immunology Center between 8/13/13 – 11/22/14 switched to once-daily DCRs whose historical genotypes predicted that DTG alone or in combination with a non-cytosine NA were the only fully active antiretrovirals (ARVs). Historical genotypes included standard genotypic assays performed 1–9 years (median 7) prior to switch. Eligible patients were either suppressed or viremic at baseline, must have attended at least two clinic visits during the study period and had a minimum of two HIV-1 RNA measurements at least four weeks apart following switch. Patients with the following baseline mutations associated with reduced susceptibility to DTG: T66K, E92Q, G118R, E138 K/A/T, G140 S/A/C, Q148 H/R/K, N155H and R263K [8] were excluded. Informed consent was waived due to the retrospective nature of the study which utilized data collected as a part of routine clinical care.

Demographics, lab values and clinical parameters were extracted from the charts of eligible patients during DCR treatment until 12/31/2018. The primary endpoint was the proportion of patients achieving or maintaining an HIV-1 RNA < 50 copies/mL following switch. Descriptive statistics were calculated for participant baseline demographic and clinical characteristics, virologic outcomes, and discontinuations throughout the study. The Sterling Institutional Review Board (IRB) determined that the study met IRB exemption criteria based on the retrospective nature of the study (Sterling IRB ID 7115).

Results

During the study period, 559 treatment-experienced patients were switched to a DCR containing ≥ 3 ARVs. Of these, 19 (3%) were found to be on DTG functional monotherapy and 20 (3%) were found to be on functional dual therapy with DTG plus a non-cytosine NA (9 on DTG + tenofovir disoproxil fumarate (TDF) and 11 on DTG + abacavir (ABC). The median age (range) of patients was 53 (40–74) years, 28 (72%)

had baseline HIV-1 RNA < 50 copies/mL, and 11 (28%) had baseline HIV-1 RNA ≥ 50 copies/mL (Table 1). The median number (range) of ARV regimens prior to switch was 4 (1–11), 25 (64%) had previously used ≥ 2 nucleoside reverse transcriptase inhibitors (NRTIs), and 24 (62%) were integrase strand transfer inhibitor (INSTI)-experienced. All patients had virus with the M184 V/I however 23 (59%) had additional NRTI resistance associated mutations (RAMs). Reasons for regimen switch included reducing pill burden (17/39), patient co-morbidities (9/39), persistent viremia (4/39), side effect concerns from prior regimen (2/39) and 7/39 had no reason documented (Table 1).

Table 1
Baseline demographic and clinical characteristics

Characteristic	N = 39
Median Age (range)	53 (40–74)
Sex	36 (92)
Male, n (%)	3 (8)
Female, n (%)	
Race/Ethnicity	31 (80)
Caucasian, n (%)	4 (10)
Black, n (%)	4 (10)
Hispanic, n (%)	0
Other, n (%)	
Median BMI (range)	25.9 (17.3–36.4)
Baseline HIV Viral Load	28 (72)
<50 copies/mL, n (%)	6 (15)
50–200 copies/mL, n (%)	2 (5)
201–399 copies/mL, n (%)	3 (8)
≥400 copies/mL, n (%)	
Median Baseline $CD4^+$ cell count, cells/mm^3 (range)	564 (92-1217)
HIV Disease status	32 (82)
Asymptomatic, n (%)	7 (18)
Symptomatic, n (%)	0
AIDS, n (%)	
Prior ARV Experience	25 (64)
>2 NRTIs, n (%)	22 (56)
1 INSTI, n (%)	2 (5)
>1 INSTI, n (%)	4 (1–11)
Median Number of ARV regimens prior to DCR (range)	
Baseline DCR	19 (49)
DTG functional monotherapy, n (%)	20 (51)
DTG + non-cytosine nucleoside analog, n (%)	9 (23)
DTG + TDF, n (%)	11 (28)
DTG + ABC, n (%)	

Abbreviations.

BMI, body mass index; ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; DCR; DTG containing regimen; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; ABC, abacavir; RAM, resistance associated mutation

Characteristic	N = 39
Baseline genotypic resistance	39
Overall Group, n	16 (41)
Pattern of NRTI RAMs	5 (13)
M184V/I alone, n (%)	18 (46)
M184V/I + 1 NRTI RAM, n (%)	2 (0–9)
M184V/I + > 1 NRTI RAM, n (%)	2 (0–6)
Number of RAMS	4 (0–14)
NRTI RAMs, median (range)	0 (0–1)
NNRTI RAMs, median (range)	19 (49)
PI RAMs, median (range)	5 (2–9)
INSTI RAMs, median (range)	0 (0–1)
DTG functional monotherapy, n (%)	20 (51)
NRTI RAMs, median (range)	1 (0–8)
INSTI RAMs, median (range)	0 (0–1)
DTG + non-cytosine nucleoside analog, n (%)	
NRTI RAMs, median (range)	
INSTI RAMs, median (range)	

Abbreviations.

BMI, body mass index; ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; DCR; DTG containing regimen; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate; ABC, abacavir; RAM, resistance associated mutation

Following switch, 32/39 (82%) patients achieved or maintained an HIV-1 RNA < 50 copies/mL, and 7 (18%) patients experienced persistent HIV-1 RNA ≥ 50 copies/mL. The median duration (range) of follow-up was 50 weeks (12–244). Eighty-nine percent (17/19) of patients treated with functional DTG monotherapy had HIV-1 RNA < 50 copies/mL compared to 75% (15/20) of those treated with functional dual therapy with DTG + non-cytosine NA. Of those with persistent viremia, 2 were on DTG functional monotherapy, and 5 were on functional dual therapy (2 on DTG + TDF and 3 on DTG + ABC) (Table 2). Three had baseline HIV-1 RNA < 50 copies/mL, and four had baseline HIV-1 RNA ≥ 50 copies/mL. All had baseline M184V/I, and 2 had additional NRTI RAMs. Five had suboptimal adherence documented throughout the study period whereas 2 had “100% adherence” documented at all visits. The majority (5/7) had genotypic testing performed post-switch and there was no evidence of treatment-emergent resistance in 5/5 patients. At the end of the study period, one viremic patient was lost to follow-up and 6/7 were switched to alternative regimens; in 5 of these patients the alternative regimen included DTG. All patients achieved HIV-1 RNA < 50 copies/mL on their new regimens (Table 2).

Table 2
Clinical details and follow-up for patients with persistent HIV-1 RNA ≥ 50 copies/mL (N = 7)

	Baseline DCR	Baseline RAMs	Active ARVs in DCR	HIV-1 RNA (cps/mL)	Suspected reason for non-response	Treatment-emergent RAMs	Date of DCR DC and new ARV regimen	HIV-1 RNA following DCR DC (cps/mL)
Patient 1	DTG + TDF/FTC	M184V/I	DTG + TDF	BL: <50 W24: 50, 51 W48: 2598	Unclear, 100% compliance reported	No post-treatment GT	DC at W48, changed to ETR/DRV/r/DTG	W52: <50 on new regimen
Patient 2	DTG + ABC/3TC	M184V/I	DTG + ABC	BL: <50 W12:250 W52:1023	Non-compliance	None, GT performed 9 months after W52	DC at W52, changed to ABC/3TC/DTG/DRV/r	W55: <50 on new regimen
Patient 3	DTG/ABC/3TC	M184V/I	DTG + ABC	BL:<50 W8:<50 W28:<50 W48:80, 90	Unclear, 100% compliance reported	No post-treatment GT	DC at W48, switched to DTG/DRV/c	W56: <50 on new regimen
Patient 4	DTG + TDF/FTC	M41L, M184V/IT215Y	DTG + TDF	BL: 70 W8:30 W16:130 W32:570 W48:120	Non-compliance	None, GT performed 2 weeks after W48	DC at W48, switch to ETR/TDF/FTC/DRV/r	W53: <50 on new regimen
Patient 5	DTG + RPV	M184V/IE138E/K	DTG	BL: 170 W20: 320 W28: 130 W40: 150 W56:600 W80:90 W92:120 W104:210	Non-compliance	None, GT performed 16 months after W104	DC at W104, changed to DTG/DRV/c	W108: <50 on new regimen
Patient 6	DTG + ABC/3TC	M184V/IM41L T215Y L74L/I	DTG	BL: 280 W4: 90 W12:90 W24:110	Non-compliance	None, GT performed 4 weeks after W24	DC at W24, changed to DTG/DRV/r	W48:60 W52: <50 on new regimen
Patient 7	DTG + ABC/3TC	M184V/I	DTG + ABC	BL:1400 W4:<50 W36:724, 801	Non-compliance	None, GT performed 2 weeks after W36	Regimen continued, LTFU after W36	LTFU after W36

Abbreviations. DCR, dolutegravir containing regimen; RAM, resistance associated mutation; ARV, antiretroviral; DC, discontinuation; DTG, dolutegravir; TDF, tenofovir; FTC, emtricitabine; ABC, abacavir; 3TC, lamivudine; RPV, rilpivirine; BL, baseline; W, week; GT, genotype; ETR, etravirine; DRV, darunavir; r, ritonavir; c, cobcistat; LTFU, lost to follow up

Discussion

Data from randomized clinical trials has demonstrated that 6–10% of virologically suppressed patients switched to DTG monotherapy experienced VF, and of those 29–100% developed INSTI resistance [4–6]. Studies evaluating virologically suppressed patients switched to dual DTG-based therapy with 3TC and RPV demonstrated VF rates of 1–3% and zero patients developed treatment-emergent INSTI resistance [2, 3]. In the case of DTG + RPV, 54% of VFs developed resistance to RPV [2]. In our cohort, 2/19 (11%) treated with DTG functional monotherapy and 5/20 (25%) treated with functional dual therapy with DTG plus a non-cytosine NA experienced VF. Of these, five had post-switch genotypes and none developed treatment emergent INSTI resistance (Table 2).

The most likely reasons for VF in our cohort included suboptimal adherence and the presence of significant baseline resistance. Of non-adherent VFs, two were on functional DTG monotherapy, and three were on DTG + non-cytosine NA. Of those on functional monotherapy, one was on DTG + RPV and had baseline E138E/K which reduces RPV susceptibility [8]. The other was on DTG + ABC/3TC and had baseline M184V/I, L74I, M41L and T215Y, the combination of which severely reduces susceptibility to 3TC and ABC [8]. In both patients, the presence of these baseline RAMs may have contributed to VF.

Among the three non-adherent VFs on functional dual therapy, two were on DTG + ABC and only had baseline M184V/I whereas the other was on DTG + TDF and had baseline M184V/I, M41L and T215Y. In addition to reduced 3TC and emtricitabine susceptibility, the M184V/I mutation is associated with low-level ABC resistance and may have contributed to VF in those on DTG + ABC [8]. In contrast, this mutation is associated with increased TDF susceptibility and the delay of treatment emergent TDF resistance [8]. However, in the patient on DTG + TDF this “hypersensitizing” effect may have been reduced by the presence of baseline M41L and T215Y which in combination are associated with low-to-intermediate-level TDF resistance and may have contributed to VF in this patient [8]. Nonetheless, 32/39 patients in our cohort with similar baseline resistance on functional DTG-based mono-and-dual therapy achieved or maintained virologic suppression suggesting that the primary reason for VF in these patients was likely non-adherence. This is also supported by the fact that 4/5 non-adherent VFs had baseline HIV-1 RNA ≥ 50 copies/mL which likely indicates a history of non-adherence prior to study entry.

Post-switch genotypes were only available for the 5 non-adherent VFs, and 4 of these were obtained on DTG. We observed no treatment-emergent NRTI or INSTI resistance, and 3/5 patients subsequently went on to achieve HIV-1 RNA < 50 copies/mL on a different DCR after discontinuation of the study regimen. One patient achieved HIV-1 RNA < 50 copies/mL on a non-DCR and the other was lost to follow up (Table 1). Though based on a small sample, this observation reinforces the high genetic barrier to resistance of DTG and its forgiveness in the setting of non-adherence, even in patients with pre-existing ARV resistance.

Two VFs were documented as 100% adherent, both were on functional dual therapy; one was on DTG + TDF and the other was on DTG + ABC. Both had baseline M184V/I without additional NRTI mutations. In the patient on DTG + ABC, the reduction in ABC susceptibility conferred by the M184V/I may have contributed to VF. However, in the other on DTG + TDF, this mutation is expected to increase TDF susceptibility and does not fully explain VF development. Baseline mutations may have contributed to VF in these cases; however, it is unknown how accurate their documented adherence patterns were and whether non-adherence may have also played a role.

In 32/39 patients on functional DTG-based mono-and dual therapy, HIV-1 RNA < 50 copies/mL was achieved and maintained throughout the study period. All patients received DCRs with ≥ 3 ARVs, and though baseline resistance testing predicted either functional-mono or, dual therapy, we acknowledge the possibility of partial activity from other ARVs deemed not fully active. This may explain the high virologic response rates observed in our study and the lack of treatment emergent INSTI resistance in those with VF due to “protection” of DTG by these partially active agents.

Limitations of this study include a small sample size, the retrospective nature of the analysis, the lack of control group, possible inaccuracy of documented information, and that data are from a single center in the Southeastern United states. However, this is the first report of outcomes of patients treated with functional DTG-based mono-and-dual therapy from a US cohort and may provide important insight into DTG-based treatment strategies with fewer ARVs.

Declarations

Funding:

This work was supported by a research grant from ViiV Healthcare, ViiV GSK 209995 (PI: Rolle). The funder had no role in the study design, data collection, data interpretation, writing of the report or decision to submit the article for publication.

Address for reprint requests:

Charlotte-Paige Rolle, MD MPH

Orlando Immunology Center

Department of Global Health, Emory University Rollins School of Public Health

1707 N. Mills Avenue

Orlando, FL 32803

Author Contributions:

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline.

The specific credit roles of the authors are included below:

Charlotte-Paige Rolle: conceptualization, data curation, formal analysis, funding acquisition, preparation of the original draft, review and editing, and final approval of the submitted version

Vu Nguyen: methodology, formal analysis, and final approval of the submitted version

Federico Hinestrosa: conceptualization, review and editing, and final approval of the submitted version

Edwin DeJesus: conceptualization, funding acquisition, preparation of the original draft, review and editing and final approval of the submitted version

Author Disclosures:

Dr. Charlotte-Paige Rolle has received research grants and honoraria from Gilead Sciences, ViiV Healthcare, Theratechnologies and Janssen Infectious Diseases during the conduct of this study. Dr. Federico Hinestrosa has received honoraria from Gilead Sciences, Merck, and AbbVie during the conduct of this study. Dr. Edwin DeJesus has received honoraria from Gilead Sciences, Theratechnologies, and Janssen Pharmaceuticals during the conduct of this study.

References

1. Cahn, P., et al., Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection - 96-week results from the GEMINI studies. Presented at the 10th International AIDS Conference on HIV Science (IAS 2019), 21-24th July 2019, Mexico City, Mexico., 2019.
2. van Wyk J, O.C., Rubio R et al. Durable suppression and low rate of virologic failures 3 years after switch to DTG+RPV 2-Drug Regimen: SWORD 1&2 Studies. Presented at the 25th Annual Conference of the British HIV Association (BHIVA 2019), 2-5th April 2019, Bournemouth, United Kingdom., 2019.
3. Van Wyk, J., et al., Switching to DTG+3TC fixed dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) in maintaining virologic suppression through 48 weeks (TANGO study). . Presented at the 10th International AIDS Conference for HIV Science (IAS 2019), 21-24 July 2019, Mexico City, Mexico., 2019.
4. Wijting, I., et al., *Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial.* Lancet HIV, 2017. **4**(12): p. e547-e554.
5. Blanco, J.L., et al., *Dolutegravir-based maintenance monotherapy versus dual therapy with lamivudine: a planned 24 week analysis of the DOLAM randomized clinical trial.* J Antimicrob Chemother, 2018. **73**(7): p. 1965-1971.
6. Hocqueloux, L., et al., *Dolutegravir Monotherapy Versus Dolutegravir/Abacavir/Lamivudine for Virologically Suppressed People Living With Chronic Human Immunodeficiency Virus Infection: The Randomized Noninferiority MONotherapy of TiviCAY Trial.* Clin Infect Dis, 2019. **69**(9): p. 1498-1505.
7. Boffito, M., et al., *Perspectives on the Barrier to Resistance for Dolutegravir + Lamivudine, a Two-Drug Antiretroviral Therapy for HIV-1 Infection.* AIDS Res Hum Retroviruses, 2020. **36**(1): p. 13-18.
8. Wensing, A.M., et al., *2017 Update of the Drug Resistance Mutations in HIV-1.* Top Antivir Med, 2017. **24**(4): p. 132-133.