Real world use of dolutegravir two drug regimens

Conor Bowman[a], Alissa Ambrose[a], Tanmay Kanitkar[a], Katia Flores[a], Pedro Simoes[a], Jennifer Hart[a], Alan Hunter[a], Jane Akodu[a] and Tristan J. Barber[a,b]

Background: Since 2015, we prescribed dolutegravir (DTG)-based two drug regimens (DTG-2DR) for 620 people [total cohort 3133 (19.8%)].

Method: Clinic database search 1 January 15 to 31 October 21. Demographic, tolerability and HIV related data analysed.

Results: In total, 620 people identified; 561 had complete data. 446 male (79.5%); median age 54 years (interquartile range 46, 59). 343 (61.1%) MSM. Nine people who initiated naïvely achieved viral suppression (100%). 546/552 (99.0%) switched or continued and were suppressed at data censor. 460/552 (83.3%) received DTG-lamivudine (DTG/3TC), 74/552 (13.4%) received DTG-rilpivirine (DTG/RPV) and 18/552 (3.3%) received DTG-emtricitabine (DTG/FTC). 70 (12.5%) switched off DTG-2DR (55 DTG/3TC, 13 DTG/RPV, two DTG/FTC) due to side-effects. 41 episodes of blip (1 off >50 copies/ml) occurred in 30 people (5.3%). 11/41 on DTG-RPV [$n = 7$ multi-tablet regimen (MTR), $n = 4$ single tablet regimen (STR)]. 27/41 DTG-3TC, 3/41 DTG/FTC ($n = 26$ MTR, $n = 4$ STR). Six people (1.1%) failed (confirmed viral load >200 copies/ml or persistent low level viraemia) ($n = 4$ DTG-3TC STR, $n = 1$ DTG-3TC MTR, $n = 1$ DTG-RPV MTR). Four failures due to low level viraemia, one due to non-adherence and one due to high viral load. Resistance tests performed for 5/6 – mutations detected only in latter person with high viral load failure (on DTG-3TC MTR) who developed triple class resistance.

Conclusion: Majority of experience is in DTG/3TC stable switch. Minority of patients developed side-effects. Low number of virological failures, one developed integrase inhibitor resistance. Viral failure associated with MTR, commensurate with trial data showing no failure with resistance if DTG/3TC STR used. Overall DTG-2DR demonstrates high efficacy in real-world setting.

AIDS 2023, **37**:785–788

Keywords: antiretroviral therapies, dolutegravir, dolutegravir-based two drug regimens, HIV, tolerability

[a]Ian Charles Day Centre, Royal Free Hospital, and [b]Institute for Global Health, University College London, London, UK.
Correspondence to Conor Bowman, King's College Hospital NHS Foundation Trust, London, UK.
E-mail: conor.bowman@doctors.org.uk
Received: 20 September 2022; revised: 30 December 2022; accepted: 4 January 2023.

DOI:10.1097/QAD.0000000000003480

Introduction

Major guidelines now include two-drug regimens (2DR) for the treatment of HIV [1,2]. These recommendations are based on the findings of multiple randomized clinical trials, including GEMINI, TANGO and SWORD, which found non-inferiority of 2DR to three-drug regimens (3DR) in achieving or maintaining virological suppression in people with HIV (PWH) [3–5]. 2DR combinations varied between the studies but all included dolutegravir (DTG) with either lamivudine (3TC) or rilpivirine (RPV). Most studies used single tablet regimens (STRs), though GEMINI used multi-tablet regimens (MTRs).

These promising results, in conjunction with updated HIV guidelines, will likely result in an increase in 2DR use. In our centre, a tertiary London teaching hospital, we have experience managing a large number of PWH on DTG-based 2DR (DTG-2DR). Hence, this retrospective study aims to provide real-world evaluation of DTG-2DR in clinical practice.

Methods

A retrospective review of electronic patient data and prescription records was performed in a single centre, using designated proformas. A search was conducted for all PWH prescribed DTG-2DR from 1 January 2015 to the date of data censor on 31 October 2021. The study population included all adults (>18 years old) with confirmed HIV infection who had ever received DTG-2DR. Regimens included DTG with 3TC, RPV or emtricitabine (FTC), prescribed as either STR or MTR. People missing vital data sets (such as complete drug histories) were excluded from further analysis. All analyses were descriptive and performed using Excel (Microsoft Corp., Redmond, WA, USA).

Results

In total, 620 people (19.8% of total cohort, $n = 3133$) were prescribed DTG-2DR. 59 were excluded for missing drug histories, hence data from 561 people were reviewed for this analysis.

Demographics

The predominant demographic in our cohort was of middle-aged, white men [median age 54 years; white ethnicity $n = 323$ (57.6%); male sex $n = 446$ (79.5%)], and the primary risk factor for HIV acquisition was MSM ($n = 343$, 61.1%). Detailed demographic data are presented in Table 1.

Table 1. Demographics ($n = 561$ people).

Sex:	Male: 446 (79.5%)	Female: 115 (20.5%)
Age:	Median age 54 (IQR 46,59)	
Ethnicity:	White	$n = 323$ (57.6%)
	Black	$n = 136$ (24.2%)
	Not stated	$n = 25$ (4.5%)
	Mixed	$n = 12$ (2.1%)
	Asian (Indian subcontinent)	$n = 12$ (2.1%)
	Any other ethnicity	$n = 40$ (7.1%)
	Any other Asian background	$n = 13$ (2.3%)
HIV exposure:	MSM	$n = 343$ (61.1%)
	Heterosexual sex	$n = 177$ (31.6%)
	Not documented	$n = 16$ (2.9%)
	Injecting drug use	$n = 10$ (1.2%)
	Blood transfusion	$n = 4$ (0.71%)
	Oral sex	$n = 3$ (0.53%
	Needle stick injury	$n = 1$ (0.18%)
	Other reason	$N = 7$ (1.25%)

IQR, interquartile range.

Prior treatment experience

The vast majority of PWH (98.4%, $n = 552/561$) were established on a wide range of antiretroviral therapies (ART) at the time of DTG-2DR switch or continuation. Nine were treatment-naïve (five of these had ART initiated as part of the GEMINI study). One person was continued on DTG-2DR after initiation at a transferring centre. 458 (83%) switched to DTG-2DR from 3DR, 86 (16%) from alternative 2DR and eight (1.4%) from monotherapy. 79 (14.3%) of the 3DR switches contained DTG.

Levels of suppression

In total, 537 (96.4%) PWH had an undetectable viral load at the time of starting DTG-2DR. A small number of people ($n = 21$, 3.7%), some of whom were treatment-naïve, had a viral load more than 50 copies/ml prior to DTG-2DR switch or initiation. Median viral load was 5258 copies/ml [interquartile range (IQR) 132, 5370]. In three people, pre-DTG-2DR viral loads were not performed.

Time to dolutegravir-based two drug regimens prescription

The median time to DTG-2DR prescription from HIV diagnosis was 16 years. The median time on treatment was 11 months for DTG with either 3TC or FTC (DTG-XTC) and 28 months for DTG-RPV.

Efficacy

The great majority of people ($n = 546/552$, 99%) who switched to or continued on DTG-2DR were virally suppressed at data censor. All nine ART-naïve people initiated on DTG-2DG also virally suppressed. Of the 21 people with a viral load more than 50 copies/ml at initiation, 13 (62%) had a viral load less than 50 copies/ml at the time of data censor. Of the remaining eight people, six experienced blips and two failed, as described in 'Blips and failure' section. The most common regimen prescribed was DTG/3TC as MTR ($n = 398$, 72.1%) (Table 2).

Table 2. Dolutegravir-based two drug regimens ($n = 552$ people switched to or continued dolutegravir-based two drug regimens).

DTG/RPV	74	13.4%
MTR	48	8.7%
STR	26	4.7%
DTG/3TC	460	83.3%
MTR	398	72.1%
STR	62	11.23%
DTG/FTC	18	3.3%

Discontinuing dolutegravir-based two drug regimens

In total, 70 people (12.5%) discontinued DTG-2DR ($n = 57$ DTG/XTC; $n = 13$ DTG/RPV). 59 were switched due to side effects (10.7%) and 11 for blipping or virological failure (2%). The most common side effects were neurological ($n = 13$, 22%), psychiatric ($n = 12$, 20.3%) and weight gain ($n = 10$, 16.9%, average gain of 7.5 kg) (Table 3). Four people (0.1%) died, but the causes of death were not HIV or ART-associated; two deaths were cancer-related, one secondary to a fall and one secondary to pulmonary embolism. All four were virally suppressed at the time of death.

Blips and failure

In total, 41 episodes of blip (1 of > 50 copies/ml) occurred in 30 people (5.3%). Most of these blips occurred on DTG-XTC MTR ($n = 26$, 63%). These prompted a switch to alternative regimens in five people (DTG/RPV STR × 1; DTG/RPV MTR × 1; and DTG/3TC MTR × 3), while the remainder re-suppressed on continuation of the same regimen. The median height of blips was 105 copies/ml (IQR 77, 458) for those who switched and 91 copies/ml (IQR 66, 205) for those who continued.

Six people (1.1%) encountered failure defined as viral load more than 200 copies/ml or persistent low level viraemia (LLV), all which led to discontinuing DTG-2DR. Per regimen, four people failed on DTG/ 3TC STR, one on DTG/3TC MTR and one on DTG/RPV MTR. Four failures were at LLV only and rapidly re-suppressed on regimen switch. One person developed a high viral load (DTG/3TC MTR) and one failure was due to non-adherence.

Table 3. Discontinuing dolutegravir-based two drug regimens ($n = 70$, 13 dolutegravir/rilpivirine, 57 dolutegravir/XTC).

	No. of people	Percentage people (%)
Neurological	13	18.6
Psychiatric	12	17.1
Weight gain	10	14.3
Failure	6	8.6
Gastrointestinal	6	8.6
Not documented	5	7.1
Blip	5	7.1
Intolerance (not otherwise documented)	4	5.7
Rationalization of medications	2	2.9
Rash	2	2.9
Itch	2	2.9
Patient preference	2	2.9
Drug interaction	1	1.4

Resistance

In total, 56 people (10%) had integrase resistance tested prior to DTG initiation. Of these, two were found to have resistant mutations ($n = 1$ F121Y, $n = 1$ N155H); both suppressed on DTG-2DR.

Five failures were investigated with resistance tests and mutations were identified in one person. Genotyping revealed reverse transcriptase (M184V, K103N) and integrase (T66A, G118R, E138K) mutations.

Discussion

The current single-centre retrospective cohort study explores the demographic and baseline HIV status of PWH who were treated with DTG-2DR. It also describes reasons for discontinuation of DTG-2DR, including virological failure. Most data on DTG-2DR use arise from trials where participants receive curated care that may not represent a real-world setting. However, our study represents mostly real-life experience, with only five people having initiated DTG-2DR as part of the GEMINI study; as far as we are aware, it is the largest single-centre cohort to describe DTG-2DR use in a real-world setting.

The vast majority of people maintained or achieved virological suppression on DTG-2DR. It is important to note that this cohort includes people who had experience with taking ART. In addition, the majority were virally suppressed at the time of switch to DTG-2DR.

Treatment discontinuation was not common in this cohort; however, side-effects that were encountered were in keeping with those documented in the literature and in pharmaceutical sources (the Electronic Medicines Compendium lists neurological and psychiatric side-effects of DTG as very common or common, respectively) [1,6].

In total, 41 episodes of blip occurred, and this led to discontinuing DTG-2DR in five people, with the majority re-suppressing on continuation of the same regimen. Median heights of blip were similar in people who switched or continued (105 copies/ml and 91 copies/ml, respectively), suggesting that some of those who switched may have re-suppressed if continued. In our centre, MTR was prescribed before STR was available, and it is interesting to note that the majority of blips occurred in people taking MTR. The literature finds that STR is associated with higher adherence, and improved adherence results in an increased likelihood of achieving viral suppression (though direct effects of STR versus MTR remains unclear) [7,8].

The person who developed failure with a high viral load was also found to have mutations. They had previously failed on abacavir/3TC/efavirenz but resistance testing at the time revealed wild-type virus. Later they received tenofovir disoproxil/3TC/DTG, alongside multiple cardiovascular medicines, and switched to DTG/3TC MTR due to tenofovir related side-effects. They suppressed initially but months later their viral load was detected at more than 4000 copies/ml. Genotyping revealed reverse transcriptase (M184V, K103N) and integrase (T66A, G118R, E138K) mutations. They switched to tenofovir alafenamide/FTC/darunavir/cobicistat STR and re-suppressed.

Limitations of this study include its retrospective nature, its single-centre cohort, and its initial use of MTR, which may not reflect current use of STR. It should also be stated that 59 (9.5%) people didn't have complete data available for analysis. While it's unlikely these data represent significant failures or resistances, these possibilities can't be excluded. Strengths include its large cohort and observation of real-world practices. In future analyses of this cohort, data can be strengthened by including comparator groups and survival analysis statistics.

Conclusions

The current study analyses real-world data from a large cohort of PWH prescribed DTG-2DR. In keeping with other contemporary studies, our study further evidences the efficacy of DTG-2DR in maintaining virological suppression in PWH, as well as high levels of tolerability and low levels of failure. Overall, these data support the use of DTG-2DR as a suitable treatment option in HIV, as per current recommendations.

Acknowledgements

Conflicts of interest

TJB has received conference support, speakers fees and advisory board honoraria from Gilead Sciences, GSK, Janssen, MSD, Roche, Theratechnologies, and ViiV Healthcare. He holds research/educational grants from Gilead Sciences, Roche and ViiV Healthcare.

References

1. European AIDS Clinical Society. *Guidelines. Version 11.0. October 2021*. EACS, 2021. https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf. [Accessed 19 September 2022]
2. Saag MS, Gandhi RT, Hoy JF, Landovitz RJ, Thompson MA, Sax PE, *et al*. **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society–USA Panel.** *JAMA* 2020; **324**:1651–1669.
3. Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, *et al*. **Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment-naive adults with HIV-1 infection: 96-week results from the GEMINI-1 and GEMINI-2 randomized clinical trials.** *J Acquir Immune Defic Syndr* 2020; **83**:310–318. Erratum in: J Acquir Immune Defic Syndr. 2020 Jul 1;84(3):e21. PMID: 31834000; PMCID: PMC7043729.
4. Llibre J, Hung C, Brinson C, Castelli F, Girard P-M, Kahl LP, *et al*. **Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, noninferiority SWORD-1 and SWORD-2 studies.** *Lancet* 2018; **391**:839–849.
5. Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, *et al*. **Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide–based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study.** *Clin Infect Dis* 2020; **71**:1920–1929.
6. European Medicines Compendium. *Tivicay 10 mg film-coated tablets*. Datapharm, 2022. https://www.medicines.org.uk/emc/product/5248/smpc#gref. [Accessed 19 September 2022]
7. Furtado Dos Santos S, Almeida-Brasil CC, Costa JO, Reis EA, Afonso Cruz M, Silveira MR, Ceccato MDGB. **Does switching from multiple to single-tablet regimen containing the same antiretroviral drugs improve adherence? A group-based trajectory modeling analysis.** *AIDS Care* 2020; **32**:1268–1276.
8. Sutton S, Magagnoli J, Cummings T. **Adherence after treatment switch from a multiple tablet antiretroviral regimen to a single tablet antiretroviral regimen.** *Therapies* 2021; **76**:567–576.