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SHORT COMMUNICATION

Virological response and resistance profile in highly treatment-experienced HIV-1-infected patients switching to dolutegravir plus boosted darunavir in clinical practice

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Objectives

We evaluated the virological response and resistance profile in combined antiretroviral therapy (cART)-experienced HIV-1-infected patients starting a dual therapy with dolutegravir (DTG) and boosted darunavir (bDRV) for the first time.

Methods

Survival analyses were used to evaluate virological success (VS) and virological rebound (VR) in viraemic and virologically suppressed patients, respectively. Major resistance mutations (MRMs) and genotypic susceptibility score (GSS) were evaluated at baseline and after switch.

Results

Overall, 130 patients [62 (47.7%) viraemic; 68 (52.3%) virologically suppressed] were retrospectively analysed. At the moment of switch, 81.5% accumulated one or more MRM [protease inhibitor (PI), 35.7%; nucleoside(t)ide reverse transcriptase inhibitor (NRTI), 77.5%; non-NRTI, 69.0%; integrase inhibitor (INI), 10.1%), but 77.7% harboured strains fully susceptible to DTG + bDRV. In viraemic patients, the overall probability of VS by 12 months of treatment was 91.7%. In virologically suppressed patients, the overall probability of VR was 10.5% by 24 months after therapy start. Patients with previous time under virological suppression $\leq$ 6 months showed a higher VR probability compared with others (37.5% *vs.* 6.7%, $P < 0.002$). Among 13 non-responding patients for whom a genotypic resistance test result at failure was available, only two (15.4%) accumulated further resistance in integrase (Y143C/H/R; S147G and N155H) and protease (V32I, L33F, I54L).

Conclusions

In highly treatment-experienced patients, the use of dual therapy based on DTG + bDRV appears to be a very good regimen for switch therapy, with a high rate of virological control in both viraemic and virologically suppressed patients. Among non-responding patients, the selection of further resistance is a rare event.

Keywords: darunavir, dolutegravir, drug resistance, dual therapy, genotypic susceptibility score, HIV-1, virological response

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Introduction

The use of modern combined antiretroviral therapy (cART) has led to unprecedented success in the control of viral replication among people living with HIV/AIDS, thanks to the advent of potent and high genetic barrier

antiretrovirals. As a result of the continuous quest for simpler regimens and more convenient therapy, the standard triple therapy is being challenged by the use of two-drug regimens (2DR), and today it is possible to consider switching a person from one effective regimen to a simplified one [1–3]. Following this paradigm shift, the 2DR is increasingly used for both optimization and in salvage reverse transcriptase inhibitor (RTI)-sparing regimens. Given that it is fundamental to maintain virological suppression without jeopardizing future treatment options, a full patient's ART history including cumulative resistance and time of virological suppression before switch should always be considered [4]. In this regard, regimens containing protease inhibitors (PIs) or second-generation integrase inhibitors (INIs) are the best candidates for 2DR in switch strategies due to their exceptional efficacy and high genetic barrier. The use of dolutegravir (DTG) or ritonavir/cobicistat-boosted darunavir (bDRV) in combination with lamivudine or rilpivirine are supported by large clinical trials [5–9], and are recommended as part of a 2DR switch for maintenance of virological suppression [4,10]. Nowadays, due to their long treatment history, certain failing patients with a high resistance level (e.g. with exhausted RTI options) might need to switch to potent but tolerable and simple treatments. They might therefore have an advantage in switching to a 2DR containing high genetic barrier drugs such as DTG and DRV. So far, only one clinical trial has investigated a 2DR switch based on DTG + bDRV, in which individuals having documented major DRV or INI resistance were excluded [11]. The observational studies reporting this combination had a limited sample size, and frequently showed partial information about previous drug resistance [12–18]. Based on these considerations, we evaluated the virological response and resistance profile in cART-experienced HIV-1-infected individuals in Italy starting dual therapy with DTG + bDRV for the first time.

Methods

Patients

We included in the study ART-experienced patients (both viraemic and virologically suppressed) followed in two clinical centres in north-central Italy, who switched to a dual DTG + bDRV-based regimen for the first time and with a complete therapeutic history and virological follow-up. Reasons for switch were categorized as follows: treatment simplification (decreased number of drugs and/or pills), treatment intensification (switching from PI-monotherapy or from dual therapy including drugs with low genetic barrier), virological failure (switching from a previous failed treatment) and intolerance.

Genotyping and drug resistance evaluation

Sequences of protease, reverse transcriptase and integrase were obtained through commercially available kits (ViroSeq HIV-1 Genotyping System, Abbott Molecular, Des Plaines, IL, USA; Trugene-HIV-1 Genotyping-Kit, Bayer HealthCare LLC, Tarrytown, NY, USA) and/or a home-made system, as previously described [19,20].

Major resistance mutations (MRMs) to PIs, nucleoside(t)ide RTIs (NRTIs), non-NRTIs (NNRTIs) and INIs reported in the Stanford HIV-1 drug resistance database (https://hivdb.stanford.edu/, last updated 25/10/2019) were evaluated at baseline (as cumulative plasma resistance) and after DTG + bDRV switch. Cumulative genotypic susceptibility score (GSS) at baseline was calculated, using the Stanford HIVdb algorithm (https://hivdb.stanford.edu/). In individuals who did not respond therapy [both never achieving virological success (VS) and experiencing virological rebound (VR) after VS], resistance was also evaluated.

Statistical analysis

Analyses were performed using the software package SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Survival analysis was used to assess the probability of VS (the achievement of viraemia < 50 copies/mL) by 12 months after switch in viraemic patients, and of VR (the first of two consecutive vireamia values > 50 copies/mL or one value > 1000 copies/mL) by 24 months after switch in virologically suppressed patients after DTG + bDRV start.

Results

Baseline patient characteristics

Overall, 130 patients [62 (47.7%) viraemic, 68 (52.3%) virologically suppressed], comprising mainly males (70.8%) with a median (interquartile range, IQR) age of 50 (45–55) years, were analysed (Table 1). The majority of viraemic patients (80.6%) switched to DTG + bDRV after virological failure, while virologically suppressed patients switched to a simplified regimen (64.7%) or to improve genetic barrier and efficacy from an obsolete previous regimen (26.5%).

Patients had a long treatment history with a median (IQR) of nine (4–12) previous regimens; most of them had

Table 1 Baseline characteristics of patients starting a dual regimen based on dolutegravir (DTG) plus boosted darunavir (bDRV)

Variables	Overall (*N* = 130)	Viraemic (*N* = 62)	Virologically suppressed (*N* = 68)	*P*-value
Male [*n* (%)]	92 (70.8)	45 (72.6)	47 (69.1)	0.665
Age (years) [median (IQR)]	50 (45–55)	49 (43–53)	52 (47–57)	0.120
HIV-1 B subtype [*n* (%)]	106 (81.5)	48 (77.4)	58 (85.3)	0.248
DRV 600 mg BID [*n* (%)]	11 (8.5)	5 (8.1)	6 (8.8)	0.877
DTG 50mg BID [*n* (%)]	5 (3.8)	4 (6.5)	1 (1.5)	0.347
Time under cART (years) [median (IQR)]	19.5 (10.4–21.9)	**17.2 (8.6–19.8)**	**20.9 (13.6–24.2)**	**0.002**
Baseline plasma HIV-1 RNA (log_{10}copies/mL[†]) [median (IQR)]	–	3.2 (2.1–4.4)	–	–
Baseline CD4 cell count (cells/μL) [median (IQR)]	444 (324–728)	**412 (237–636)**	**614 (434–747)**	**< 0.001**
Viremia zenith (log_{10} copies/mL) [median (IQR)]	5.4 (4.8–5.7)	5.4 (5.0–5.7)	5.3 (4.7–5.7)	0.471
Nadir CD4 count (cells/μL) [median (IQR)]	115 (42–240)	96 (27–257)	128 (53–227)	0.915
Time under virological suppression before treatment switch (months[‡]) [median (IQR)]	–	–	57 (27–100)	–
Previous DRV exposure [*n* (%)]	98 (75.4)	**41 (66.1)**	**57 (83.8)**	**0.019**
Previous DTG exposure [*n* (%)]	12 (9.2)	4 (6.5)	8 (11.8)	0.371
Previous INI exposure [*n* (%)]	78 (60.0)	**30 (48.4)**	**48 (70.6)**	**0.012**
Previous PI exposure [*n* (%)]	121 (93.1)	**53 (85.5)**	**68 (100.0)**	**< 0.001**
Number of previous regimens experienced [median (IQR)]	9 (4–12)	8 (4–11)	9 (6–12)	0.083
No. of DRV MRMs [*n* (%)]				
0	**100 (76.9)**	**56 (90.3)**	**44 (64.7)**	**< 0.001**
1	**10 (7.7)**	**5 (8.1)**	**5 (7.4)**	
2	**11 (8.5)**	**1 (1.6)**	**10 (14.7)**	
≥ 3	**9 (6.9)**	**0 (0.0)**	**9 (13.2)**	
No. of PI MRMs	0 (0–2)	**0 (0–1)**	**0 (0–4)**	**0.035**
≥ 1 PI MRM	46 (35.4)	18 (29.0)	28 (41.2)	0.148
≥ 1 NRTI MRM	100 (76.9)	**42 (67.7)**	**58 (85.3)**	**0.018**
≥ 1 NNRTI MRM	89 (68.5)	40 (64.5)	49 (72.1)	0.355
≥ 1 INI MRM[§]	8 (10.0)	6 (12.0)	2 (6.7)	0.703
Class resistance[¶]				
0	**18 (13.8)**	**11 (17.7)**	**7 (10.3)**	**0.512**
1	**24 (18.5)**	**13 (21.0)**	**11 (16.2)**	
2	**49 (37.7)**	**23 (37.1)**	**26 (38.2)**	
3	**35 (26.9)**	**13 (21.0)**	**22 (32.4)**	
4	**4 (3.1)**	**2 (3.2)**	**2 (2.9)**	
DRV fully susceptible GSS [*n* (%)]	107 (82.3)	**59 (95.2)**	**48 (70.6)**	**< 0.001**
DTG fully susceptible GSS [*n* (%)]	122 (93.8)	59 (95.2)	63 (92.6)	0.720
Regimen susceptibility by GSS[#] [*n* (%)]				
DRV S + DTG S (fully susceptible)	**101 (77.7)**	**57 (91.9)**	**44 (64.7)**	**0.003**
DRV I + DTG S	**19 (14.6)**	**2 (3.2)**	**17 (25.0)**	
DRV S + DTG I	**6 (4.6)**	**2 (3.2)**	**4 (5.9)**	
DRV R + DTG S	**2 (1.5)**	**0 (0.0)**	**2 (2.9)**	
DRV I + DTG I	**2 (1.5)**	**1 (1.6)**	**1 (1.5)**	
Reason for switch [*n* (%)]				
Virological failure	**50 (38.5)**	**50 (80.6)**	**0 (0.0)**	**< 0.001**
Treatment simplification	**44 (33.9)**	**0 (0.0)**	**44 (64.7)**	
Treatment intensification	**18 (13.8)**	**0 (0.0)**	**18 (26.5)**	
Other[††] /unknown	**18 (13.8)**	**12 (19.4)**	**6 (8.8)**	

Significant differences are indicated In bold: $P < 0.05$ according to χ^2, Fisher exact test or Mann–Whitney test, as appropriate. For patients without previous integrase GRT and INI-naïve, GSS-DTG was considered fully susceptible. For patients who previously failed an INI-based treatment, DTG-GSS was considered intermediate resistant.

BID, twice a day; DRV, cobicistat/ritonavir-boosted darunavir; GSS, genotypic susceptibility score: I, intermediate resistant GSS; INI, integrase inhibitor; MRM, major resistance mutation; NRTI, nucleoside(t)ide reverse transcriptase inhibitor; NNRTI, non-NNRTI; PI, protease inhibitor; R, fully resistant GSS; S, fully susceptible GSS.

[†]Evaluated only in viraemic patients.

[‡]Evaluated only in virologically suppressed patients; 9/68 patients were virologically suppressed for a period < 12 months (< 6 months, *n* = 8; 6–12 months, *n* = 1).

[§]Information about baseline INI resistance was available for 80/130 patients: 50 viraemic and 30 virologically suppressed.

[¶]Resistance to PI/NRTI/NNRTI and/or INI.

[#]GSS was calculated according to Stanford HIVdb ver 8.9–1.

[††]Other: six patients switched for intolerance.

previously received DRV (75.4%) or INI (60.0%; DTG, 9.2%). The majority of patients received DRV 800 mg + DTG 50 mg once a day (Table 1). The baseline median (IQR) plasma HIV-1 RNA in viraemic patients was 3.2 (2.1–4.4) log_{10}copies/mL, while the median (IQR) time under virological suppression before treatment start in virologically suppressed patients was 57 (27–100) months. Even though at baseline 86.2% (*n* = 112) of

patients had accumulated at least one MRM (PI, 35.7%; NRTI, 77.5%; NNRTI, 69.0%; INI, 10.1%), 77.7% (n = 101) of them harboured strains fully susceptible to DTG + bDRV (DTG, 93.8%; DRV, 82.3%). Among the remaining 29 patients, 27 harboured viral strains susceptible to one of the two drugs, while two harboured viral strains with intermediate resistance to both DTG and bDRV (Table 1). Compared with viraemic patients, virologically suppressed patients showed a higher level of baseline DRV resistance (≥ 3 DRV MRMs: 13.2% *vs.* 0.0%, $P < 0.001$; fully susceptible DRV-GSS: 70.6% *vs.* 95.2%, $P < 0.001$). However, only two patients (2.9%) were infected with a virus fully resistant to DRV. DTG susceptibility was high in both groups (INI resistance: 6.7% *vs.* 12.0%, $P = 0.703$; fully susceptible DTG-GSS: 92.6% *vs.* 95.2%, $P = 0.720$).

Virological response and resistance profiles

By 12 months of treatment, the overall probability of VS in the 62 viraemic patients was 91.7%, achieved in a median (95% confidence interval, CI) time of 1.9 (1.0–2.9) months. The few patients receiving a non-fully active regimen had a lower probability of VS (80.0%) compared with those who received a fully active treatment (93.3%), even though statistical significance was not reached ($P = 0.660$; Fig. S1a), probably due to the low sample size. Concerning response in virologically suppressed patients, by 12 months and 24 months after switch, the overall probabilities of VR were 4.7% and 10.5%, respectively, with a total of only six VR events recorded at a median (IQR) viraemia of 266 (104–142 761) copies/mL. Patients receiving non-fully active regimens also had a higher probability (16.4%) of VR compared with those receiving fully active regimens (7.3%, $P = 0.651$; Fig. S1b). No significant association with resistance was found due to the low number of events. Moreover, patients with a previous time under virological suppression ≤ 6 months showed a higher VR probability compared with others (37.5% *vs.* 6.7%, $P < 0.002$; Fig. S1c).

Among the 27 patients who did not respond to therapy (viraemic group: eight never achieved VS; 13 experienced VR after VS; virologically suppressed group: six experienced VR), 14 (51.9%) were not tested for resistance because seven (25.9%) re-suppressed viraemia in a median time of 4 (3–8) months and the remaining 7 (25.9%) were lost to follow-up, whereas 13 (48.2%) patients were tested for resistance in a median (IQR) time of 12.4 (9.2–27.4) months after switch. Of these, eight (61.5%) were previously exposed to raltegravir or DTG. Two patients (15.4%), both with non-fully susceptible baseline GSS accumulated further resistance in integrase and protease (ID 357: Y143C/H/R; ID 392: S147G, N155H and V32I, L33F, I54L) (Table 2). It is worth noticing that most mutations present in previous GRTs performed before switch were no longer present in plasma GRT at failure.

Discussion

This study evaluated the virological response and resistance profile in cART-experienced HIV-1-infected patients (viraemic and virologically suppressed) starting a 2DR with DTG + bDRV for the first time, a combination not recommended yet for dual therapy or only recommended if no other alternative options are available [4,10].

Nowadays, DTG + bDRV regimen is mainly prescribed in highly treatment-experienced patients and with high prevalence of MRMs, not only in the NRTI class, but also in the PI class [12,14–16].

Our results show that, overall, viraemic patients switching to a DTG + bDRV-based regimen achieved a high level of VS (91.2%) by 12 months of treatment, despite previous exposure and baseline resistance to INI (48% and 10.0%, respectively) and PI (86% and 35.4%, respectively) in some patients. Despite the limited sample size, the randomized DUALIS study showed that switching to DTG + bDRV was non-inferior to continuing boosted DRV plus two NRTIs [11]. Likewise, the efficacy of DTG + bDRV reported in other observational studies among viraemic patients was promising [12,13,15,17], confirming the attractiveness of this option. However, despite this high efficacy, our results showed that patients receiving a non-fully active regimen showed a lower probability of VS (80.0%), suggesting that careful review of GRT results must also be considered.

Regarding virological response in virologically suppressed patients, we observed a low overall probability of VR by 24 months (only 10.5%), confirming its good efficacy in VS maintenance as reported in other studies [11,12,16,18]. Around 26% of these patients received DTG + bDRV to improve previous obsolete treatments (mainly based on PI monotherapy and dual therapy containing raltegravir), confirming the flexibility and effectiveness of this dual regimen also in this context.

Once more, patients not receiving a fully active regimen experienced more rebounds compared with those who received a fully active regimen; however, due to the low number of rebound events, no statistical significance was reached. Another important observation was that a few patients who switched with previous time ≤ 6 months under virological suppression experienced a significantly higher probability (37.5%) of VR than those who were suppressed for > 6 months (6.7%, $P = 0.002$). This

Table 2 Overview of resistance in patients failing a dual therapy based on dolutegravir (DTG) plus boosted darunavir (bDRV)

Patient ID	Plasma HIV-RNA at BL (copies/mL)	Time under DTG + bDRV (months)	Previous DRV experience	Previous INI experience	Baseline DRV/DTG GSS[†]	Plasma HIV-RNA at failure GRT (copies/mL)	PI MRMs	NRTI MRMs	NNRTI MRMs	IN MRMs	INI ARMs
357	< 50	11.3	Yes	RAL	R/S	297 560	*V32I, M46I, I47V, I54M, V82A, I84V, L90M*	*M41ML, D67DN, T69TADEKN, L74IV, M184V, T215TNSY*	*K103KN, V108VI, Y181C, H221HFLY, K238KT*	*N155H*, **Y143C/H/R**	None
1236	< 50	34.9	Yes	INI naïve	S/S	61	None	*M41L*, M184V, *T215F*	None	None	None
3272	< 50	15.9	Yes	RAL	I/S	354 018	*M46ML, I54MV, I84V*	*M184V*	*K101EQ, G190S*	None	None
361	429 230	32.0	No	RAL	S/I	124	M46I, L90M	*M41L, A62V, D67NS, K70R, L74V, V75I, M184V, L210W, T215DIV, K219Q*	*L100I, K103N*, E138G	*Y143C*	*T97TA, S230R*
392	840	11.8	Yes	RAL	I/I	160	**V32I**, **L33F,** M46I, **I54L,** I84V, L90M	M41L , L210W	None	**S147G, N155H**[‡]	None
569	47 086	3.9	Yes	RAL	S/S	210	None	None	*K103KN, V108VI,* E138A, Y188YHL	Na[§,¶]	*T97A*
758	2161	46.6	No	INI-naïve	S/S	1471	None	M41L, *M184V, T215Y*	Y181C	None	None
1600	198	3.7	Yes	INI-naïve	S/S	25 878	*M46L, V82A, L90M*	*M41L, T215F*	None	None	None
4307	158	39.8	Yes	INI-naïve	S/S	4609	None	*K70R*	None	None	None
4134	57 570	9.0	Yes	RAL	S/S	10 626	None	*M184V*	K103N, V106I, *H221HY, P225PH, M230L*	None	None
8523	406 053	25.8	Yes	INI-naïve	S/S	414	None	*D67N, M184I*	V106I, *V108VI, V179D*	None	None
13 695	277	13.0	Yes	DTG	S/S	477	None	None	None	Na[§,¶]	Na[§,¶]
17 348	66	9.3	Yes	RAL	S/S	264	None	None	None	Na[§,¶]	Na[§,¶]

The table reports an overview of resistance profile in patients failing a dual treatment with DTG + bDRV. In italic character: mutations cumulated in previous plasma GRTs but not at failure; in standard character: mutations present in both cumulative and failure GRTs; in bold character: mutations that emerged at failure GRT.
ARM, accessory resistance mutation; BL, baseline; GRT, genotypic resistance test; INI, integrase inhibitor; MRM, major resistance mutation; Na, not available; NRTI, nonnucleoside(t)ide reverse transcriptase inhibitor; NNRTI, non-NNRTI; PI, protease inhibitor; RAL, raltegravir.
[†]GSS was calculated according to Stanford HIVdb v.8.9–1. For patients without a previous integrase GRT and INI-naïve, GSS-DTG was considered fully susceptible. For patients who previously failed an INI-based treatment, DTG-GSS was considered intermediate resistant.
[‡]Previous integrase GRT not available.
[§]Integrase genotyping at failure not successful
[¶]No resistance in the previous integrase GRT.

category of patients should not be eligible for treatment switch due to their short period under virological suppression, but we decided to maintain them in the analysis, due to the fact that our study is observational and based on real data in clinical settings. Thus, our results confirmed that a sufficient period of virological suppression before switch (> 6 months) and a complete knowledge of a patient's full HIV history are crucial to guide a treatment optimization. It should be noted that in the patients included in this study, treatment was tailored according to previous resistance and treatment history.

With regard to resistance, most of the MRMs at baseline are no longer present in plasma GRT, and selection of newly emerged resistance mutations is a rare event. We observed only few VR at 24 months among virologically suppressed patients, and among those with available GRT at failure, only two of the 13 patients with available GRT at failure had new mutations (one in integrase only, another in integrase and protease). The mutations that were observed in integrase had no or little effect on DTG susceptibility. In fact, most of the previous studies [11,12,17,18] investigating this combination did not find any mutation in either protease or integrase at failure. This study has some limitations, including its observational nature, which could have introduced some biases, and the low sample size. In conclusion, the use of dual therapy based on DTG + bDRV in highly treatment-experienced patients appears to be a very good regimen for switch therapy, in both viraemic patients and those who are virologically suppressed, with a high rate of virological control. The majority of resistance mutations present in previous GRTs performed before switch are no longer present in plasma GRT at failure, and selection of further resistance is a rare event. To overcome some of the limitations of this study, larger cohort studies and randomized studies are warranted to further confirm these findings.

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Author contributions

DA, YB and MMS carried out study conception and design, analysis and interpretation of data, and drafting of manuscript. FCS and CFP participated in the study conception and design. LF, GB and VB contributed to the collection of the data. RG, LF, VB, GB, AV, SC, CM, AA, FC-S and CFP carried out a critical revision of the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig. S1 Kaplan-Meier estimates of the probability of achieving virological success by 12 months and virological rebound by 24 months in patients switching to DRV + DTG-based therapy.