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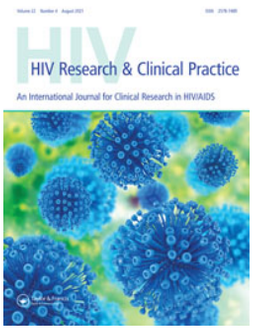

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Early discontinuation of DTG/ABC/3TC and BIC/TAF/FTC single-tablet regimens: a real-life multicenter cohort study

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Background: Data regarding the efficacy and tolerability of DTG/ABC/3TC/and BIC/TAF/FTC in switching strategies are still scarce. The rates and reasons of early discontinuation within 24 weeks from the switch to dolutegravir (DTG) or bictegravir (BIC) single-tablet regimens (STRs) were compared.

Methods: This is a multicenter cohort study. Persons living with HIV (PLWH) with HIV-1 RNA <50 copies/mL switching to BIC-STR or DTG-STR were included and followed-up 24 weeks. Major outcome was the analysis of (quantitative assessment of) discontinuation due to adverse events and self-suspension (EDAEs). Second, we assessed virologic failure (VF), and all-cause discontinuation (EDAC). Cox model for regression analysis was employed.

Results: We included 786 PLWH: 524 with DTG, 262 with BIC. At week 24, we observed 70 EDAC: 5 for VF (1 with BIC and 4 with DTG; $p = 0.6276$), 10 simplifications, more frequently with BIC than DTG ($n = 5$, 1.9% and $n = 5$, 0.9%; $p = 0.072$) and 55 EDAEs, 7 (2.7%) with BIC, 48 (9.2%) with DTG ($p = 0.0323$). EDAEs due to neurological and gastrointestinal toxicity were similar ($p = 0.2398$ and $p = 0.1160$, respectively). There were no significant differences in the rates of VF and EDAC. EDAEs rate was significantly higher for DTG than for BIC. The adjusted HR for EDAEs in DTG group was 3.28 (95% CI: 1.34–8.00; $p = 0.009$). We identified an association between EDAE in the DTG group and having an age >60 and having switched from a regimen without ABC.

Conclusions: PLWH who received DTG or BIC do not show differences in VF or EDAC rates. However, EDAEs is more frequent with DTG especially in the over-sixties and in those who come from regimens without abacavir.

KEYWORDS: DTG/ABC/3TC, BIC/TAF/FTC, STR, early discontinuation, cohort study, switch

Introduction

Since its introduction in 1996 and 1997, antiretroviral therapy (ART) has turned HIV infection from a deadly disease characterized by opportunistic infections into a chronic condition.[1] However, first ART regimens have been associated with the development of drug resistance, drug-related toxicities, and with the difficulties in maintaining long-term adherence, spurring the search towards more effective, straightforward, and better tolerated antiretroviral regimens that have resulted in better survival and quality of life among persons living with HIV (PLWH).[2] Many regimens are now available in single-tablet regimens (STR), easy to take and preferred by the PLWH,[3] with lower rates of discontinuation when compared to multi-tablet regimens.[4,5] In such a scenario, clinicians are prompted to optimize therapeutic options for their patients, with the basic tenet to maintain the virologic suppression, to deliver an optimal antiviral strategy and long-term

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benefit. Switching strategies, according to the more recent guidelines, allow to overcome ongoing toxicity (reactive switch), prevent predictable toxicity (preventive or proactive switch), promote adherence by safely reducing the number of tablets or doses, and address unfavorable drug interactions.[6]

Integrase strand transfer inhibitors (INSTIs) have become a reference drug class for their efficacy and tolerability in naïve and experienced PLWH. Moreover, recent studies seem to suggest a potential benefit of these compounds in terms of immunological recovery and also a more convenient inflammatory profile when compared to other drug classes.[7,8] Several studies have evaluated the class of INSTIs as switch options. STRIIVING study showed the non-inferiority of a fixed dose of abacavir/lamivudine/dolutegravir (DTG/ABC/3TC) compared with the current regimen. However, 10 patients in the switch arm vs. zero patients in the control arm discontinued treatment mainly due to neurological toxicity (insomnia, anxiety, depression).[9] Bictegravir (BIC) vs. DTG taken with TAF and FTC have been evaluated head-to-head in a double-blind, randomized study in naïve PLWH. Both drugs demonstrated high virologic response rates, good tolerability, and no significant safety signal in either arm.[10] The maintenance of virologic suppression was shown also in a randomized controlled trial (RCT) in adults switched from a dolutegravir or boosted protease inhibitor (PI) regimen with good tolerability.[11,12]

However, data from observational cohorts are still scarce regarding the comparison of efficacy and tolerability of DTG/ABC/3TC/and BIC/TAF/FTC in switching strategies. Thus, our main aim has been to compare rates and reasons of early discontinuation due to adverse events within 24 weeks of switching to DTG-STR or BIC-STR and investigate the discontinuation predictors. Second, we analyzed rates of virological suppression and all-cause discontinuation.

Methods

We conducted a retrospective, multicenter cohort study. The study was carried out in five different centers in Italy: Careggi University Hospital in Florence, two centers in Rome (Catholic University of the Sacred Heart, and IFO San Gallicano), Siena (Azienda Ospedaliero-Universitaria Senese), and Modena University Hospital. The enrolment period began 1 January 2015 and ended on 1 April 2020. We included all persons with the following characteristics: (i) HIV-1 infected ART-experienced over 18 years of age who had stable ART for at least 6 months, (ii) having a plasma HIV-1 RNA <50 copies/mL at the time of switching, (iii) switching for any reason to an STR containing BIC or DTG, (iv) with at least one clinical and laboratory follow-up. The primary endpoint was to evaluate the rate and reasons of discontinuation due to adverse events and self-suspension (EDAEs). Secondly, to assess virologic failure (VF), and early all-cause early discontinuation (EDAC). The PLWH were followed up from the time of the switch to BIC or DTG-STR (baseline, BL) to the discontinuation or for a maximum of 24 weeks. Study exit was the date of VF or EDAC or loss to follow-up (FU)/death. VF was defined as two consecutive HIV-RNA >50 copies/mL or one HIV-RNA >200 cp/mL.[6,13] Demographic, clinical and laboratory variables were collected at baseline and during follow-up by reviewing medical charts. If available, historical genotypes and subtypes were analyzed. Plasma HIV-RNA was measured using Test v1.5 Roche COBAS AmpliPrep, Roche TaqMan HIV-1 Test v2.0 (Roche Diagnostics, Branchburg, NJ, USA) and Siemens Versant K PCR (Siemens Healthcare GmbH, Erlangen, Germany), with lower limits of detection of 50, 20, and 37 copies/mL, respectively. Reverse transcriptase and protease mutations were assessed by TRUGENE HIV-1 genotyping assay (Siemens Healthcare GmbH, Erlangen, Germany). Integrase mutations were evaluated by ViroSeq™ HIV-1 Integrase Genotyping Kit (ViroSeq; Abbott GmbH, Wiesbaden, Germany). A genotype homebrew technology has been used by the centers involved in the study to detect the reverse transcriptase, protease, and integrase mutations before the commercial tests were available. According to the Stanford algorithm, the frequency of any major transcriptase, protease, and integrase resistance mutations was analyzed (Stanford HIV db algorithm, version 8.8) (https://hivdb.stanford.edu/).

Descriptive analysis was used to illustrate population characteristics. Categorical variables were analyzed with X2/Fisher's exact test and continuous variables with the Mann–Whitney test. Predictors of EDAEs were investigated by univariate analysis with Mantel–Haenszel method producing an adjusted RR for each potential confounder in turn. Cox model for multivariable regression analysis was employed. A statistical test was considered significant if the p-value was <0.05.

The local Ethics Committees approved data collection, and all PLWH included provided written informed consent to use their data for research purposes. The study was performed in accordance with the ethical principles of the Declaration of Helsinki (7th revision) and with the International Conference on Harmonization Good Clinical Practice guidelines.

Table 1 Clinical/demographic baseline characteristics and outcome of HIV-1 infected, ART-experienced patients with HIV-RNA level <50 copies/mL switching to BIC/TAF/FTC or to DTG/ABC/3TC in five centers in Italy

	BIC/TAF/FTC (262)		DTG/ABC/3TC (524)		*p*
Baseline characteristics					
Italian origin, *n* (%)	221	(84.3)	431	(82.2)	0.502
Male sex at birth, *n* (%)	206	(78.6)	385	(73.5)	0.171
Age at entry (years), median [IQR]	54	[44–60]	51	[41–57]	0.003
Route of HIV transmission, *n* (%)					0.044
Heterosexual unprotected sex	75	(28.6)	203	(38.7)	
MSM	121	(46.2)	212	(40.5)	
IVDU	36	(13.7)	63	(12.0)	
Other	6	(2.0)	0.4		
Not known	24	(9.1)	44	(8.4)	
Months of undetectable viremia, median [IQR]	51	[24–106]	42	[14–98]	0.006
Cardiovascular disease, *n* (%)	56	(21.4)	71	(13.6)	0.005
Neuropsychiatric illness, *n* (%)	17	(6.5)	12	(2.3)	0.003
Diabetes, *n* (%)	14	(5.3)	13	(2.5)	0.038
Chronic kidney disease, *n* (%)	6	(2.3)	4	(0.8)	0.072
Dyslipidemia, *n* (%)	32	(12.2)	30	(5.7)	0.001
Patients with at least one comorbidity, *n* (%)	115	(43.9)	117	(22.3)	<0.001
AIDS diagnosis, *n* (%)	54	(20.6)	86	(16.4)	0.147
HCV Ab positivity, *n* (%)	47	(17.9)	93	(17.7)	0.947
HIV RNA Zenit (copies/mL) Log_{10}, median [IQR]	5.1	[4.7–5.6]	5.1	[4.6–6.0]	0.5094
Nadir CD4 (cells/mL), median [IQR]	230	[110–342]	219	[77–353]	0.6184
Years since HIV diagnosis, median [IQR]	13	[5–22]	10	[4–19]	0.0081
Years of antiretroviral therapy, median [IQR]	9	[4–18]	8	[3–16]	0.0030
History of a previous virologic failure, *n* (%)[a]	104	(39.7)	194	(37.6)	0.569
CD4+ T cells at baseline/μL, median [IQR]	690	[470–944]	679	[466–949]	0.6147
CD4 < 350 cells/mL at baseline, *n* (%)	33	(12.6)	75	(14.3)	0.510
Cumulative Number of antiretroviral regimens before switch, median [IQR]	7	[5–9]	5	[3–7]	<0.001
Pre-switch therapy, *n* (%)					
Mono-therapy	2	(0.8)	5	(0.9)	0.788
Dual-therapy	21	(8.0)	36	(6.9)	0.560
Three drug-regimens NNRTI-based	17	(6.5)	136	(25.6)	<0.001
Three drug-regimens PI-based	12	(4.5)	166	(31.7)	<0.001
Three drug-regimens INSTI-based	206	(78.6)	163	(31.1)	<0.001
Other	4	(1.5)	18	(3.4)	0.126
Switch from a previous INSTI regimen, *n* (%)	209	(79.8)	185	(35.3)	<0.001
Switch from a previous ABC regimen, *n* (%)	4	(1.5)	217	(41.4)	<0.001
M184V/I mutation, *n* (%)					0.020
Yes	12	(4.6)	40	(7.3)	
No	182	(69.5)	277	(52.9)	
Unknown	68	(25.9)	207	(39.5)	
Follow-up					
Discontinuation due to all cause	13	(5.0)	57	(10.9)	0.1970*
Discontinuation due to adverse events (grade 1–2)	7	(2.7)	48	(9.1)	0.0323*
Virologic failure	1	(0.4)	5	(0.9)	0.6276*
Discontinuation for toxicities					
Gastrointestinal, *n* (%)	2	(0.7)	18	(3.4)	0.1160*
Neurological, *n* (%)	2	(0.7)	14	(2.7)	0.2398*
Bone, *n* (%)	0	(0)	1	(0.2)	–
Other, *n* (%)	2	(0.7)	13	(2.5)	0.2873*
Discontinuation for allergic reaction, *n* (%)	1	(0.4)	0	(0)	–
Self discontinuation, *n* (%)	0	(0)	2	(0.4)	–

ART, antiretroviral therapy; MSM, male who has sex with male; IVDU, intravenous drug users; ABC, abacavir; TDF/TAF, tenofovir disoproxil fumarato/tenofovir alafenamide; 3TC, lamivudine; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor.

[a]It was defined as two consecutive HIV-RNA >50 copies/mL or one HIV-RNA >200 copies/mL in previously suppressed patients.

*p value for rate ratios with the Mantel–Haenszel method.

All analyses were performed using Stata/MP v 14.0 software (StataCorp, College Station, TX).

Results

Seven hundred eighty-six PLWH were included in the study: 524 with DTG, 262 with BIC. Their baseline characteristics are shown in Table 1. In particular, 115 (43.9%) PLWH with BIC vs. 117 (23.9%) with DTG had at least one comorbidity ($p < 0.001$). Persons with a history of cardiovascular disease, neuropsychiatric illness, and diabetes were more likely to be switched to BIC rather than ABC-containing DTG regimen ($p = 0.005$, $p = 0.003$, and $p = 0.038$, respectively). No difference was observed in persons with chronic renal disease among the two groups (Table 1). The cumulative number of antiretroviral regimens before the switch was 7 vs. 5 (BIC vs. DTG group, respectively). Switch from a previous INSTI regimen occurred in 209 (79.3%) persons with BIC vs. 185 (35.3%) in persons with DTG, while 4 (1.5%) vs 117 (41.4%)

Table 2 Incidence rates (per 100-py) of virologic failure, discontinuation due to all causes and discontinuation due to treatment adverse events in HIV-1 infected patients, ART experienced with HIV-RNA level <50 copies/mL switching to BIC/TAF/FTC or to DTG/3TC/ABC in five centers in Italy

	Number of events	Person-years (×100)	Incidence rate within 3 months from the switch [95%CI]	RR	[95% CI]	*p*
BIC/TAF/FTC						
• Discontinuation due to all causes	13	0.8120	16.01 9.29–27.57	ref	–	–
• Discontinuation due to treatment adverse events	7	0.8120	8.62 4.10–18.08	ref	–	–
• Discontinuation due to virologic failure	1	0.8120	1.23 0.17–8.74	ref	–	–
DTG/ABC/3TC						
• Discontinuation due to all causes	57	2.4010	23.74 8.31–30.77	1.48	0.81–2.71	0.1970
• Discontinuation due to treatment adverse events	48	2.4010	20.01 15.7–26.5	2.32	1.11–5.16	0.0323
• Discontinuation due to virologic failure	5	2.4010	2.08 0.87–5.00	1.69	0.19–14.56	0.6276

TAF: Tenofovir alafenamide, DTG: dolutegravir, BIC: bictegravir, 3TC: lamivudine, FTC: emtricitabine.

switched from an ABC regimen ($p < 0.001$), respectively. At week 24, we observed 70 EDAC: 5 for VF [1 (0.4%) with BIC and 4 (0.9%) with DTG; $p = 0.6276$], 10 for simplification, more frequently with BIC than DTG [5 (1.9%) and 5 (0.9%); respectively, $p = 0.0720$], and 55 EDAEs, 7 (2.7%) with BIC, 48 (9.2%) with DTG ($p = 0.0323$). EDAEs due to neurological and gastrointestinal toxicity were similar between regimens ($p = 0.2398$ and $p = 0.1160$, respectively**).** In detail, the discontinuation rates due to neurological toxicities were 2.46 per 100 person-year of follow-up (PYFU) [95% CI: 0.61–9.84] and 5.83 per 100 PYFU [95% CI: 3.45–9.84] in DTG and BIC, respectively. No drug-related AEs were grade 3/4. There were no significant differences among regimens in the rates of VF and EDAC (Table 2). The EDAEs rate was significantly higher for DTG than for BIC [20.00×100 PYFU (95% CI: 15.07–26.52) and 8.62×100 PYFU (95% CI: 4.11–18.09), respectively]. The adjusted HR for EDAEs in DTG group compared to BIC was 3.28 (95% CI: 1.34–8.00; $p = 0.009$). In the multivariate analysis, we identified an association between early discontinuation of DTG and the age >60 years and switch from a regimen without ABC (Table 3). No EDAEs occurred in persons with chronic kidney disease.

Discussion

This multicenter cohort study evaluated EDAEs, virologic efficacy, and EDACs within 24 weeks of switching to DTG/ABC/3TC or BIC/TAF/FTC in PLWH who had stable current ART for at least 6 months. Persons receiving DTG or BIC did not show significant differences in the VF or EDACs rates. These data were consistent with previous studies that evaluated the efficacy of INSTI-based regimens as maintenance ART.[10,11,14] However, our results showed that the two regimens' tolerability differed. Indeed, EDAEs were more frequent with DTG. Our results showed a higher percentage of discontinuation in DTG/ABC/3TC group compared to BIC/TAF/FTC, in agreement with another comparative study on naïve individuals between the regimens mentioned above where fatigue/loss of energy, nausea/vomiting and central nervous system (CNS) disturbances were more common in the DTG group.[15]

CNS toxicity with DTG has been more frequently observed in real-life cohort studies concerning RCTs. This is not unexpected, given that the population of trials is highly selected.[16] Indeed, in various cohorts, PLWH taking DTG-based regimens were more prone to discontinue because of neuropsychiatric events than those taking raltegravir (RAL) or elvitegravir (EVG).[15,17–19] To note, there is also the possibility that reports of an association between DTG intake and neuropsychiatric events could have impacted physician prescriptions with a significant distorting effect as recently pointed out by Llibre et al.[20] Indeed, our results showed that PLWH with a history of neuropsychiatric illness were more likely to be switched to BIC rather than DTG regimen. On the other hand, data from clinical cohorts regarding neuropsychiatric events in BIC group are lacking. However, in a double-blind head-to-head study in naïve PLWH, BIC/FTC/TAF

Table 3 Multivariable cox model for discontinuation due to adverse events in HIV-1 infected, ART-experienced patients with HIV-RNA level <50 copies/mL switching to BIC/TAF/FTC or DTG/ABC/3TC in five centers in Italy

Variables	HR	95% CI	p
Group			
BIC/TAF/FTC	–	–	–
DTG/3TC/ABC	3.28*	1.34–7.99	0.009
Gender			
Male	–	–	–
Female	1.24	0.64–2.40	0.135
Transgender	4.80	0.57–40.1	0.147
Age at entry in years			
<40 years	–	–	–
40–60 years	1.89	0.81–4.35	0.136
>60 years	2.85	1.08 – 7.53	0.034
Risk behavior			
Heterosexual	–	–	–
MSM	0.67	0.31–1.44	0.306
IVDU	1.51	0.68–3.32	0.301
Other/unknown	1.12	0.44–2.87	0.798
Previous AIDS event			
No	–	–	–
Yes	1.15	0.56–2.37	0.699
Years of antiretroviral treatment			
>11 years	–	–	–
4–10 years	0.79	0.35–1.77	0.580
<3 years	1.87	0.75–4.62	0.173
CD4 baseline (cell/mm^3)			
>350	–	–	–
<350	0.63	0.27–1.45	0.279
Pre-switch regimen containing abacavir			
No	–	–	–
Yes	0.37	0.18–0.74	0.005
Pre-switch PI boosted regimen			
No	–	–	–
Yes	1.10	0.62–1.96	0.736
Previous cardiovascular disease			
No	–	–	–
Yes	0.46	0.16–1.28	0.138
Previous diabetes			
No	–	–	–
Yes	2.42	0.52–11.2	0.257
Previous dyslipidemia			
No	–	–	–
Yes	0.51	0.11–2.34	0.394
Previous neuropsychiatric illness			
No	–	–	–
Yes	1.19	0.27–5.16	0.814
Number of previous ART regimens	1.01	0.90–1.13	0.771

ART, antiretroviral therapy; IVDU, intravenous drug users; TDF, tenofovir disoproxil fumarate; ABC, Abacavir; BIC, bictegravir; TAF, tenofovir alafenamide; 3TC, lamivudine; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitors; INSTI, integrase strand transfer inhibitor.

showed a similar frequency of neuro-psychiatric adverse events compared to DTG/ABC/3TC/.[15] Moreover, a mild headache was more frequently reported in the BIC arm in a study comparing a switch to BIC/TAF/FTC to remaining on a boosted PI regimen.[10] Our study found that EDAEs due to neurological toxicity were similar between the two regimens analyzed ($p = 0.2398$). This is not surprising as we know that BIC has a structural similarity to DTG.[21] In our cohort, gastroenterological disorders occurred more frequently in the DTG group, although the data is not statistically significant. One possible explanation is that BIC/FTC/TAF would have better gastrointestinal tolerability, with less nausea, than DTG STR, presumably due to the absence of ABC in the combination.[15] Finally, it was found that EDAEs were associated with age larger than 60 years and a previous regimen without ABC ($p < 0.001$). It could be that the co-morbidities and related cumulative toxicity of drugs that people more than 60 years old can often take are an explanation for the reduced tolerability of the new regimen introduced. The tolerability of ABC in the clinical setting is not optimal for both increased adverse events and laboratory abnormalities. Indeed, Brizzi et al.[22] showed, after switching from a previous ART without ABC to DTG/ABC/3TC, that 20% of PLWH reported incidence of adverse effects, most commonly headache (7.4%), nausea (6.3%), rash (3.2%), fatigue (3.2%) and insomnia (2.1%). The major limitations of this study are the short follow-up and its retrospective nature. Although the multivariate analysis considers several potential confounding factors, the residual confounders cannot be ruled out. However, as far as we know, this is the first study comparing BIC/TAF/FTC and DTG/ABC/3TC as a switch strategy in a real-life context. Our results showed that both approaches had the same short term viral efficacy; however, older PLWH may benefit from switching to BIC/TAF/FTC rather than DTG/ABC/3TC, as BIC/TAF/FTC was more tolerated in the elderly in whom the avoiding of ABC may also reduce cardiovascular risk.

Conclusions

In this real-life multicenter cohort, treatment-experienced PLWH who received DTG- or BIC-based STR did not show significant VF or EDAC rates differences. However, EDAEs were more frequent with DTG, especially in the over-60s and in those who came from regimens without abacavir.

Disclosure statement

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