Single tablet regimen with abacavir/lamivudine/dolutegravir compared with two-drug regimen with lamivudine and dolutegravir as different strategies of simplification from a multicenter HIV cohort study

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SUMMARY

We investigated the effectiveness and safety of a dual therapy (DT) with lamivudine plus dolutegravir versus a single tablet regimen (STR) with abacavir/lamivudine/dolutegravir. We performed a retrospective analysis in a cohort of virologically suppressed HIV+ patients switching to lamivudine-dolutegravir or abacavir/lamivudine/dolutegravir. We evaluated the incidence of virological failure and treatment discontinuation, as well as their predictors. Non-parametric tests were applied to assess changes in immunological and metabolic parameters.

In all, 616 patients were analyzed: 380 began STR and 236 DT. In the STR group three patients experienced VF; in the DT group seven patients experienced VF. No differences in cause of treatment discontinuation were found. The estimated probability of continuing therapy at 48 weeks were 88.5 % in DT and 90.3% in STR, without a statistically significant difference (Log-rank 0.338). Regarding the metabolic profile, in the STR group there was a reduction in LDL cholesterol levels at week 48 (p=0.008), whereas in the in the lamivudine group there was a significant reduction in total cholesterol level at week 48 (p=0.044). In regards to renal function, in both groups we registered a reduction in estimated glomerular filtration rate (eGFR), with a median reduction of 8.4 ml/min in the STR group (p<0.001) and 10.2 mL/min in DT (p<0.001). We found a difference in strategy option: in a context of side effect and comorbidities, dual therapy strategy was preferred. Conversely, simplification and compliance improvement more frequently translated into a DTG-STR strategy.

Keywords: ARV, cohort studies, dolutegravir, single tablet regimen, simplification, HIV, dual therapy.

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INTRODUCTION

Recent guidelines on treatment of Human Immunodeficiency Virus (HIV) infection have focused on the opportunity of reducing the number of drugs and/or the number of pills daily given to patients [1, 2]. In particular, single-tablet regimens (STR) are more frequently prescribed to combine the efficacy of a 3-drug regimen and an easier adherence. On the other hand, trials and observational studies demonstrate the efficacy and good tolerability of lamivudine (3TC)-based two-drug regimen, both with boosted protease inhibitors (PIs) and with dolutegravir (DTG); moreover, the latter regimen has shown a favorable effect on metabolic profile [3-7]. At this time, no comparisons between these two choices of antiretroviral therapy (ART) optimization is present in literature; our aim is to compare the effectiveness of a DTG-based STR with a dual therapy (DT) of lamivudine plus DTG.

PATIENTS AND METHODS

We evaluated a cohort of HIV-positive, virologically suppressed (HIV-RNA <50 cps/mL) patients switching to 3TC+DTG (DT group) or abacavir/lamivudine/dolutegravir (STR group) from 8 Italian centers from 2015 to 2018. Patients with positive HBsAg at baseline and pts switching from abacavir (ABC)/3TC + DTG to ABC/3TC/DTG were excluded from analysis. The Kaplan Meier method was used to estimate the time to virologic failure (VF, defined as two consecutive HIV-1 RNA ≥50 cps/mL in a time frame of three months, or a single HIV-1 RNA ≥1,000 cps/mL), and time to treatment discontinuation (TD, defined as the interruption of any of the study drugs or the regimen intensification), and Cox-regression to evaluate predictors of both VF and TD. Censor was established at last available visit, death or loss to follow-up; when considering the time to VF-analysis, censor was also established at the time of TD. Glomerular filtration rate (eGFR) was estimated by the MDRD equation. Changes in immunological and metabolic parameters at 48 weeks and their predictors were assessed by Student's T test and linear regression analysis, respectively. The study was approved by each local Ethics Committee in all clinical centers (protocol number of the coordinating center: 5284/15) and every patient signed informed consent before data collection.

RESULTS

We analyzed 616 patients, 380 in the STR group and 236 in the DT group. Overall median age was 50.65 years (Interquartile range [IQR] 42.04-56.50), 449 (72.9%) patients were males; the median time from HIV diagnosis was 13.1 years (IQR 6.2-20.1), with a median time of ARV exposure of 10.2 years (IQR 4.7-17.2) and a median time of virological suppression of 58 months (IQR 19-101).

Median CD4+ nadir cell count was 195 cell/mm^3 (IQR 68-303), while median CD4+ cell count at baseline was 660 cell/mm^3 (IQR 474-866). One hundred and eight patients (17.5%) experienced at least one virological failure and 14 patients (2.3%) had the M184V/I resistance mutation.

Patients in the STR group switched more frequently for simplification (303 of 380, 79.7%), while those in the DT group mainly switched for simplification (87 of 236, 36.9%), dyslipidemia (73, 30.9%), other toxicities (52, 22.1%). Full patients' characteristics are summarized in Table 1.

During an observation time of 387 person-years of follow-up (PYFU), with a median follow-up time of 13.8 months, we observed 3 VF in the STR group, an overall incidence of 0.8 VF per 100 PYFU. All three failures were due to an HIV-RNA count >1000 cps/mL; however, all 3 patients maintained study regimen and achieved virological suppression subsequently in less than three months.

In the DT group, we registered 7 VF during 358.6 PYFU, with an incidence of 1.9 per 100 PYFU. Two patients who experienced VF with an HIV-RNA count >1000 cps/mL did not change their regimen and were able to re-achieve suppression in a time span of three months. The other 5 patients failed following two consecutive HIV-RNA >50 cps/mL: four of them were intensified to a 3-drug regimen and another was switched to a dual regimen including atazanavir plus DTG; all of them achieved virological suppression in a similar time span.

Time to VF was not statistically different between groups with an estimated probability of maintaining virologic suppression of 99.4% at week 48 in the STR group and a probability of 98.2% in the DT group (log-rank 0.338). Time to VF was only predicted by previous virological failure (*vs* no previous failure, aHR 13.0, 95% Confidence Interval [CI] 2.7-63.0, p=0.001).

As far as discontinuing the study regimens, we found 41 TD during 371.3 PYFU in the STR group. Reasons for these interruptions were represented by neuropsychological events (12 of 380 cases, 3.1%), gastrointestinal toxicity (9 cases, 2.4%), musculoskeletal toxicity (2, 0.5%), hypersensitivity reactions (2, 0.5%), other toxicities (5, 1.3%), concern of cardiovascular risk (4 cases, 1.1%), other reasons (7 cases, 1.8%: 2 simplification to 2-drug regimens, 5 unspecified reasons). The estimated probability of remaining in the STR group was 90.3% at week 48 and 72.8% at week 96. In the DT group, during 369.4 PYFU, 32 TD occurred; in this group, the estimated probabilities of continuing study treatment were 88.5% and 85.4% at weeks 48 and 96, respectively. Reasons for discontinuation were virological failure (4 of 236, 1.7%), neuropsychological events (8 cases, 3.3%), gastrointestinal toxicity (6 cases, 2.5%), further simplification to STR (3 cases, 1.1%), other reasons (11 cases, 4.7%: 3 deaths, 2 hypersensitivity reactions, 1 drug-drug interaction and 5 unspecified reasons). Survival analysis on time to TD showed no significative difference between

Table 1 - Patients' baseline characteristics.

Variables	*Overall n= 616*	*3TC-DTG n= 236*	*ABC/3TC/DTG n=380*	*p*
Females, N (%)	167 (27.1)	61 (25.8)	106 (27.9)	0.641
Age, Years, Median (IQR)	50.6 (42.0-56.5)	51.3 (43.4-56.7)	49.7 (40.5-56.3)	0.035
Risk factor, N (%) MSM Eterosexual IDU Others	 256 (41.6) 234 (38.0) 54 (8.8) 72 (11.7)	 93 (39.4) 86 (36.4) 23 (9.7) 34 (14.4)	 163 (42.9) 148 (38.9) 31 (8.2) 38 (10.0)	0.320
HCV Ab positive, N (%)	75 (12.2)	34 (14.4)	41 (11.4)	0.313
Years from HIV diagnosis, Median (IQR)	13.1 (6.2-20.1)	14.8 (8.4-20.1)	12.1 (4.8-20.1)	0.043
CDC C, N (%)	175 (28.4)	57 (24.2)	118 (31.4)	0.066
Zenith HIV-RNA, log10, cp/ml, Median (IQR)	4.93 (4.33-5.42)	4.98 (4.42-5.42)	4.91 (4.22-5.40)	0.221
Nadir CD4+, Median (IQR)	195 (68-303)	206 (64-294)	189 (69-311)	0.849
Years on ART, Median (IQR)	10.2 (4.7-17.2)	11.5 (5.5-17.2)	9.6 (3.9-17.3)	0.090
Previous virological failure, N (%)	108 (17.5)	91 (38.5)	17 (4.5)	<0.001
Time on virological suppression, Months, Median (IQR)	58.0 (18.7-100.9)	77.2 (35.4-100.3)	43.9 (13.4-101.7)	<0.001
CD4+ at baseline (bl), Median (IQR)	660 (474-866)	657 (500-877)	660 (460-861)	0.586
FTC/TDF before switch, N (%)	197 (32.0)	82 (34.7)	115 (30.3)	0.250
ABC/3TC before switch, N (%)	224 (36.4)	33 (14.0)	191 (50.3)	<0.001
PIs before switch, N (%)	240 (39.0)	127 (53.8)	113 (29.7)	<0.001
DTG before switch, N (%)	150 (24.4)	21 (8.9)	129 (33.9)	<0.001
Dual regimen before switch, N (%)	133 (21.6)	108 (45.8)	25 (6.6)	<0.001
Discontinuation of previous regimen for dyslipidemia, N (%)	89 (14.4)	74 (31.4)	15 (3.9)	<0.001
Discontinuation of previous regimen for other toxicities, N (%)	97 (15.7)	65 (27.5)	32 (8.4)	<0.001
Discontinuation of previous regimen for simplification, N (%)	390 (63.3)	87 (36.9)	303 (79.7)	<0.001
M184V/I mutation at baseline, N (%): Present Absent Not available	 14 (2.3) 557 (90.4) 45 (7.3)	 12 (5.1) 203 (86.0) 21 (8.9)	 2 (0.5) 354 (93.2) 24 (6.3)	0.363

study groups (log-rank p=0.846). No predictors of TD were found in both groups.
In a sub-analysis considering only patients switching to study regimens for toxicity, we found that, in the DT group, the presence of tenofovir disoproxil fumarate (TDF) in previous ART regimen (aHR 0.11, 95%CI 0.02-0.72, p=0.022) and the presence of a PI in the previous regimen (aHR 0.06, 95%CI 0.01-0.99, p=0.05) resulted inversely related to TD; no predictors of TD were found in the STR group. No significative differences were observed between STR and DT groups regarding time to TD (log-rank p=0.628) in this specific sub-analysis.
Regarding immunological recovery, we observed a significant increase in CD4+ cells at week 48 in both the STR and the DT group (+47 cell/mm^3, p=0.017 and +37 cell/mm^3, p=0.010, respectively).
As to the lipid profile, a reduction in the LDL cholesterol levels at week 48 (-2.7 mg/dL, p=0.008) had been predicted by the presence of TDF in previous ART regimen (B 21.3, 95%CI 2.9-39.0. p=0.023) and by the presence of Integrase Inhibitors (INI) in the previous regimen (B 21.7, 95%CI 1.1-42.8, p=0.039) and it had been reversely associated with baseline LDL levels (per 1 mg/dL more, B -0.3, 95%CI -0.4 to -0.2, p<0.001) in the STR group. Meanwhile, there was a significant reduction in total cholesterol level at week 48 (-2.0 mg/dL, p=0.044), predicted by presence of INI in the previous regimen (B 32.8, 95%CI 9.2-56.4, p=0.007) and reversely associated with baseline level of total cholesterol (per 1 mg/dL more, B -0.5, 95%CI -0.7 to -0.3, p<0.001) in the DT group.
In regard to renal function, we registered a significant reduction in the estimated glomerular filtration rate (eGFR) in both groups: median reduction of 8.4 mL/min in the STR group (p<0.001) and 10.2 mL/min in the 3TC group (p<0.001). This difference between the two groups was statistically significant (p=0.006). In the STR group, male sex (*vs* female sex, mean difference in change -7.9 mL/min, 95%CI -13.5 to -2.2, p=0.007) and baseline eGFR (per 1 mL/min more, -0.4 ml/min, 95%CI -0.5 to -0.4) predicted a more pronounced decrease in eGFR. Whereas, switching from a DTG-containing regimen was reversely associated with eGFR deterioration (+7.9 mL/min, 95%CI 2.5-13.4, p=0.005). Baseline MDRD (-0.3, 95%CI -0.4 to -0.2, p<0.001) and switching from a FTC/TDF-based regimen (vs other backbone, -20.2, 95%CI -36.1 to -4.4, p=0.013) had been the 2 factors which predicted a more pronounced reduction of the eGFR at week 48 in the DT group.

DISCUSSION

In our multicenter cohort, both simplification strategies showed similar effectiveness and high tolerability. In the STR group, 3 patients experienced VF but all of them maintained study regimen and rapidly re-achieved viral suppression; also, the 7 patients experiencing VF in the DT group were able to regain viral suppression in less than three months, with 2 of them maintaining study regimen and 1 of them switching to another DTG-based 2-drug regimen. These data are encouraging, particularly for the 2-drug regimen group, and are probably to be due to the high genetic barrier to resistance of dolutegravir [8].
There was no difference in the causes of discontinuation between groups, with an incidence of TD inferior to 12 per 100 PYFU in both of them. Neuropsychological events were rare in our cohort and the rate of discontinuation for neurological toxicity was similar between groups, apparently in contrast with other studies showing a higher risk of CNS toxicity in DTG-based regimens containing abacavir [9].
Although 3 patients in the STR group, discontinued following concerns of cardiovascular disease, it is to be noted that no cardiovascular adverse events occurred during observation period in patients taking abacavir [10]. Moreover, both regimens showed an improvement in blood lipids' levels, a common finding in DTG-based simplification regimens [11].
Lastly, we found a significant decrease of eGFR with both regimens, with a more pronounced decrease in the DT group. However, it is to be noted that no patient in the 3TC group discontinued the regimen for eGFR decline. These findings are consistent with previous works describing the apparent decline in eGFR in patients taking DTG, probably due to the inhibition of the renal protein organic cation transporter 2 [12].
Limitations of our study include the retrospective design and the possibility of study bias due to differences in patients' baseline characteristics between groups.

CONCLUSIONS

In our multicenter cohort, both simplification strategies showed similar effectiveness and high tolerability; in our clinical practice setting, we found a difference in strategy option: indeed, in a contest of side effect and comorbidities, dual therapy strategy was preferred. Conversely, simplification and compliance improvement more frequently translated into a DTG-STR strategy [11].

Competing interests

SR received grants research support, compensation for CME activities or advisory boards form ViiV Healthcare, BMS, MSD, Gilead Sciences and Janssen, outside the submitted work. GS received personal fees for lectures from Gilead, Janssen, MSD, ViiV and travel grants from Gilead, ViiV, MSD. BR reports non-financial support from Janssen, ViiV Healthcare Italy, Abbvie, Gilead, and consulting fees from Merck Sharp and Dohme, outside the submitted work. AB reported grants from Bristol-Myers Squibb and Gilead, non-financial support from Bristol-Myers Squibb, Viiv and Janssen-Cilag. AC has received a personal grant from AB, Gilead and ViiV. SDG was a paid consultant or member of advisory boards for Gilead, ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme and Bristol-Myers Squibb. All other authors have no interests to declare.

Authors' contributions

GB, ACi, Aca, and SDG participated in the conceptualization of the study. SR, GM, GS, AF, AGiacometti, LC, AL, BR, MVC, A Giacomelli and FL collected data. GB and ACi were involved with formal data analysis, methodology, project administration, and supervision. All authors participated in drafting the manuscript and critically reviewed it.

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