Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk

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Objective: To compare the efficacy, safety, and impact on lipid fractions of switching from a ritonavir-boosted protease inhibitor (PI/r) to a dolutegravir (DTG) regimen.

Methods: HIV type 1-infected adults more than 50 years or with a Framingham score more than 10% were eligible if plasma HIV RNA less than 50 copies per ml for at least 24 weeks while on a PI/r regimen. Patients were randomized to switch to DTG or to remain on PI/r. Primary endpoints were: proportion maintaining HIV RNA less than 50 copies per ml and percentage change from baseline of total cholesterol at week 48.

Results: In total, 415 patients (32 sites in six European countries) were randomized: 205 to DTG and 210 to continue PI/r. About 89% were men, 87% more than 50 years, 74% had a Framingham score more than 10%, with a median CD4$^+$ cell count of 617 cells per μl and suppressed viremia for a median of 5 years. At week 48, in the intent-to-treat analysis, treatment success rate was 93.1% in DTG group and 95.2% in PI/r group (difference −2.1%, 95% confidence interval −6.6 to 2.4, noninferiority demonstrated). There were four virological failures with DTG and one with PI/r with no emergent resistance mutations. There was no significant difference in severe adverse events or grade 3 or 4 adverse events or treatment modifying adverse events. Total cholesterol and other lipid fractions (except high-density lipoprotein cholesterol) improved significantly ($P < 0.001$) in the DTG group regardless of PI/r at baseline.

Conclusion: Switching to a DTG regimen in virologically suppressed HIV type 1 patients with high cardiovascular disease risk was noninferior, and significantly improved lipid profiles.

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Introduction

Dolutegravir (DTG) is an integrase strand transfer inhibitor (INSTI) of the HIV type 1 (HIV-1) [1−6]. DTG is a generally well tolerated [7] once daily drug, can be coformulated [8], has a low potential for drug−drug interactions [9], with infrequent emergence of resistance mutations when given as part of a combination regimen [10−13] and a neutral lipid profile [14]. In antiretroviral-naive patients, DTG has demonstrated noninferiority to raltegravir [15,16] and superiority to efavirenz [17] and the ritonavir-boosted protease inhibitors (PI/r) darunavir [18] and atazanavir [19].

Consensus guidelines recommend several treatment switch strategies in HIV-1-infected patients, who have achieved virological suppression with triple-drug treatment, to prevent or aid in the management of comorbidities, address adverse events or drug−drug interactions, to simplify the antiretroviral regimen, or to reduce costs [20−22]. HIV-1 infection may accentuate the risk of cardiovascular disease (CVD) regardless of control of viremia and after adjusting for established cardiovascular risk factors [23−25].

The most common switching strategy by far has been to focus on third agent switch by switching from a PI/r regimen to a new regimen with an unboosted protease inhibitor [26], to a more lipid friendly PI/r [27], a nonnucleoside reverse transcriptase inhibitor [28], and more recently to a INSTI [5,6,29,30]. The main objective of all these studies has been to improve plasma lipid profile and gastrointestinal symptoms in addition to avoiding potential drug−drug interactions and improving convenience for patients.

Raltegravir, the first INSTI to be investigated in switch studies, resulted in significant lipid improvements while maintaining virological suppression in the Switching Protease Inhibitors to Raltegravir (SPIRAL) [5] study but not in the SWITCHMRK 1 and 2 studies [6]. Elvitegravir requires boosting with cobicistat so the issue of drug−drug interactions remains [9,31]. In the STRIIVING study [30], an unselected population of virologically suppressed HIV-1 infected patients were randomized to switch from their current regimen to a single tablet of DTG/abacavir/lamivudine or to continue with the current regimen. Noninferiority criteria were met but the lipid profile did not improve probably because in 77% of the population the background regimen included tenofovir disoproxil fumarate [32] that was replaced by abacavir [30].

We performed a randomized, noninferiority, strategic trial to compare the efficacy, safety, and impact on lipid parameters of switching to DTG to that of remaining on a PI/r regimen in a targeted population with potential high CVD risk (HIV-a infection and age above 50 years and/or a Framingham [33,34] CVD risk score more than 10% at 10 years).

Methods

Study design and patients
NEAT022 was a randomized, open-label, noninferiority trial conducted in 32 clinical sites in six European countries (see supplementary Table 1 in Supplemental Digital Contents, http://links.lww.com/QAD/B180). Patients were recruited between May 2014 and November 2015. Eligible patients were HIV-1-infected adults older than 50 years or older than 18 years with a Framingham CVD risk score 10-year risk score more than 10% [33,34]. They had to be on a stable (>6 months) triple antiretroviral regimen consisting on a PI/r (that could be ritonavir-boosted lopinavir, darunavir, atazanavir, saquinavir, or fosamprenavir) and two nucleoside (tide) reverse transcriptase inhibitors (NtRTIs) and have a plasma HIV RNA less than 50 copies per ml for at least the previous 6 consecutive months. We excluded patients with prior evidence of primary viral resistance [35] to backbone nucleos(t)ides. We also excluded patients with previous episodes of documented virological failures. The full list of inclusion and exclusion criteria are in the supplementary Table 2 in Supplemental Digital Contents, http://links.lww.com/QAD/B180.

Ethics
The trial was conducted in accordance to the Good Clinical Practice and ethical principles of the declaration of Helsinki. The protocol was reviewed and approved by the ethics committees of all participating hospitals. All participants gave their written informed consent before undergoing study procedures. The study was registered on ClinicalTrials.gov NCT02098837 and EudraCT 2013-003704-39.

Randomization and masking
Eligible participants were randomly assigned (1 : 1) to either switch to DTG 50 mg per day and the same two NtRTIs or to continue with the same triple therapy regimen including a PI/r for 48 weeks after which all patients remaining on a PI/r were switched to DTG. We

assigned patients to treatment groups by computer-generated permuted blocks of four and stratified by country. The study design was open label, so participants and investigators were not masked to group allocation but only the trial statistician had access to the entire randomization list during the trial.

Study procedures

Participants attended study centres at screening, baseline, weeks 4 (DTG group only), 12, 24, 36, and 48. All participants remained in the study up to the week 48 visit unless consent was withdrawn. Each visit included general assessment of vital signs, including arterial blood pressure (BP) and adverse events, physical examination, and collection of blood samples for full blood cell counts and serum chemistry, liver, renal function, and immuno-virological measurements. CD4$^+$ cell counts and plasma viral loads were measured at screening, baseline, week 24, and week 48. Fasting (overnight or $>$6 h) serum lipids were measured at all visits. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemilogy Collaboration method [36]. HIV RNA measurements in plasma and, if indicated, testing for antiretroviral resistance by genotype sequencing were done at local laboratories (the local laboratories were required to meet Clinical Laboratory Improvement Amendments regulations or the country's equivalent). Virological failure was defined as two consecutive measurements of plasma viral load above 50 copies per ml separated at least by 2 weeks during the assigned treatment. A viral blip was defined by a plasma viral load more than 50 copies of HIV RNA per ml followed by a second measurement less than 50 copies of HIV RNA per ml. Safety was assessed at all visits by monitoring of all adverse events and serious adverse events (SAEs), vital signs, and laboratory values. Adherence during the trial was monitored by participant questioning at each medical visit regarding missed tablets, at any moment during the trial or the prior week. Patients and investigators were advised not to change administration of lipid-lowering agents during the study period unless strictly necessary. Patients were also advised at each medical visit to give up smoking, to exercise daily to pay attention to their body weight, diet, and alcohol intake, and to control BP using a written predefined healthy life style guidance formulary. AIDS events and deaths, SAEs, adverse events grade 3 or above, adverse events leading to modification of study drugs, all protocol discontinuations, and all protocol-defined episodes of virological failures required confirmation by an independent endpoint review committee, whose members were unaware of individual patient's treatment regimens.

Endpoints

The two coprimary endpoints were: the proportion of patients able to maintain treatment response (HIV RNA $<$50 copies per ml with no discontinuation of the study treatment) up to week 48; the percentage change from baseline in total cholesterol (TC) to week 48.

Nonresponse was defined as any of the following: virological failure, death from any cause, loss to follow-up, consent withdrawal or permanent change or interruption of randomized treatment for any reason.

Main secondary endpoints were: frequency of all clinical and laboratory adverse events up to week 48; change in CD4$^+$ cell count from baseline to week 48; percentage change from baseline to week 48 of other lipid fractions: non–high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides, and TC : HDL cholesterol ratio and changes from baseline to week 48 of Framingham CVD risk score at 10 years.

Statistical analyses

A total of 420 participants (210 per group) was estimated providing at least 90% power to exclude a noninferiority margin of 10% for the difference in proportion of participants reaching the primary endpoint, assuming 90% of participants have treatment success in the continuous PI/r therapy group and a one-sided α of 0.025 (two-sided $\alpha = 0.05$). The study is powered for the first primary endpoint as this is the criterion that requires the larger sample size. However, with 210 patients per group, the study will have more than 99% power to detect a between treatment difference of 12% in the mean percentage change from baseline in TC, with a SD of 13.8%, a type I error of 0.05, and a two-tailed nonparametric test. No multiplicity adjustment is needed for having two coprimary endpoints.

All patients who underwent randomization were included in the intent-to-treat (ITT) population. In the primary, ITT analysis, the proportion of participants who had treatment success was estimated with Kaplan−Meier methods, censoring at week 48 or last follow-up date if missing viral load values at week 48. Treatment success was defined by the absence of virological failure and absence of a permanent discontinuation of study/study drugs (DTG or PI/r). Any discontinuation in the background NtRTIs for any reason with an undetectable viral load was not considered as failure. The difference in percentage of participants in treatment success (DTG − PI/r) was estimated and two-sided 95% confidence interval (CI) of the difference was obtained with bootstrap Standard error (SE) (1000 replicates) as proportions were estimated by time-to-event method. Log-rank test was also used to compare the two survival functions.

In the prespecified sensitivity analysis on the perprotocol population, individuals were ignored if they did not fulfil the eligibility criteria, withdrew consent, lost to follow-up or discontinued study medication for any reasons other than virological failure or adverse event. DTG containing regimens were considered noninferior to PI/r containing regimens if the lower bound of CI was below −10% for both ITT and per protocol analysis.

Subgroups analyses were performed stratified by participating country and by Framingham 10-year CVD risk score (<15%, ≥15%). The mean percentage change from baseline in lipid fractions: TC, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and TC/HDL cholesterol ratio at week 48, the mean change from baseline in $CD4^+$ cell counts, and eGFR to week 48 were analyzed with the ITT population, with the last observation carried forward approach. The nonparametric Mann−Whitney test was used to compare the changes from baseline between the two groups.

Post hoc analyses were also conducted to study the treatment effect by PI/r at screening (darunavir, atazanavir, other PI), Framingham 10-year CVD risk score [33,34] (<15% vs. ≥15%), and Framingham CVD 10-year risk score and age (age ≤50 year and CVD risk >10%, age >50 year and CVD risk>10%, age>50 year and CVD risk ≤10%) for all lipid fractions. Safety analysis was performed with randomized patients who received at least one-time any study treatment. Any adverse events, grade 3 and 4 adverse events, antiretroviral therapy-related adverse events (all grade), treatment-modifying adverse events (all grade), death, SAEs, and finally adverse events occurring in at least 5% of participants were described and compared by group, using Fisher's exact test.

Variables were summarized as proportions for categorical variables (based on the nonmissing sample size), the median and interquartile range for continuous baseline variables, and the mean and SD for continuous variables used as endpoints. All reported P values are two-tailed with a significant level of 0.05. Analyses were performed with International Business Machines SPSS Statistics version 24 (IBM, Armonk, New York, USA) and STATA SE version 13 (ATATA Corp, College Station, Texas, USA).

Results

Between May 2014 and November 2015, 455 patients from 32 sites in six European countries were screened and 415 randomized: 205 to switch to a DTG-based regimen and 210 to continue the PI/r-based regimen (ITT population; Fig. 1 and supplementary table 1 in Supplemental Digital Contents, http://links.lww.com/QAD/B180). At least one dose of study treatment was received by 412 patients: 204 in the DTG group and 208 in the PI/r-treatment group (Fig. 1). Baseline characteristics were balanced between study groups including the duration of previous virological suppression, the distribution of the baseline PI/r with tenofovir disoproxil fumarate or abacavir-based regimens and the percentage of patients receiving lipid-lowering agents (Table 1). A genotypic resistance test without mutations was available in 204 (49%) of the 415 patients.

Efficacy
At week 48, 14 patients in the DTG group and 10 in the PI/r group had experienced treatment failure; corresponding to a treatment success rate of 93.1 and 95.2%, respectively (difference −2.1%, 95% CI −6.6 to 2.4, noninferiority demonstrated); Fig. 2a and Supplementary Figure 1 in Supplemental Digital Contents,
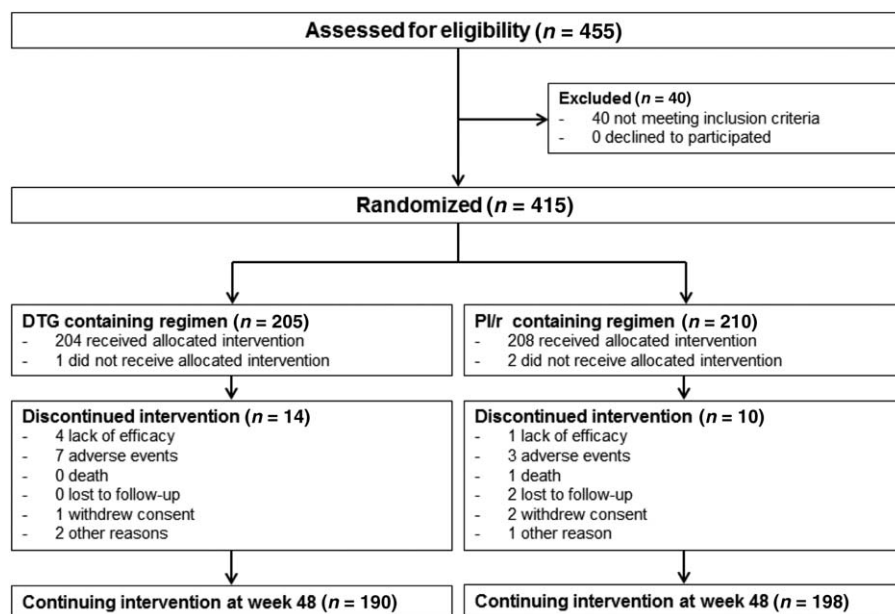

Fig. 1. Trial profile. DTG, dolutegravir; PI/r, ritonavir-boosted protease inhibitors. A genotypic resistance test was available in 19 (47.5%) of the 40 patients assessed for eligibility but not randomized. Presence of resistance mutations was the reason in two (5%) of these 40 patients.

Table 1. Baseline characteristics.

	DTG ($n = 205$)	PI/r ($n = 210$)	Total ($n = 415$)
Age (years)	54 (51–58)	53 (51–57)	54 (51–58)
Age >50 years	179 (87.3)	184 (87.6)	363 (87.5)
Framingham score at 10 years			
<10%	50 (24.4)	59 (28.1)	109 (26.3)
10–15%	62 (30.2)	53 (25.2)	115 (27.7)
15–20%	41 (20.0)	48 (22.9)	89 (21.4)
>20%	52 (25.4)	50 (23.8)	102 (24.6)
Male sex	181 (88.3)	189 (90.0)	370 (89.2)
White race	173 (84.4)	180 (85.7)	353 (85.1)
Mode of HIV-1 transmission			
Male homosexual sexual intercourse	130 (63.4)	131 (62.4)	261 (62.9)
Heterosexual sexual intercourse	43 (23.9)	48 (22.9)	97 (23.4)
Other[a]	26 (12.7)	31 (14.8)	57 (13.7)
CD4$^+$ cell count (cells per μl)	635 (495–819)	585 (471–830)	617 (477–820)
HIV RNA >50 copies per ml	7 (3.4)	1 (0.5)	8 (2)
Hepatitis C IgG antibodies	27 (13.4)	24 (11.6)	51 (12.5)
Time since undetectable viral load (<50 copies per ml); years	4.9 (2.5–9.1)	5.3 (2.3–8.5)	5 (2.4–8.8)
Backbone nucleos (t)ides			
Tenofovir disoproxil fumarate/emtricitabine	134 (65.4)	135 (64.3)	269 (64.8)
Abacavir /lamivudine	63 (30.7)	67 (31.9)	130 (31.3)
Other	8 (3.9)	8 (3.8)	16 (3.9)
PI/r at baseline			
Lopinavir	13 (6.4)	23 (11.0)	36 (8.7)
Darunavir	105 (51.5)	107 (51.0)	212 (51.2)
Atazanavir	77 (37.7)	74 (35.2)	151 (36.5)
Other	9 (4.4)	6 (2.9)	15 (3.7)
Current smokers	78 (38.0)	79 (37.8)	157 (37.9)
Diabetes mellitus	11 (5.5)	13 (6.3)	24 (5.9)
Family history of cardiovascular disease	87 (43.3)	89 (43.4)	176 (43.3)
Receiving lipid-lowering agents	63 (30.7)	60 (28.6)	123 (29.6)
High blood pressure[b]	72 (35.3)	79 (37.6)	151 (36.5)
Daily exercise[c]	64 (31.2)	59 (28.2)	123 (29.7)
Cardiovascular risk factors[d]			
0	54 (26.3)	56 (26.7)	110 (26.5)
1	71 (34.6)	63 (30.0)	134 (32.3)
2	49 (23.9)	60 (28.6)	109 (26.3)
≥3	31 (15.1)	31 (14.8)	47 (11.3)
Fasting plasma lipids (mmol per l)			
Total cholesterol	5.2 (4.5–5.8)	5.1 (4.5–5.6)	5.1 (4.5–5.7)
Triglycerides	1.6 (1.2–2.3)	1.6 (1.2–2.2)	1.6 (1.2–2.2)
Non-HDL cholesterol	3.3 (2.9–4.0)	3.8 (3.1–4.4)	3.8 (3.2–4.5)
LDL-cholesterol	3.1 (2.5–3.7)	3.1 (2.5–3.6)	3.1 (2.5–3.6)
HDL-cholesterol	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)
Total cholesterol/HDL cholesterol ratio	4.2 (3.4–5.4)	4.1 (3.4–5.2)	4.1 (3.4–5.3)
eGFR (ml per min)	90.8 (80.7–99.7)	91.4 (78.3–101.8)	91.1 (80–100.2)

Data are *n* (%) or median (interquartile range). HDL cholesterol levels above 1.5 mmol per l, implicates a subtraction of one risk factor. DTG, dolutegravir; eGFR, estimated glomerular filtration rate; PI/r, ritonavir-boosted protease inhibitors.
[a]Mode of HIV transmission was unknown in 22 (38.6%) of the 57 and 28 (49.1%) of the 57 were intravenous drugs users.
[b]Defined by SBP more than 140 mmHg or DBP more than 110 mmHg or receiving antihypertensive treatment addition.
[c]Defined as self-reported some exercise (duration not specified) every day.
[d]An addition of male patients with age more than 50 years or female patients with age more than 60 years, current or past smoker within the last 3 years, HDL cholesterol less than 1 mmol per l, high blood pressure, diabetes mellitus, family history of cardiovascular diseases.
Adapted with permission [36].

http://links.lww.com/QAD/B180. The perprotocol analysis gave a similar estimated difference of −3.0% (95% CI −6.8 to 0.8); Fig. 2b. Reasons for nonresponse were similar between groups. Approximately 90% of patients in both group reported 100% adherence at all–time points. There were four protocol–defined virological failures in the DTG group (plasma viral load at failures from 58 to 130 HIV RNA copies per ml) and one in the PI/r group (plasma viral load at failure 3373 HIV RNA copies per ml) with no emergent resistance mutations in the two of the five samples that could be amplified (supplementary Figure 2 in Supplemental Digital Contents, http://links.lww.com/QAD/B180). All these five patients but one reported 100% adherence at all–time points. Subgroup analysis for treatment response by country or by age and Framingham CVD risk score at baseline showed similar effect across all subgroups and can be seen in supplementary Figure 3 in Supplemental Digital Contents, http://links.lww.com/QAD/B180. Overall, 21 episodes of viral blips occurred in 19 participants: 12 in 10 participants in the DTG group and nine in nine participants in the PI/r group. (Supplementary Figure 2 in Supplemental Digital Contents, http://links.lww.com/QAD/B180). All these 19 patients but

(a) Intent-to-treat (ITT) analysis
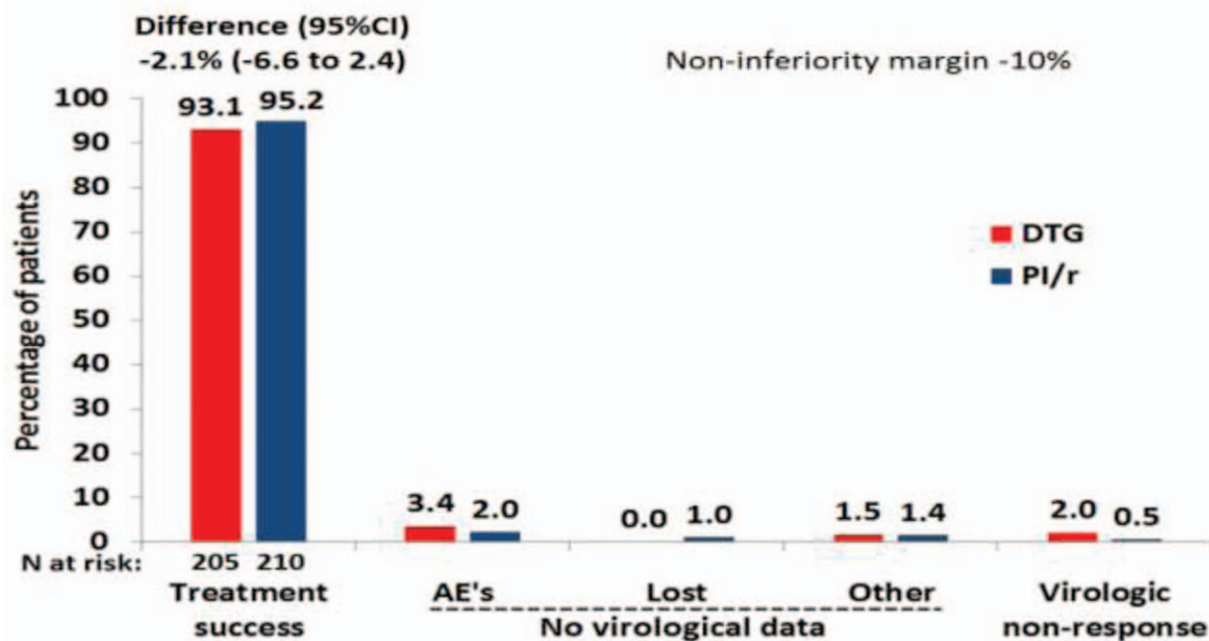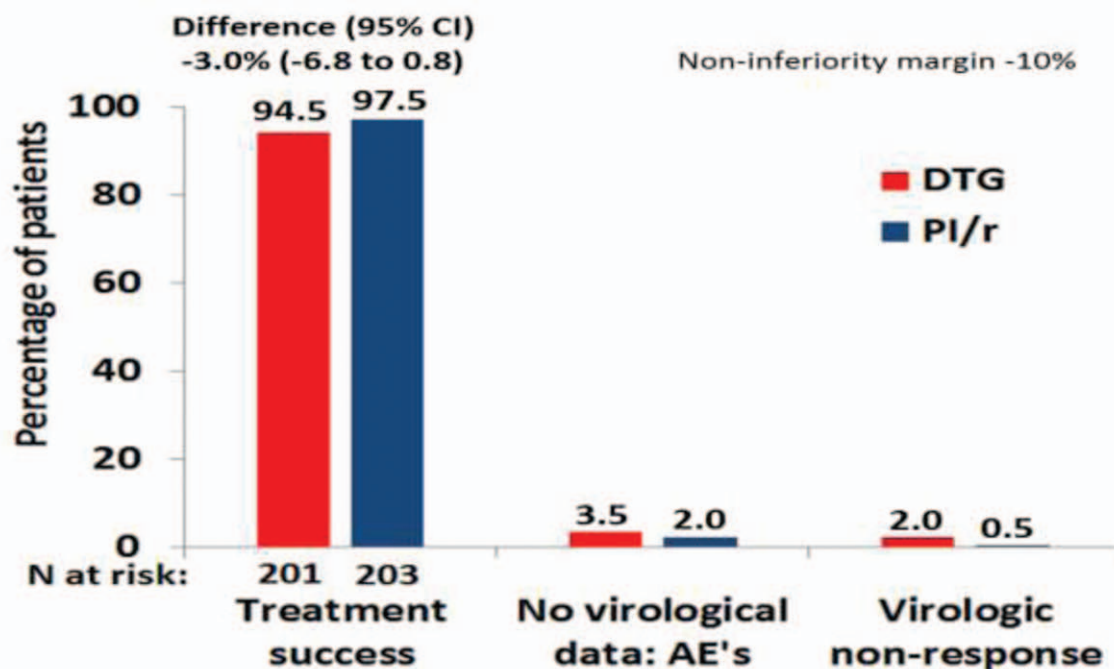

(b) Per-protocol analysis

Fig. 2. Outcomes at 48 weeks of primary efficacy endpoint (Kaplan–Meier estimates). CI, confidence interval; DTG, dolutegravir; PI/r, ritonavir-boosted protease inhibitors. (a) Intent-to-treat analysis. (b) Perprotocol analysis.

three reported 100% adherence at all-time points. Mean increases in $CD4^+$ cell count from baseline to week 48 were 26 ± 151 cells per µl in the DTG group and -1 ± 156 cells per µl in the PI/r group ($P = 0.028$).

Changes in lipids and in other cardiovascular disease risk factors

TC and other proatherogenic lipid fractions significantly ($P < 0.001$) decreased in the DTG group: TC $-8.7 \pm$
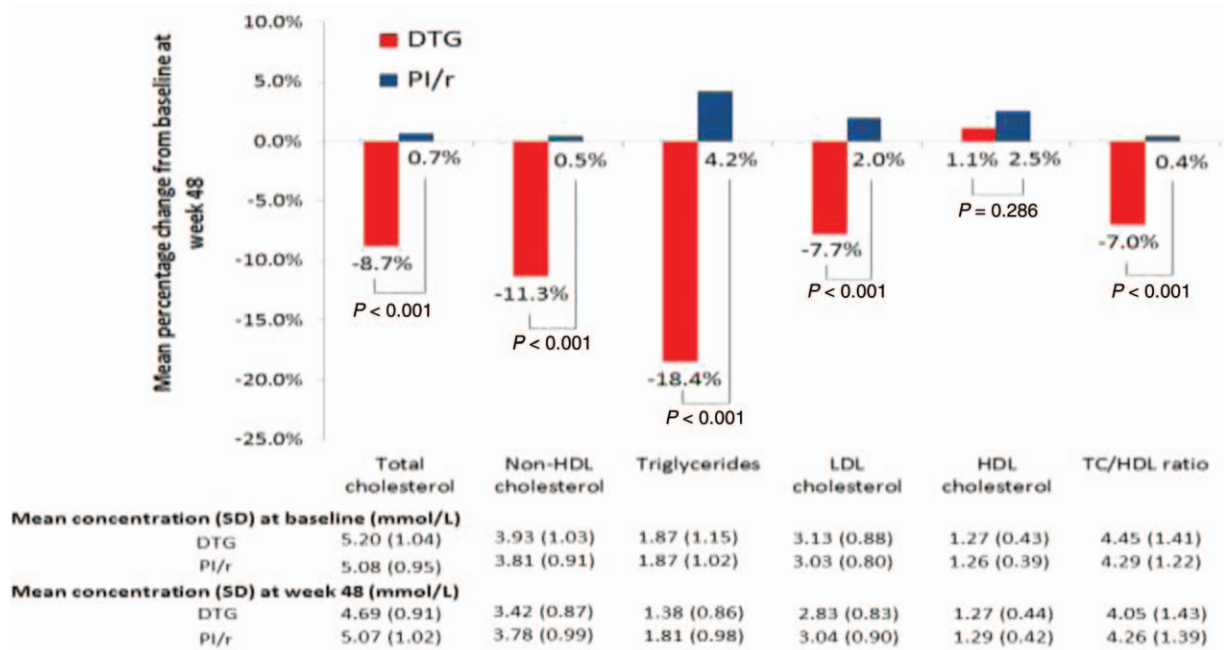
Fig. 3. Changes in fasting lipid concentration from baseline to week 48 (N = 415). DTG, dolutegravir; PI/r, ritonavir-boosted protease inhibitors; TC, total cholesterol.

13.8% vs. 0.7 ± 15.6%, LDL cholesterol −7.7 ± 22.3% vs. 2.0 ± 23.9%, non-HDL cholesterol −11.3 ± 17.4% vs. 0.5 ± 20.9%, TC/HDL cholesterol ratio −7.0 ± 23.7% vs. 0.4 ± 23.1% and triglycerides −18.4 ± 40.7% vs. 4.2 ± 41.4% (Fig. 3). Similar significant improvements were detected in the DTG group when analysis of lipid changes were stratified by baseline age and Framingham CVD risk score, by baseline PI/r, and also by backbone administration of tenofovir or abacavir (supplementary Figures 4a, 4b, 4c, 4d and 4e in Supplemental Digital Contents, http://links.lww.com/QAD/B180). The change from baseline to week 48 in the percentage of patients receiving lipid-lowering agents, receiving or requiring [37] lipid-lowering agents, currently smoking, taking daily exercise, and with high BP was 0, −3.9, −0.9, 6.4, and −4.5%, respectively, in the DTG group and 2.8, 4.3, −1, 5.8, and −2.4%, respectively, in the PI/r group. None of these changes were statistically significant. No statistically significant changes from baseline to week 48 occurred in the Framingham CVD risk score. More than 95% of patients, in both groups, reported having received healthy life style guidance at all clinical visits.

Safety

Adverse events, all grades and causalities, were reported in 153 patients (75%) of 204 in the DTG group and in 132 patients (63.5%) of 208 in the PI/r group (P = 0.01) of whom 12 (5.9%) in the DTG group and 16 (7.7%) in the PI/r group (P = 0.56) were considered SAEs (Table 2). Seven (3.4%) patients in the DTG group (six because of mood disturbances or insomnia) and three (1.4%) in the PI/r group discontinued the study drug because of

adverse events (P = 0.22). The six cases in the DTG group who discontinued because of mood disturbances or insomnia occurred between weeks 0 and 18 after switching to DTG (between September 2014 and February 2016). The most frequent adverse events occurring in at least 5% of patients were digestive, muscular, or skeletal, respiratory, neuropsychiatric, or dermatological and were comparable between groups except genitourinary which were slightly more frequent (P = 0.02) in the DTG group (Table 2). A major cardiovascular event occurred in one patient in the DTG group and in two patients in the PI/r group (Table 2). One death event occurred during the trial in the PI/r group because of an accidental fall with a temporal bone fracture and a subdural hematoma.

Grade 3 or 4 laboratory adverse events were observed in 2.5% of the patients in the DTG group and 13.9% in the PI/r group (P < 0.01; Table 2). There was also a small but significant (P < 0.001) decrease in the calculated eGFR in the DTG group compared with the PI/r group (supplementary Figure 5 in Supplemental Digital Contents, http://links.lww.com/QAD/B180).

Discussion

This is the first study, to specifically examine switching from a regimen containing two NtRTIs and a PI/r to a regimen with the same backbone and DTG in virologically stable patients with high CVD risk (87%

Table 2. Adverse events in 412 patients who received either dolutegravir ($n = 204$) or ritonavir boosted protease inhibitor ($n = 208$).

	DTG ($n = 204$)		PI/r ($n = 208$)		
	Patients n (%)	Adverse events (n)	Patients n (%)	Adverse events (n)	P value
Summary of adverse events					
Any adverse event	153 (75.0)	395	132 (63.5)	352	0.01
Grade 3 or 4 adverse events	12 (5.9)	17	19 (9.1)	32	0.26
Serious adverse events	12 (5.9)	14	16 (7.7)	27	0.56
Discontinuation because of adverse event	7 (3.4)[a]	7	3 (1.4)[b]	3	0.22
Any adverse event related to antiretroviral therapy	26 (12.8)	41[c]	15 (7.2)	21[c]	0.07
Death	0		1 (0.5)[d]		1.00
Adverse events, any grade, occurring in at least 5% of patients in either group					
Digestive	42 (20.6)	52	38 (18.3)	54	0.62
Muscular or skeletal	51 (25.0)	66	39 (18.8)	56	0.15
Cardiovascular	11 (5.4)	13[e]	21 (10.1)	23[e]	0.10
Respiratory	64 (31.4)	94	49 (23.6)	66	0.08
Dermatological	36 (17.6)	43	27 (13.0)	38	0.22
Genitourinary	28 (13.7)	33	14 (6.7)	26	0.02
Systemic	27 (13.2)	28	31 (14.9)	38	0.67
Neuropsychiatric	44 (21.6)	64	36 (17.3)	47	0.32
Grade 3 or 4 laboratory adverse events					
Any grade 3 or 4 laboratory adverse event	5 (2.5)	8	29 (13.9)	46	<0.01
Alanine aminotransferase concentration $>5 \times$ ULN	1 (0.5)	1	1 (0.5)	1	1.00
Bilirubin $>2.5 \times$ ULN	2 (1.0)	4	16 (7.7)	28	<0.01
LDL cholesterol >4.9 mmol per l	0 (0.0)	0	10 (4.8)	13	<0.01

Data are number of patients (%) or number of events. P value: comparison of proportion of patients with at least one adverse event between the two groups. DTG, dolutegravir group; LDL, low-density lipoprotein; PI/r, ritonavir-boosted protease inhibitor; ULN, upper limit of normality.
[a]One case of acute hepatitis C and six cases of mood and/or sleep disorders.
[b]One case of hepatitis C, one case of dyspepsia, and one case of declining renal function.
[c]15/41 and 6/21 were episodes of mood, sleep, or central nervous system disorders.
[d]Accidental fall with a temporal bone fracture and subdural hematoma.
[e]1/13 and 2/23 were a major cardiovascular event.

of the patients were both older than 50 years and with a Framingham risk score >10%). The study demonstrated noninferiority for maintenance of control of HIV RNA in the switch group and maintaining the CD4$^+$ cell response and without an overall significant increase in SAEs or in any grade adverse events related with antiretroviral therapy.

In the DTG group, a reduction of the LDL cholesterol of 7.7% (approximately 0.3 mmol per l) from baseline values was achieved. This level of reduction in the general population is associated with a significant reduction in the relative risk of major cardiovascular events in all baseline strata of cardiovascular risk [38]. As 60% of study participants switched away from PI/r regimens containing ritonavir-boosted lopinavir [39] or darunavir [40] both independently associated in the Data Collection on Adverse Events of Anti-HIV Drugs study with an increased CVD risk there may be an additional favourable impact on estimated CVD risk. CVD is a major cause of morbidity and mortality in persons with HIV-1 infection with an estimated risk of approximately 1.5–2.0-fold higher among HIV-1-infected individuals compared with the general population [41]. Data from the Data Collection on Adverse Events of Anti-HIV Drugs study showed that CVD accounts for approximately 11% of deaths among HIV-1-infected persons [42] and, the EuroSIDA study showed that cardiovascular events account for about

one-third of non–AIDS-defining clinical events in the HIV-1-infected population [43].

Proatherogenic lipid fractions are important risk factors for CVD. The US National Lipid Association [44] suggests that lipid goals be based on the number of risk factors present which include LDL cholesterol and non-HDL cholesterol and that HIV-1 infection status may be counted as a risk factor. The effect of antiretroviral therapy *per se* [39,40,45] or through its effect on lipids should also be considered as contributing to risk of CVD [46]. HIV-1-treatment guidelines recommend evaluating and managing serum lipids according to specific goals; for patients on antiretroviral therapy, in addition to lifestyle changes and lipid-lowering therapy, modifications of antiretroviral regimen can be an important part of overall CVD risk reduction through improvement of proatherogenic lipid fractions [47,48]. Although there are no clinical trial data to demonstrate that interventions to modify plasma lipids reduces CVD risk in the context of HIV-1 disease, there is good evidence from the general population that reducing TC and LDL cholesterol reduces CVD risk [38]. There is an ongoing Aids Clinical Trials Group study in HIV-1 disease to examine the long-term cardiovascular impact of adding pitavastatin [49].

Few studies have compared the effects of switching antiretrovirals or treating dyslipidemia in HIV-1 infected

individuals with statins and most are limited to small, mostly nonrandomized or nonplacebo-controlled trials with a limited follow-up [50−52]. Switching antiretrovirals to improve lipid profiles is a supplemental strategy to the use of lipid-lowering agents and may also have the advantage of reducing the daily pill burden. Switching from PI/r to nonnucleoside reverse transcriptase inhibitor or to INSTI in virologically suppressed patients usually maintains antiviral activity, may improve gastrointestinal symptoms, may offer more convenient dosing, may reduce pill burden, and result in fewer potentially serious drug−drug interactions; however, impact on lipid profile is variable and largely nonsignificant [5,6,27,29,53]. For those with a high CVD risk, the INSTI DTG, may have advantages as a switch choice because of its neutral effect on plasma lipids and our study with patients with high CVD risk showed that virological suppression could be maintained. TC and other proatherogenic lipid fractions significantly ($P < 0.001$) improved in the DTG group even when stratified by baseline age and Framingham risk score and also by baseline PI/r. Most switching studies have not included in the analysis non-HDL cholesterol fractions an important risk factor for CVD that has been recently incorporated into the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [37]. Switching to DTG significantly decreased the TC : HDL cholesterol ratio, a factor used in some CVD risk equations, which is usually unaffected in other antiretroviral switch studies. The study was not powered for differences in cardiovascular events and only three major cardiovascular events were observed. Another limitation of the study can be that most (85%) of the study population were White men all of them coming from developed western European countries.

There are some risks associated with switching to a new regimen in virologically suppressed patients. In our study, protocol defined virological failures were numerically more common in the DTG group (four vs. one in the PI/r group) albeit all at low level and not associated with emergent resistance mutations. Although there were few discontinuations, there were more in the DTG group which is often seen when patients are switching from a regimen that they have been tolerating from a long period of time. Of note, six out of seven discontinued because of mood disturbances or insomnia which have been recently highlighted [54−56] as side-effects of DTG. Moreover, switching from a PI/r regimen to an INSTI regimen may have additional potential benefits in reducing inflammation [5,57,58], immune activation [59], and residual viral replication [60,61].

In conclusion, compared with continuing a PI/r-based regimen switching to a DTG regimen in virologically suppressed HIV-1-infected patients with high CVD risk was noninferior, well tolerated, and significantly improved lipid profiles.

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Conflicts of interest

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G.M. has received honoraria for lectures or advisory boards from Gilead Sciences, MSD, Tobira Therapeutics, and Thera Technologies.

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M.J. has received consultancy fees from Gilead Sciences, ViiV Healthcare, and MSD.

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M.M. has received honoraria for lectures or advisory boards and his institution research grant from ViiV Healthcare, Gilead Sciences, MSD, and Janssen.

M.G. has received educational support to attend CROI from BMS and is undertaking clinical trial work for Merck Sharp & Dohme, Gilead Sciences, and Janssen.

S.D.W. has received honoraria for lecture from Janssen and his institution has received research grants from BMS, Gilead Sciences, Janssen, MSD, and ViiV Healthcare.

E.F. and his institution have received research grants and honoraria for advisory boards participation from BMS, Gilead Sciences, Janssen, MSD, and ViiV Healthcare.

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A.L.P. has received honoraria for lectures or advisory boards, and his institution research grants from ViiV Healthcare, Gilead Sciences, MSD, and Janssen.

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