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*Published in:*
International Journal of STD & AIDS

*DOI:*
10.1177/0956462419848962



*Publication date:*
2019

*Original research article*

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
2019, Vol. 30(11) 1042–1048

DOI: 10.1177/0956462419848962
journals.sagepub.com/home/std
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# Changes in renal, bone, lipid, and inflammation markers in HIV-1 patients after combination antiretroviral therapy simplification to dolutegravir monotherapy

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## Abstract

Combination antiretroviral therapy (cART) can cause metabolic toxicities. How cART simplification to dual or monotherapies affects metabolic markers is unknown. We analyzed the metabolic effects of cART simplification to dolutegravir (DTG) monotherapy in the randomized clinical DOMONO (DOlutegravir MONOtherapy for HIV) trial including HIV-positive participants. Renal function, Framingham risk score (FRS), inflammation, and bone mineral density (BMD) with trabecular bone score (TBS) were measured during 48 weeks after simplification. The changes at 48 weeks by on-treatment analyses overall and for prior tenofovir disoproxil fumarate (TDF) exposure were analyzed separately, using Bonferroni corrected alpha ($p = 0.00096$). Ninety-five patients initiated DTG monotherapy, including 80 discontinuing TDF. At week 48, the switch to DTG monotherapy resulted in an expected −7.8 ml/min estimated glomerular filtration decline. In patients on prior TDF, proteinuria improved ($p < 0.00096$), but proximal tubular dysfunction proportions did not change. Fasting lipids, FRS, and the inflammation markers C-reactive protein and CD4:CD8 T-cell ratio remained stable. Lumbar spine BMD improved (+1.7%, $p < 0.00096$), while hip BMD and TBS remained comparable. Simplification of TDF-containing cART to DTG monotherapy ameliorated lumbar spine BMD and proteinuria with neutral effect on lipids and inflammation markers. Although DTG monotherapy should not be used in routine care and its role in strictly selected patients with primary HIV infection needs to be further elucidated, these observations remain relevant regarding DTG-based dual therapy without TDF. www.clinicaltrials.gov registration number: NCT02401828.

## Keywords

Dolutegravir, tenofovir disoproxil fumarate, renal markers, bone markers, lipids, inflammation markers

Date received: 6 February 2019; accepted: 14 April 2019

## Introduction

Combination antiretroviral therapy (cART) can result in metabolic toxicities. One of the most commonly used drugs in cART is tenofovir disoproxil fumarate (TDF), which is associated with nephrotoxicity and bone mineral density (BMD) loss. TDF-associated nephrotoxicity is associated with an accelerated decline in estimated glomerular filtration rate (eGFR) and proximal

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tubular dysfunction (PTD),[1–3] which may be reversible.[4] TDF's bone toxicity reduces the BMD but its effect on the trabecular bone score (TBS), an additional measure for bone microarchitecture, is unclear.[5–7] However, a lower TBS can increase the osteoporotic fracture risk independently of the BMD, which can aid in optimal fracture prediction.[8] A beneficial effect of TDF is its lipid lowering effect.[9,10] Despite the availability of tenofovir alafenamide fumarate, toxicities of TDF-containing cART remain important, given the generic availability of TDF, the use of TDF as treatment of hepatitis B, and TDF as part of pre- and post-exposure prophylaxis.

In the DOMONO study, cART of HIV-1 infected patients was simplified to dolutegravir (DTG) maintenance monotherapy.[11] DTG has neutral BMD and lipid effects, and inhibits tubular creatinine transport resulting in eGFR alterations without actual changes in renal function.[12] Suboptimal viral suppression results in inflammation and is associated with comorbidities (e.g. cardiovascular diseases [CVDs]).[13,14] Simplification strategies should therefore also evaluate changes in inflammation markers.

In the randomized DOMONO trial, we previously demonstrated that DTG maintenance monotherapy increases the risk of virological failure (VF) and is associated with the development of DTG resistance. It should therefore no longer be studied as a simplification strategy. However, DTG as part of dual therapy in combination with rilpivirine has recently been approved as dual cART and DTG in combination with lamivudine is being evaluated as a simplification strategy. The metabolic consequences of these integrase strand transfer inhibitor-based simplification strategies are as yet unknown. We studied renal, bone, lipids, and inflammation markers after simplifying cART to DTG monotherapy.

## Materials and methods

Participants of DOMONO (NCT02401828) provided written informed consent, and the study was approved by the ethics committee (METC Erasmus MC, MEC2015-043) and done in accordance with the Helsinki Declaration. In DOMONO, well-suppressed HIV-1 patients on cART were randomized to either DTG monotherapy immediately or to start DTG monotherapy after 24 weeks of ongoing cART. The main inclusion and exclusion criteria of the DOMONO study were as follows: HIV-1 infected adults with an HIV-RNA zenith $<$100,000 c/ml and a CD4 T-cell nadir $\geq$200 cells/mm$^3$, with self-reported adherence $>$95%, no history of VF on cART, and no documented genotypic resistance. Detailed information about the selection of patients is given elsewhere.[11]

The study was discontinued prematurely for virological nonefficacy; 8 of 95 patients in the on-treatment analysis developed VF during the use of DTG monotherapy, of whom 3 had emergence of resistance associated mutations in the integrase gene.[11] The analysis of metabolic changes during DTG monotherapy was included as a predefined secondary endpoint. We measured metabolic markers at week 0, 24, and 48 unless VF was observed. First, we assessed renal changes as glomerular and proximal tubular function. eGFR (CKD-EPI) changes on DTG monotherapy were further differentiated based on the previously used third antiretroviral agents each in combination with a nucleoside reverse transcriptase inhibitor backbone: rilpivirine (RPV), efavirenz (EFV), nevirapine (NVP), or another third agent (other). Other evaluated renal markers were urine protein:creatinine ratio (UPCR), urine albumin:creatinine ratio (UACR), urine beta2-microglobulin:creatinine ratio (UB2MGCR), albumin:protein ratio, and fractional excretion of phosphate ($FePO_4$). PTD was diagnosed when $\geq$2 of the following markers were present simultaneously: UPCR $>$ 15 mg/mmol, UB2MGCR $>$0.4 mg/l, UAPR $<$ 0.4 provided UPCR $>$ 15 mg/mmol, hypophosphatemia $<$ 0.8 mmol/l, $FePO_4 > 20\%$, $FePO_4 > 10\%$ in hypophosphatemic patients, and normoglycemic glucosuria. Chronic kidney disease (CKD) was defined as eGFR $<$ 60 ml/min or $\geq$60 ml/min with UACR $>$ 3 mg/mmol.[15] Second, we measured fasting lipids: total cholesterol (TC), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), TC:HDL-cholesterol ratio, and triglycerides, and assessed the ten-year CVD risk by Framingham risk score (FRS) before and after switch.[16] Inflammation was assessed by CD4:CD8 T-cell ratio and C-reactive protein (CRP). In the 80 patients previously on TDF, DEXA scans were used to assess changes in lumbar spine and total hip BMD, T-scores, and lumbar TBS. A T-score$>-1$ and a TBS $>$ 1.350 were considered normal. PTD, BMD, and TBS were assessed.

We used paired T-tests and Wilcoxon Rank Sum tests for normally and nonnormally distributed continuous data, and McNemar tests for categorical data to compare week 0 with week 48. With 54 comparisons, a Bonferroni-corrected alpha of 0.00096 was used to draw conclusions on statistical significance.

## Results

A total of 95 patients switched from cART to DTG monotherapy. Seventy-eight of them had reached the week 48 endpoint, when the study was discontinued prematurely due to suboptimal virological suppression as described elsewhere.[11] Patients were mostly male (92.6%) of mean age 46 years (Table 1). At DTG initiation, the mean (standard deviation, SD) eGFR was

**Table 1.** Baseline characteristics of participants of the DOMONO study before switch to DTG monotherapy.

| | All patients (N = 95) |
|---|---|
| Male gender, N (%) | 88 (92.6) |
| Age (years), mean (SD) | 46 (11) |
| Ethnicity, N (%) | |
| Caucasian | 78 (82.1) |
| African descent | 13 (13.7) |
| Other | 4 (4.2) |
| HIV-RNA zenith, copies/ml, median (Q1, Q3) | 37.000 (13.825, 64.675) |
| CD4 T-cell nadir, cells/mm$^3$, median (Q1, Q3) | 360 (270, 510) |
| Third antiviral agent before switch: | |
| RPV | 44 (46.3) |
| NVP | 16 (16.8) |
| EFV | 16 (16.8) |
| PI/b | 4 (4.2) |
| Comorbidity, N (%) | |
| Hypertension | 16 (16.8) |
| Dyslipidemia | 12 (12.6) |
| Diabetes mellitus | 3 (3.2) |
| History of CKD | 11 (11.6) |
| Smoking, N (%) | |
| Current | 31 (32.6) |
| Previous | 17 (17.9) |
| Never | 46 (48.4) |
| Unknown | 1 (1.1) |
| Framingham risk score | |
| <10%, N (%) | 54 (56.8) |
| 10–19.9%, N (%) | 19 (20) |
| ≥20%, N (%) | 16 (16.8) |
| No data available, N (%) | 6 (6.3) |
| Renal parameters | |
| $eGFR_{CKD\text{-}EPI}$ ml/min, mean (SD) | 91 (17) |
| Phosphate, mmol/l, mean (SD) | 0.94 (0.15) |
| Urine total protein g/l, median (Q1, Q3) | 0.10 (0.06, 0.17) |
| Urine total albumin g/l, median (Q1, Q3) | 0.008 (0.003, 0.023) |
| UPCR mg/mmol, median (Q1, Q3) | 9.09 (6.37, 13.71) |
| UACR mg/mmol, median (Q1, Q3) | 0.69 (0.39, 1.58) |
| UB2MCR mg/mmol, median (Q1, Q3) | 0.029 (0.015, 0.063) |
| $FePO_4$ %, median (Q1, Q3) | 11.7 (7.4, 15.7) |
| <2 markers of PTD, N (%) | 67 (70.5) |
| ≥2 markers of PTD, N (%) | 22 (23.2) |
| No data available on PTD markers, N (%) | 6 (6.3) |
| Lipid parameters, mean (SD) | |
| Total cholesterol, mmol/l | 4.7 (1.1) |
| HDL-C, mmol/l | 1.41 (0.53) |
| LDL-C, mmol/l | 2.99 (0.88) |
| TC/HDL | 3.7 (1.3) |
| Triglycerides, mmol/l | 1.21 (0.66) |
| Inflammation parameters, median (Q1, Q3) | |
| C-reactive protein, mg/l | 1.2 (0.50, 2.60) |
| CD4:CD8 T-cell-ratio | 1.06 (0.74, 1.51) |
| Bone parameters, mean (SD) | |
| *For patients previously on TDF* | |
| BMD spine, g/cm$^2$ | 1.179 (0.162) |
| BMD hip, g/cm$^2$ | 1.013 (0.154) |
| TBS spine | 1.316 (0.119) |
| LS BMD ≥ −1.0, N (%) | 47 (58.8) |
| −1.0 > LS BMD ≥ −2.5, N (%) | 21 (26.3) |
| LS BMD <−2.5, N (%) | 1 (1.3) |
| No data available on LS BMD, N (%) | 11 (13.8) |
| TH BMD ≥ −1.0, N (%) | 48 (60.0) |
| −1.0 > TH BMD ≥ −2.5, N (%) | 19 (23.8) |
| TH BMD < −2.5, N (%) | 1 (13) |
| No data available on TH BMD, N (%) | 12 (15.0) |

BMD: bone mineral density; CKD: chronic kidney disease; DOMONO: DOlutegravir MONOtherapy for HIV; EFV: efavirenz; $eGFR_{CKD\text{-}EPI}$: estimated glomerular filtration rate according to CKD-EPI; $FePO_4$: fractional excretion of phosphate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; LS: lumbar spine; NVP: nevirapine; PI/b: boosted protease inhibitor; PTD: proximal tubular dysfunction; RPV: rilpivirine; SD: standard deviation; TBS: trabecular bone score; TC/HDL: total cholesterol:HDL ratio; TDF: tenofovir disoproxil fumarate; TH: total hip; UACR: urine albumin:creatinine ratio; UB2MCR: urine beta2-microglobulin:creatinine ratio; UPCR: urine protein:creatinine ratio.

91 (17) ml/min. One patient's eGFR was 52 ml/min, 13 patients had eGFR ≥60 but ACR >3. The overall median (IQR) uPCR was 9.09 (IQR 6.37–13.71) mg/mmol. Eighty of the 95 patients included were on TDF-containing cART, and 62 of them reached the week 48 endpoint. Twenty-two patients in total, including 18 on TDF (22.5%) had ≥2 markers of PTD. PTD markers were hypophosphatemia in 13/80 (16.3%), an abnormal $FePO_4$ in 17/80 (21.3%), an UPCR >15 mg/mmol in 14/80 (17.5%) with an UAPR <0.4 in 12/14. One patient had normoglycemic glucosuria. Plasma lipid levels were low with a mean (SD) LDL-C and TC/HDL ratio of 2.99 (0.88) mmol/l and 3.7 (1.3) in all patients. The median FRS was 7.9% (IQR 3.3–13.2). The median CRP was 1.2 mg/ml (IQR 0.5–2.6) and median CD4:CD8 T-cell ratio was >1.0 in the majority (52%). Per protocol, DEXA scans were done exclusively in the patients previously on TDF as part of their cART. A BMD result of the lumbar spine at baseline was available for 69 and a total hip BMD for 68, of them, 21 and 19 had osteopenia at respective sites and one patient had osteoporosis. Seven of the patients with T-scores <−1 also had signs of PTD or CKD. The mean TBS was slightly decreased, with 36 patients scoring <1.350. Predominantly due to premature study discontinuation, lumbar spine and hip BMD as well as PTD markers were unavailable in 25% of the patients.

Forty-eight weeks after the initiation of DTG monotherapy, the eGFR had decreased by mean 7.8 (10.7) ml/min overall, and 7.6 (10.5) ml/min in those on prior TDF. UPCR, UACR, and UB2MGCR improved significantly by week 48 in

TDF patients (Figure 1(a) to (d), Table 2). The proportion of patients with PTD at week 48 did not change compared with baseline. In those on prior TDF, the proportion with an abnormal UPCR decreased from 17.5 to 9.2% (6/65) of which most had an UAPR <0.4 (5/6). Week 48 lipids remained comparable: LDL-C changes in those on prior TDF/FTC with either RPV or NVP were +0.3 mmol/l ($p = 0.01$) and with prior EFV −0.4 mmol/l ($p = 0.02$) (Table 3). Both median FRS and proportions of low, intermediate, and high FRS remained stable after the switch to DTG monotherapy ($p \geq 0.05$). No clinically relevant changes

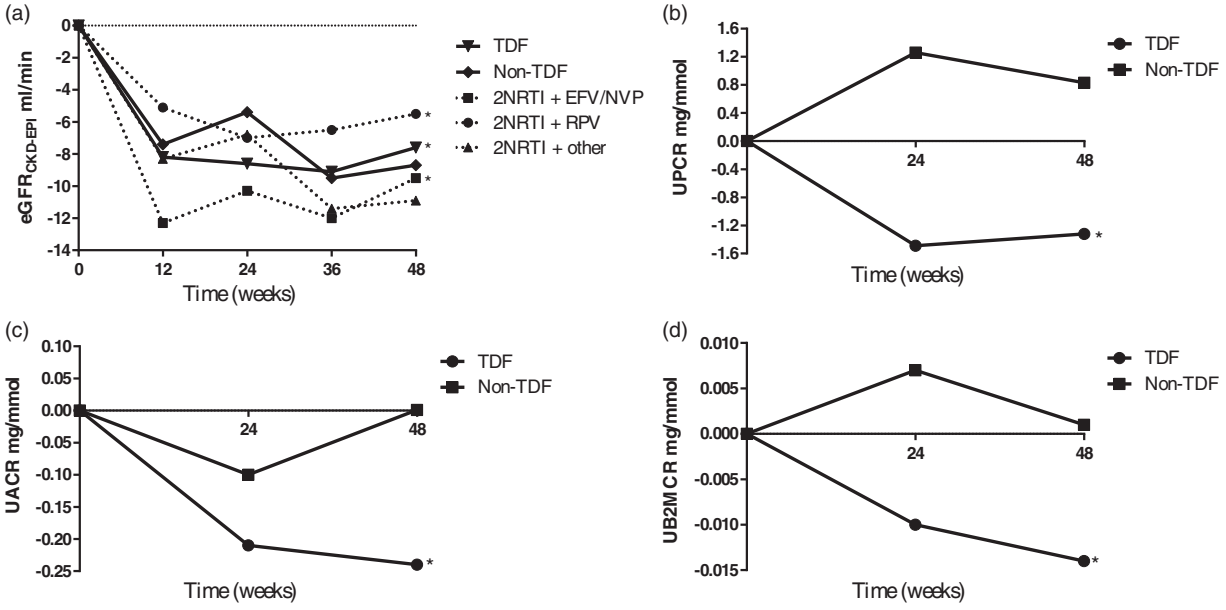


**Figure 1.** (a) Changes in eGFR, (b) UPCR, (c) UACR, (d) UB2MGCR. *=$p < 0.00096$ by paired T-tests (a) and Wilcoxon Rank Sum tests (b) to (d). TDF = the entire subgroup of patients with a TDF-containing cART regimen before switch to DTG; non-TDF = the subgroup of patients with a cART-regimen without TDF before switch to DTG; 2NRTI + EFV/NVP = the entire subgroup of patients with two NRTIs + efavirenz or nevirapine before switch to DTG; 2NRTI + RPV = the entire subgroup of patients with two NRTIs + rilpivirine before switch to DTG; 2NRTI + other = the entire subgroup of patients with two NRTIs and another third agent than RPV, NVP, or EFV.

**Table 2.** Absolute changes in renal parameters from baseline in TDF patients, non-TDF patients, previous EFV/NVP users, and previous RPV users.

| | TDF | TDF + EFV/NVP | TDF/RPV | Non-TDF |
|---|---|---|---|---|
| Absolute change at week 24 | | | | |
| $eGFR_{CKD\text{-}EPI}$ ml/min, mean (SD) | −8.6 (11.3) | −10.0 (11.4) | −6.9 (8.6) | −5.4 (12.9) |
| UPCR mg/mmol, median (Q1, Q3) | −1.49 (−4.80, 0.13) | | | 1.26 (−1.20, 6.85) |
| UACR g/mmol, median (Q1, Q3) | −0.21 (−0.65, 0.03) | | | −0.10 (−1.17, 0.41) |
| UB2MCR mg/mmol, median (Q1, Q3) | −0.010 (−0.044, 0.001) | | | 0.007 (−0.004, 0.014) |
| $FePO_4$ %, median (Q1, Q3) | 0.3 (−2.5, 6.0) | | | 1.1 (−2.9, 4.9) |
| Serum phosphate mmol/l, mean (SD) | 0.05 (0.16) | | | 0.02 (0.20) |
| Absolute change at week 48 | | | | |
| $eGFR_{CKD\text{-}EPI}$ ml/min, mean (SD) | −7.6 (10.5)* | −8.8 (11.2) | −5.3 (6.9)* | −8.7 (12.0) |
| UPCR mg/mmol, median (Q1, Q3) | −1.32 (−5.12, 0.32)* | | | 0.83 (−1.04, 5.40) |
| UACR g/mmol, median (Q1, Q3) | −0.24 (−0.69, −0.02)* | | | 0.01 (−0.17, 0.23) |
| UB2MCR mg/mmol, median (Q1, Q3) | −0.014 (−0.058, 0.001)* | | | 0.001 (−0.001, 0.009) |
| $FePO_4$ %, median (Q1, Q3) | 0.1 (−2.9, 4.8) | | | 5.6 (−1.5, 7.8) |
| Serum phosphate mmol/l, mean (SD) | 0.01 (0.17) | | | 0.08 (0.21) |

EFV: efavirenz; $eGFR_{CKD\text{-}EPI}$: estimated glomerular filtration rate according to CKD-EPI; $FePO_4$: fractional excretion of phosphate; NVP: nevirapine; RPV: rilpivirine; TDF: tenofovir disoproxil fumarate; UACR: urine albumin:creatinine ratio; UB2MGCR: urine beta2-microglobulin:creatinine ratio; UPCR: urine protein:creatinine ratio.

*Indicates statistically significant changes ($p < 0.00096$) by paired T-tests and Wilcoxon Rank Sum tests, analyses only at week 48 data.

were observed in CRP or CD4:CD8 T-cell ratio (Table S1 of supplementary data). Week 48 BMD improved: The lumbar spine BMD increased significantly by +1.7% (SD 3.1, $p < 0.00096$) and the total hip BMD increased with +1.4% (SD 3.2, $p = 0.025$) while TBS did not change (+0.011 (SD 0.08), $p > 0.1$). Lumbar spine BMD improvements of >2.5% and >5% were observed in 24 (42.1%) and 6 (10.5%) patients, and total hip BMD improvements of >2.5% and >5% were observed in 17 (30.4%) and 1 (1.8%). These changes did not alter the proportions of patients with normal BMD, osteopenia, or osteoporosis ($p > 0.3$, Figure 2 and Figure S2 of supplementary data).

## Discussion

The aim of this study was to describe the changes in renal, bone, lipid, and inflammation markers 48 weeks after simplifying cART to DTG maintenance monotherapy. Overall, these markers remained stable. In patients on prior TDF-containing cART, proteinuria and spinal BMD improved significantly. As expected, the eGFR declined as a result of DTG's inhibition of transporters involved in tubular creatinine handling. Given that RPV also inhibits tubular creatinine excretion, the eGFR decline was less substantial in those on prior RPV (Figure 1(a)).[17,18]

The effects of cART simplification in those patients on prior TDF are of particular interest given TDF's specific toxicity profile. The observed improvements in proteinuria are concordant with previous studies. In an aging HIV population, the observed increases in BMD might eventually translate into a decreased fracture risk, especially with larger increases. Despite TDF's previously observed beneficial effect on lipids, no major changes were observed after TDF discontinuation. This might be due to the inclusion of patients with favorable CVD risk profiles, but also due to the simultaneous discontinuation of drugs associated with unfavorable lipid changes like EFV.

Readily available markers for inflammation in patients with HIV are CD4:CD8 T-cell ratio and CRP, which are both associated with mortality.[19] These parameters did not change during simplification to DTG monotherapy. This suggests that clinically relevant alterations in chronic immune activation do not occur after cART simplification as long as the plasma viral load remains <50 copies/ml. This is reassuring regarding potential concerns about increased immune activation in ongoing simplification studies on dual therapy. However, data on more specific markers for inflammation, as well as markers for T-cell activation were not available. Therefore, more detailed insights

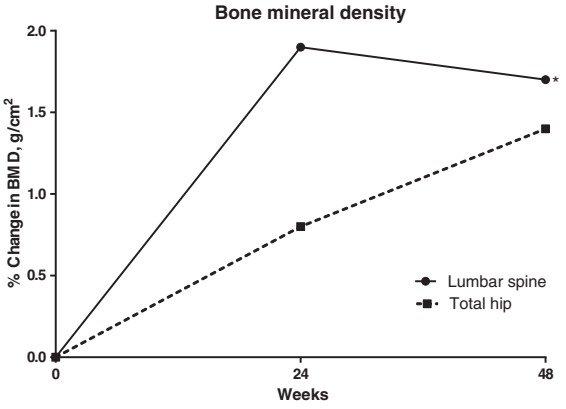


**Figure 2.** Changes in BMD from baseline in patients who were on TDF-containing cART before switch. *indicates a significant change from baseline ($p < 0.00096$) by paired T-tests. BMD: bone mineral density.

**Table 3.** Changes in lipid parameters from baseline in previous TDF-users and non-TDF-users.

| | TDF + NVP/RPV | TDF + EFV | TDF | Non-TDF |
|---|---|---|---|---|
| Absolute change at week 24, mean (SD) | | | | |
| Total cholesterol, mmol/l | 0.2 (0.7) | 0.0 (0.7) | 0.2 (0.7) | −0.7 (1.0) |
| HDL-C, mmol/l | 0.0 (0.4) | 0.1 (0.3) | 0.0 (0.4) | 0.0 (0.2) |
| LDL-C, mmol/l | 0.2 (0.7) | −0.1 (0.6) | 0.2 (0.7) | −0.1 (0.5) |
| TC/HDL | 0.2 (0.9) | −0.2 (0.6) | 0.0 (0.9) | −0.7 (1.2) |
| Triglycerides, mmol/l | 0.1 (0.6) | 0.0 (0.7) | 0.1 (0.6) | −0.3 (0.7) |
| Absolute change at week 48, mean (SD) | | | | |
| Total cholesterol, mmol/l | 0.2 (1.1) | −0.4 (0.6) | 0.1 (1.0) | −0.4 (0.8) |
| HDL-C, mmol/l | 0.0 (0.4) | 0.0 (0.3) | 0.0 (0.4) | 0.1 (0.6) |
| LDL-C, mmol/l | 0.3 (0.7) | −0.4 (0.5) | 0.1 (0.7) | −0.2 (0.6) |
| TC/HDL | 0.2 (1.0) | 0.1 (2.1) | 0.1 (1.2) | −0.6 (1.0) |
| Triglycerides, mmol/l | 0.2 (0.6) | −0.2 (0.5) | 0.1 (0.6) | −0.4 (0.9) |

EFV: efavirenz; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NVP: nevirapine; RPV: rilpivirine; TC/HDL: total cholesterol:HDL ratio; TDF: tenofovir disoproxil fumarate.
No changes were statistically significant ($p < 0.00096$) by paired T-tests.

into immunological consequences of cART simplification should still be further elucidated.

Our study has limitations. The study's sample size was calculated for the primary virological efficacy endpoint. Also, as the study was halted prematurely, the week 48 sample size was smaller than anticipated. Therefore, absence of evidence of a significant change in some of these secondary endpoints may be the result of lack of statistical power (e.g. the nonsignificant increase in hip BMD) and should therefore be interpreted with this in mind. Also, the five patients with VF before week 48 who restarted cART were not included in the analysis and therefore our conclusions only apply to patients with a suppressed plasma viral load. Finally, given our study population of middle-aged male patients, extrapolation to other groups including elderly or female patients should be done with caution.

The DOMONO study clearly demonstrated that DTG monotherapy as simplification strategy is inferior to cART and should not be used as maintenance therapy, which is confirmed by the randomized clinical noninferiority MONCAY trial.[20] However, our results remain relevant in light of the ongoing simplification studies investigating DTG dual therapies. Interestingly, simplification of cART to DTG maintenance monotherapy had promising results in one trial involving patients who were diagnosed during primary HIV infection. Future simplification strategies to dual or monotherapies therefore remain of interest in order to avoid side effects of long-term TDF-containing cART, provided that efficacy is ensured.[21] Indeed, given the neutral effect of lamivudine on BMD and lipids, the improvement in proteinuria and BMD we observed can be expected to be similar in patients switching to DTG with lamivudine dual therapy.

## Authors' contribution

BJAR and CR designed the study and wrote the protocol. IEAW, CR, and BJAR contributed to literature search and conduct of the study. IEAW, CR, BJAR, SS, and MCZ collected, analyzed and interpreted data, wrote and reviewed the manuscript. IEAW, CR, and BJAR developed the figures and tables, TEMSV-S, CAMS, HIB, MEE, ECMG, JLN, and AV included patients and reviewed the manuscript. WFWB included patients, collected and interpreted data, and reviewed the manuscript.

## Acknowledgments

The data presented in this study have been presented earlier in the Conference on Retroviruses and Opportunistic Infections, 2018, Boston, MA, USA, abstract 725.

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Erasmus University Rotterdam Trustfund (grant number 97030.34/15). The institute of WB received reimbursement of expenses for investigator initiated study from Janssen Pharmaceuticals and compensation of expenses for participating in multicenter trial from GSK. BJAR received a grant from the EUR Trustfund during the study (Grant number 97030.34/15). CR and IEAW report personal fees from Gilead and Viiv outside the submitted work.

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