Changes in renal, bone, lipid, and inflammation markers in HIV-1 patients after cART simplification to dolutegravir monotherapy.

I.E.A. Wijting, C. Rokx, M.C. Zillikens, A.A.A. Smits, T.E.M.S. de Vries-Sluijs, C.A.M. Schurink, H.I. Bax, M.E. van der Ende, E.C.M. van Gorp, J.L. Nouwen, A. Verbon, W.F.W. Bierman, B.J.A. Rijnders.

Submitted.

ABSTRACT

Introduction

Combination antiretroviral therapy (cART) can result in metabolic deregulations. Antiretroviral therapy simplification strategies might overcome triple cART toxicities. We evaluated renal, bone, lipids, and inflammation markers after simplifying cART to dolutegravir (DTG) monotherapy.

Methods

Randomized clinical trial including HIV patients switching cART to DTG monotherapy (DOMONO, NCT02401828). Markers were measured at week 0, 24, and 48 of DTG monotherapy: (1) estimated glomerular filtration rate (eGFR), proteinuria and renal tubular function, (2) fasting lipids and Framingham risk score (FRS), (3) C-reactive protein and CD4:8 T-lymphocyte-ratio. In patients discontinuing TDF, Bone Mineral Density (BMD) and Trabecular Bone Score (TBS) were measured as well. Endpoints were changes at week 48 by on-treatment analyses overall and for prior TDF exposure separately. A Bonferroni corrected alfa was set at 0.00096.

Results

95 patients initiated DTG monotherapy, including 80 on prior TDF. As expected, the switch to DTG monotherapy resulted in an eGFR-decline of -7.8 ml/min ($p<0.00096$). In those on prior TDF, proteinuria improved ($p<0.00096$), but the proportion of patients with proximal tubular dysfunction did not change. Lipids, FRS, and inflammation markers remained stable. In patients discontinuing TDF, lumbar spine BMD improved (+1.7%, $p<0.00096$), while hip BMD and TBS did not change significantly (+1.4%, $p=0.025$ and +0.011, $p=0.28$).

Conclusions

In well-suppressed HIV patients on TDF-containing cART, simplifying to DTG monotherapy ameliorated lumbar BMD and proteinuria and had neutral effect on lipids and inflammation markers. Although DTG monotherapy should no longer be studied as a simplification strategy, these observations remain relevant regarding the ongoing DTG dual therapy studies.

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 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] TDF also has lipid modulating effects.[9,10]

In the DOMONO study, the cART regimen of HIV-1 infected patients was simplified to dolutegravir (DTG) maintenance monotherapy.[11] DTG has neutral BMD and lipids effects, and it 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 (CVD)).[13,14] Simplification strategies should therefore also evaluate changes in inflammation markers.

In the randomized DOMONO study we previously demonstrated that DTG maintenance monotherapy increases the risk of of virological failure 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.

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. Inclusion and exclusion criteria of the DOMONO study resulted in a study population of very compliant patients in which virological failure had never occurred in the past. Detailed information about the selection of patients is given elsewhere.[11]

The study was discontinued prematurely for virological non-efficacy, which is reported elsewhere.[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 virological failure (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 (NRTI) backbone: rilpivirine (RPV), efavirenz (EFV), nevirapine (NVP), or another third agent (other). Other renal evaluated markers were: urine protein:creatinine-ratio (UPCR), albumin:creatinine-ratio (UACR), beta2-microglobuline:creatinine-ratio (UB2MGCR), albumin:protein-ratio (APR), and fractional excretion of phosphate (FePO4). Proximal tubular dysfunction (PTD) was diagnosed when ≥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, FePO4 > 20%, FePO4 > 10% in hypophosphatemic patients, and normoglycemic glucosuria. Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min or ≥ 60 mL/min with UACR > 3 mg/mmol.[15] Second, we measured fasting lipids: total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) cholesterol, TC:HDL-cholesterol-ratio (TC/HDLR) and triglycerides (TG), and we assessed the 10-year CVD risk by Framingham Risk Scores (FRS) before and after switch. (16) Inflammation was assessed by CD4:CD8 T-lymphocyte ratio and C-reactive protein (CRP). In the 80 patients on TDF only, 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 non-normally distributed continuous data, and McNemar tests for categorical data to compare week 0 with week 48. With 54 comparisons, a Bonferroni-corrected alfa of 0.00096 was used to draw conclusions on statistical significance.

RESULTS

A total of 95 patients switched from cART to DTG monotherapy. A total 78 of them had reached the week 48 endpoint, when the study was discontinued prematurely due to suboptimal virological suppression as described elsewhere.[11] The baseline characteristics are shown in Table 1.

	All patients (N=95)
Male sex, N (%)	88 (92.6)
Age, 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-lymphocyte 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$_{CKD-EPI}$ 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)
FePO4 %, 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)
CD4:8 T-cell-ratio	1.06 (0.74,1.51)
Bone parameters, mean (SD)	
***For patients on TDF only**	
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)

Table 1. Baseline characteristics of participants of the DOMONO study before switch to DTG monotherapy. TDF=Tenofovir Disoproxil Fumarate, SD=Standard Deviation, RPV=rilpivirine, NVP=nevirapine, EFV=efavirenz, PI/b=boosted Protease Inhibitor, CKD=Chronic Kidney Disease, eGFRCKD-EPI=estimated Glomerular Filtration Rate, UPCR=Urine Protein:Creatinine-Ratio, UACR=Urine Albumin:Creatinine-Ratio, UB2MCR=Urine Beta2Microglobuline:Creatinine-Ratio, FePO4=Fractional Excretion of Phosphate, PTD=Proximal Tubular Dysfunction, HDL-C=High Density Lipoprotein Cholesterol, LDL-C=Low Density Lipoprotein-Cholesterol, TC/HDL=Total Cholesterol:HDL ratio, BMD=Bone Mineral Density, TBS=trabecular bone score, LS=lumbar spine, TH=total hip.

Patients were mostly male (92.6%) of mean age 46 years. At DTG initiation, the mean (standard deviation, SD) eGFR was 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. 80 of the 95 patients included were on TDF-containing cART, and 62 of them reached the week 48 endpoint. 22 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 in 17/80 (21.3%), an UPCR >15mg/mmol in 14/80 (17.5%) with an APR <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 1.2mg/mL (IQR 0.5-2.6) and median CD4:8 T-cell ratio was >1.0 in the majority (52%). Per protocol, DEXA scans were exclusively done

in the patients on TDF. 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 and hip BMD as well as PTD markers were unavailable in 25% of the patients.

48 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 (Table 2, Figure 1A-D).

	TDF	TDF+EFV/ NVP	TDF+ RPV	Non-TDF
Change at week 24,				
$eGFR_{CKD-EPI}$ 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)
FePO4 %, 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)
Change at week 48,				
$eGFR_{CKD-EPI}$ 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)
FePO4 %, 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)

Table 2. Changes in renal parameters from baseline in TDF patients, non-TDF patients, previous EFV/NVP users, and previous RPV users. *indicates statistically significant changes (p<0.00096) by paired T-tests and Wilcoxon Rank Sum tests, analyses only at week 48 data. TDF=tenofovir disoproxil fumarate, EFV=efavirenz, NVP=nevirapine, RPV=rilpivirine, eGFR CKD-EPI=estimated glomerular filtration rate according to CKD-EPI, UPCR=urine protein:creatinine-ratio, UACR=urine albumin:creatinine-ratio, UB2MGCR=urine beta2-microglobuline:creatinine-ratio, FePO4=fractional excretion of phosphate.

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 APR <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 -0.4mmol/L (p=0.02) (Table 3).

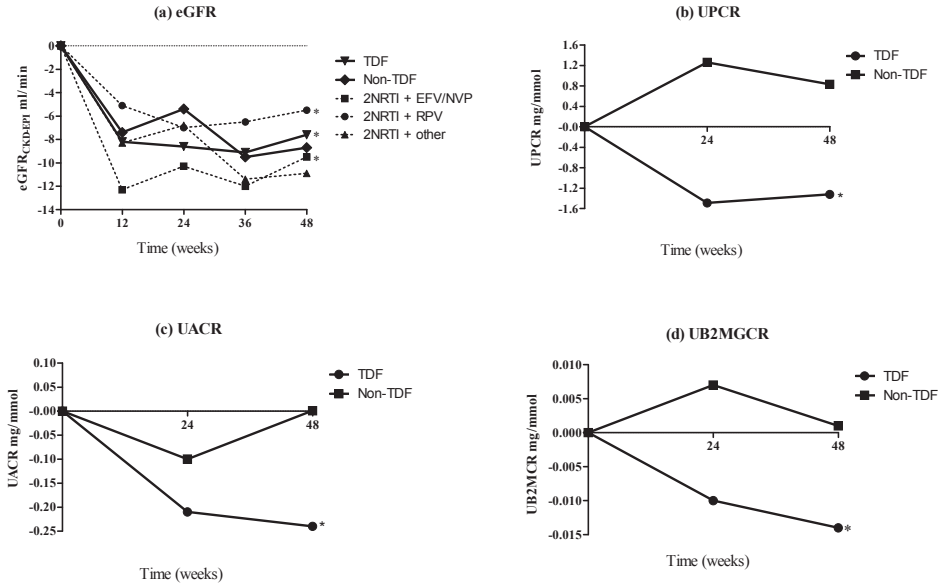

Figure 1A-D. Changes in eGFR (a), urine protein:creatinine-ratio (UPCR) (b), urine albumin:creatinine-ratio (UACR) (c), and urine beta2-microglobuline:creatinine-ratio (UB2MGCR) (d). *=p<0.00096 by paired T-tests (a) and Wilcoxon Rank Sum tests (b-d). 'TDF'=the entire subgroup of patients with a TDF-containing 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 2 NRTIs + efavirenz or nevirapine before switch to DTG. '2NRTI + RPV'=the entire subgroup of patients with 2 NRTIs + rilpivirine before switch to DTG. '2NRTI + other'=the entire subgroup of patients with 2 NRTIs and another 3rd agent than RPV, NVP, or EFV.

	TDF + NVP/RPV	TDF+EFV	TDF	Non-TDF
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)
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)

Table 3. Changes in lipid parameters from baseline in previous TDF-users, non-TDF-users. No changes were statistically significant (p<0.00096) by paired T-tests. TDF=tenofovir disoproxil fumarate, NVP=nevirapine, RPV=rilpivirine, EFV=efavirenz, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TC/HDL=total cholesterol:HDL-ratio.

Both median FRS and proportions low, intermediate, and high FRS remained stable after the switch to DTG monotherapy (p≥0.05). No clinically relevant changes were observed in CRP or CD4:CD8 T-lymphocyte ratio (Table 4).

	All patients	TDF	Non-TDF
Change at week 24, median (Q1,Q3)			
C-reactive protein, mg/L	0.0 (-0.50,0.30)	0.0 (-0.4,0.5)	-0.3 (-1.0,0.0)
CD4:8 T cell-ratio	0.0 (-0.1,0.1)	0.0 (-0.1,0.1)	0.0 (-0.1,0.1)
Change at week 48, median (Q1,Q3)			
C-reactive protein, mg/L	0.00 (-0.60,0.70)	0.0 (-0.6,0.7)	-0.1 (-1.2,0.3)
CD4:8 T cell-ratio	0.00 (-0.11,0.11)	0.0 (-0.1,0.1)	-0.1 (-0.1,0.1)

Table 4. Changes in inflammation parameters from baseline in all patients, in previous TDF-users, and in previous non-TDF-users. No changes were statistically significant (p<0.00096) by Wilcoxon Rank Sum tests. TDF=tenofovir disoproxil fumarate.

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 3).

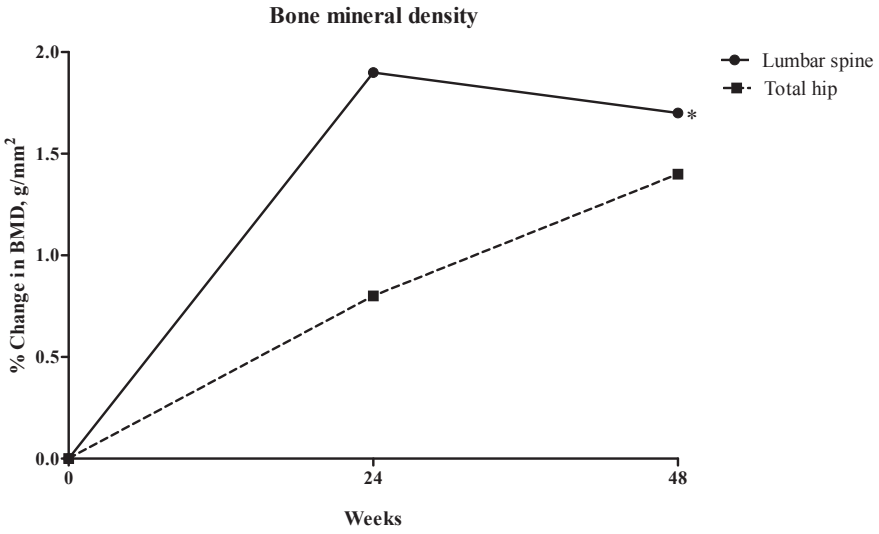

Figure 2. Percentual changes in bone mineral density from baseline in patients who were on tenofovir disoproxil fumarate-containing cART before switch. *indicates a significant change from baseline (p<0.00096) by paired T-tests. BMD=bone mineral density.

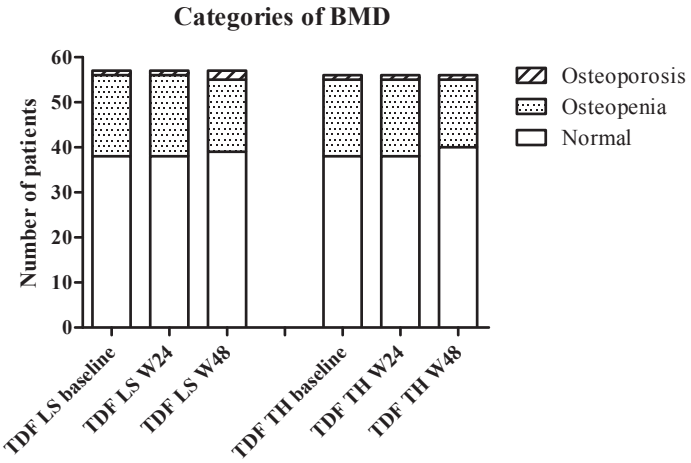

Figure 3. Changes in categories of lumbar spine (LS) and total hip (TH) bone mineral density (BMD) from baseline in previous TDF-users. No changes were statistically significant ($p<0.00096$) by McNemar tests. TDF=tenofovir disoproxil fumarate.

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 1A).[17,18]

The effects of simplification of cART 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 when a change of >2.5% is observed. 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-lymphocyte 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.

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 non-significant increase in hip BMD) and should therefore be interpreted with this in mind. Also, the 5 patients with virological failure 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. However, our results remain relevant in light of the ongoing simplification studies investigating DTG duo therapies. 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 lamivudine dual therapy.

REFERENCES

1. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis.* 2011;**57**:773-780.
2. Kinai E, Hanabusa H. Progressive renal tubular dysfunction associated with long-term use of tenofovir DF. *AIDS Res Hum Retroviruses* 2009;**25**:387-394.
3. Rokx C, Alshangi H, Verbon A, Zietse R, Hoorn EJ, Rijnders BJ. Renal toxicity of Concomitant Exposure to Tenofovir and Inhibitors of Tenofovir's Renal Efflux Transporters in Patients Infected With HIV Type 1. *J Infect Dis* 2016;**213**:561-568.
4. Jose S, Hamzah L, Campbell LJ *et al*. Inclompete reversibility of estimated glomerular filtration rate decline following tenofovir disoproxil fumarate exposure. *J Infect Dis.* 2014;**210**:363-373.
5. Grant PM, Kitch D, McComsey GA *et al*. Long-term Bone Mineral Density Changes in Antiretroviral-Treated HIV-Infected Individuals. *J Infect Dis* 2016;**214**:607-611.
6. Güerri-Fernández R, Molina-Morant D, Villar-García J *et al*. Bone density, microarchitecture and tissue quality after long-term treatment with tenofovir/emtricitabine or abacavir/lamivudine. *J Acquir Immune Defic Syndr.* 2017; DOI: 10.1097/QAI.0000000000001396.
7. Calmy A, Chevalley T, Delhumeau C *et al*. Long-term HIV infection and antiretroviral therapy are associated with bone microstructure alterations in premenopausal women. *Osteoporos Int,* 2013;**24**:1843-1852.
8. McCloskey EV, Odén A, Harvey NC *et al*. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its relationship to FRAX. *J Bone Miner Res*, 2016; **31**:940-948.
9. Santos JR, Saumoy M, Curran A *et al*. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. *Clin Infect Dis,* 2015;**61**:403-408.
10. Arribas JR, Thompson M, Sax PE *et al*. Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. *J Acquir Immune Defic Syndr,* 2017;**75**:211-218.
11. Wijting IEA, Rokx C, Boucher CAB *et al*. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised, non-inferiority trial. *Lancet HIV,* 2017;**4**:e547-554
12. Cottrell ML, Hadzic T, Kashuba AD. Clinical pharmacokinetic, pharmacodynamics and drug-interaction profile of the integrase inhibitor dolutegravir. *Clin Pharmacokinet,* 2013;**52**: 981-994.
13. Nordell AD, McKenna M, Borges AH *et al*. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. *J Am Heart Assoc* 2014;**3**:e000844.
14. Borges AH, O'Connor JL, Philips AN *et al*. Factors associated with plasma IL-6 levels during HIV infection. *J Infect Dis* 2016;**212**:585–595.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl,* 2013;**3**:1–150.
16. Copenhagen HIV Programme (CHIP). Framingham Risk Score Tools. Available at https://www.chip.dk/Tools-Standards/Clinical-risk-scores.
17. Zaharatos GJ, Wainberg MA. Update on rilpivirine: a new potent non-nucleoside reverse transcriptase (NNRTI) of HIV replication. *Ann Med,* 2013;**45**: 236-241.
18. Rasch MG, Engsig FN, Feldt-Rasmussen B *et al*. Renal function and incidence of chronic kidney disease in HIV patients: a Danish cohort study. *Scand J Infect* Dis 2012;**44**:689–696.
19. Serrano-Villar S, Sainz T, Lee SA *et al*. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and

increased risk of non-AIDS morbidity and mortality. *PLoS Pathog,* 2014;**10**:DOI 10.1371/journal.ppat.1004078.