Bone, Renal, and Inflammation Markers in the Dolutegravir Monotherapy (DOMONO) Study.

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Introduction

Tenofovir disoproxil fumarate (TDF) is associated with nephrotoxicity, bone mineral density (BMD) decline, and it decreases LDL.

TDF-associated nephrotoxicity can lead to an estimated Glomerular Filtration Rate (eGFR) decline and/or proximal tubular dysfunction (PTD).

Besides BMD, the trabecular bone score (TBS) is a relatively new measure of bone strength that also includes information about bone-microarchitechture. Both BMD and TBS are useful in predicting fracture risk.

In the DOMONO-study (NCT02401828), patients on cART switched to dolutegravir (DTG) monotherapy, 85 of whom switched from a TDF containing cART regimen.

Several secondary endpoints were predefined, of which those related to metabolism and inflammation are described here:
1. To evaluate the metabolic effects of a switch from TDF containing cART to DTG monotherapy.
2. To evaluate the impact of a switch from cART to DTG monotherapy on inflammation markers.

Aim

To describe the effects on lipids, renal, bone, and inflammation markers of switching from TDF-containing cART to DTG maintenance monotherapy.

Methods

DOMONO was a randomized, clinical, non-inferiority trial, switching patients from cART to DTG maintenance monotherapy.[1] The primary endpoint (not discussed here) was virological suppression at week 24 during DTG maintenance monotherapy.

Renal markers evaluated were: $eGFR_{CKD\text{-}EPI,}$ urine protein:creatinine ratio (UPCR), urine albumin:creatinine ratio (UACR) and beta2-microglobuline:creatinine ratio (B2MGCR).

Bone markers were: lumbar and hip BMD, proportions of normal BMD/osteopenia/osteoporosis, and lumbar TBS, and these were only measured in patients that had been on a TDF-containg cART regimen.

Inflammation markers evaluated were: CD4:CD8 ratio and C-reactive protein (CRP).

A Bonferroni-corrected significance level was defined as p<0.0017. Paired T-tests, Wilcoxon Rank Sum tests, and McNemar tests were used when appropriate.

Results

95 patients started DTG maintenance monotherapy. 78 had reached the week 48 endpoint, when the study was discontinued prematurely as 8 patients had been observed with virological failure (VF) and 3 of them developed integrase inibitor resistance associated mutations. 85 patients had been on a TDF-containing cART regimen.[2]

No significant changes in any of the lipid markers nor any of the inflammation markers were observed during the 48 weeks of DTG monotherapy.

	All patients (N=104)	TDF (N=85)
Male sex, N (%)	95 (91.3)	76 (89.4)
Age, mean (SD)	46 (11)	47 (11)
Ethnicity, N (%)		
Caucasian	86 (82.7)	70 (82.4)
Black or African	14 (13.5)	12 (14.1)
HIV-RNA zenith, copies/ml, median (Q1,Q3)	37 900 (14.800,67.000)	37 900 (14.500,64.200)
CD4 T-cell nadir, cells/mm³, median (Q1,Q3)	340 (273,508)	320 (250,483)
On TDF before switch, N (%)	85 (81.7)	85 (100)
On PI/b before switch, N (%)	3 (2.9)	3 (3.5)
Comorbidity, N (%)		
Hypertension	17 (16.3)	14 (16.5)
Dyslipidemia	12 (11.5)	10 (11.8)
Diabetes mellitus	4 (3.8)	3 (3.5)
History of AKI or CKI	12 (11.5)	4 (4.7)
Renal parameters		
eGFR$_{CKD\text{-}EPI}$ ml/min, mean (SD)	91 (17)	90 (15)
Urine total protein g/L, median (Q1,Q3)	0.10 (0.06,0.17)	0.11 (0.06,0.17)
Urine total albumin g/L, median (Q1,Q3)	0.009 (0.003,0.024)	0.008 (0.003,0.021)
UP:CR mg/mmol, median (Q1,Q3)	9.56 (6.49,14.13)	9.68 (6.73,13.79)
UA:CR g/mol creatinine, median (Q1,Q3)	0.70 (0.40, 1.84)	0.69 (0.40,1.44)
UB2M:CR mg/mmol, median (Q1,Q3)	0.028 (0.014,0.063)	0.033 (0.017,0.082)
FePO4 %, median (Q1,Q3)	11.7 (7.4,15.8)	11.7 (7.4,16.0)
Tubular proteinuria, N (%)	29 (27.9)	27 (31.8)
Hypophosphatemia, N (%)	17 (16.3)	14 (16.5)
Abnormal FePO4, N (%)	22 (21.2)	18 (21.2)
Normoglycaemic glucosuria, N (%)	1 (1.0)	1 (1.2)
PTD, N (%)		
No	80 (76.9)	65 (76.5)
Yes	15 (14.4)	14 (16.5)
No data available	9 (8.7)	6 (7.1)
Lipid parameters, mean (SD)		
Total cholesterol, mmol/L	4.8 (1.1)	4.6 (1.0)
HDL, mmol/L	1.43 (0.55)	1.39 (0.48)
LDL, mmol/L	3.01 (0.89)	2.92 (0.81)
TC:HDLR	3.6 (1.3)	3.5 (1.0)
Triglycerides, mmol/L	1.19 (0.65)	1.14 (0.57)
Inflammation parameters, median (Q1,Q3)		
C-reactive protein, mg/L	1.2 (0.50,2.70)	1.1 (0.50,2.75)
CD4:8-ratio	1.02 (0.74,1.49)	1.02 (0.75,1.46)
Bone parameters, mean (SD)		
BMD spine, g/cm²	1.177 (0.164)	1.174 (0.161)
BMD hip, g/cm²	1.021 (0.163)	1.009 (0.156)
TBS spine	1.317 (0.117)	1.313 (0.119)
Categories BMD T-score spine, N (%)		
≥ -1.0	52 (50.0)	48 (56.5)
-1.0 > BMD ≥ -2.5	26 (25.0)	22 (25.9)
<-2.5	1 (1.0)	1 (1.2)
No data available	25 (24.0)	14 (16.5)
Categories BMD T-score hip, N (%)		
≥ -1.0	55 (52.9)	48 (56.5)
-1.0 > BMD ≥ -2.5	22 (21.2)	21 (24.7)
<-2.5	1 (1.0)	1 (1.2)
No data available	26 (25.0)	15 (17.6)

Table 1. *Baseline characteristics of all participants ('all') and TDF-users ('TDF').*

PI/b = boosted Protease Inhibitor,

AKI = Acute Kidney Injury.

CKD = Chronic Kidney Disease

$eGFR_{CKD\text{-}EPI}$ = estimated GFR using CKD-epi

UP:CR = Urine Protein:Creat-Ratio,

UA:CR = Urine Albumin: Creat-Ratio

UB2M:CR = Urine Beta2Microgl:Creat-Ratio

FePO4 = Fractional Excretion of Phosphate

PTD = Proximal Tubular Dysfunction

BMD = Bone Mineral Density

TBS = trabecular bone score

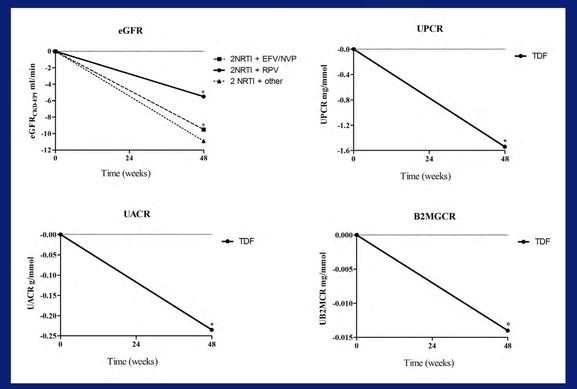
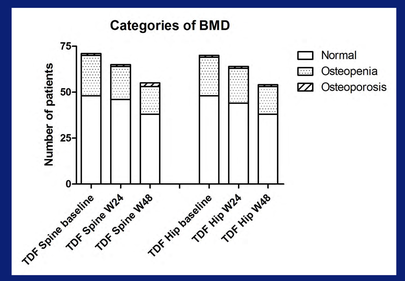


Figure 1. *Changes in eGFR, UPCR, UACR, and B2MGCR from baseline in different groups. * = P<0.0017. '2NRTI + EFV/NVP' = the entire subgroup of patients with 2 NRTIs + efavirenz or nevirapine before switch to DTG. '2NRTI + RPV' = the entire subgroup of patients with 2 NRTIs + rilpivirine before switch to DTG. '2NRTI + other' = the entire subgroup of patients with 2 NRTIs and another 3rd agent than RPV, NVP, or EFV. "TDF = the entire subgroup of patients with a TDF-containing cART-regimen before switch to DTG.*

The observed decrease in eGFR during DTG monotherapy (Figure 1) is explained by the inhibition of tubular creatine excretion. As this decrease was also observed (although to a lesser extent) in patients who had discontinued a RPV containing cART regimen, this demonstrates that DTG has a stronger effect on tubular creatine excretion than RPV.

The mean lumbar and hip BMD, and lumbar TBS improved in the 85 patients who had switched to DTG monotherapy from a TDF containing c-ART regimen: Spine BMD +1.8% (p<0.001), Hip BMD +1.5% (p=0.024), TBS +0.012 (p>0.1). This did not lead to significant changes in the classification of patients regarding the presence of osteoporosis (Figure 2).

Figure 2. *Distribution of lumbar and hip BMD according to BMD subgroups (normal, osteopenia, osteoporosis).*



Discussion and conclusions

In patients without virological failure during DTG monotherapy, a switch from TDF containing cART to DTG monotherapy improved renal tubular and bone markers, whereas lipids and inflammation markers remained stable.

As expected, the discontinuation of TDF improved proteinuria and improved BMD.

During DTG monotherapy, inflammation markers remained stable. Because patients with virological failure restarted cART, this conclusion can only be made for patients without virological failure while on DTG. The inflammation markers remaining stable suggests that as long as virological control is maintained, duotherapy or monotherapy has no negative impact on inflammation.

[1] **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-e554.**
[2] **Wijting IEA, Lungu C, Rijnders BJA et al.** ***HIV-1 resistance dynamics in patients failing dolutegravir maintenance monotherapy.*** **J Infect Dis 2018, in press.**