New Microbiologica, **38**, 531-540, 2015

Backbone switch to abacavir/lamivudine fixed-dose combination: implications for antiretroviral therapy optimization"

Alessandra Fantauzzi[1], Marco Floridia[2], Francesca Falasca[3], Pierpaolo Spanedda[4], Ombretta Turriziani[3], Vincenzo Vullo[5], Ivano Mezzaroma[1]

[1]Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy;
[2]Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità (ISS), Rome, Italy;
[3]Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy;
[4]Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy.;
[5]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

SUMMARY

Current guidelines recommend treatment optimization in virologically suppressed patients through switching/simplification strategies to minimize long-term toxicities and improve adherence. The assessment of inflammation/coagulation profiles may support therapeutic decisions. We undertook a prospective, non-randomized study to evaluate the efficacy and safety of switching to ABC/3TC from ZDV/3TC or TDF/FTC backbones, in 40 HIV-1 infected patients with HIV-RNA levels <37 copies/mL (>24 months). Main endpoints were viral load levels, CD4+ T cells and toxicities after 48 weeks. Serum inflammation/coagulation markers (ESR, CRP, D-dimer and fibrinogen) and pro-inflammatory cytokines (IL-6, TNF-α, adiponectin, resistin) were evaluated. Baseline characteristics were similar in the two arms, with significantly lower values of e-GFR in patients on TDF/FTC. Markers of inflammation/coagulation and cytokine profile were also similar, except for higher values of resistin in patients on TDF/FTC. During follow up, CD4+ T cells increased and viral load remained undetectable in both groups. Patient from ZDV/3TC had significantly greater changes in total cholesterol and serum creatinine. Markers of inflammation/coagulation remained unchanged. Adiponectin significantly increased in patients from ZDV/3TC.
Switching to ABC/3TC was effective and safe. Inflammatory markers remained low in both groups. Some changes in metabolic, kidney and cytokine profiles were apparently specific for baseline cART treatment.

KEY WORDS: Antiretroviral therapy, Backbone regimen, Switch strategies, Inflammatory cytokines.

Received March 3, 2015 *Accepted* August 23, 2015

INTRODUCTION

The availability of several combination antiretroviral regimens (cART) has made possible a prolonged disease-free survival in the majority of Human Immunodeficiency Virus type-1 (HIV-1) infected individuals (Hogg *et al.,* 1998; Mocroft *et al.,* 2003). However, long-term treatment with cART is often complicated by the development of antiretroviral resistance and drug-related toxicities, mainly represented by metabolic abnormalities, impairment of bone and renal function, and cardiovascular disease (CVD). Among nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs], fixed dose combinations of tenofovir-difumarate/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC) are widely used, due to their high antiviral potency, good tolerability, and low risk of side effects (DeJesus *et al.,* 2004; Gallant *et al.,* 2006). These backbones have been extensively evaluated in controlled trials (Eron *et al.,* 2006; Albrecht, 2008; Sax *et al.,* 2011), generally displaying comparable virological and immunological efficacy, but with distinct toxicity profiles. Al-

Corresponding author
Ivano Mezzaroma, MD
Department of Clinical Medicine
Sapienza, University of Rome
Viale dell'Università, 37 - 00185 Rome, Italy
E-mail: ivano.mezzaroma@uniroma1.it

though data from clinical trials indicate a low incidence of serious renal adverse events, prolonged TDF use has been associated with renal impairment (Cooper *et al.,* 2010), whose reversibility is still unclear, and cohort studies have linked TDF use to reduced estimated glomerular filtration rate (eGFR) (Fux *et al.,* 2007), accelerated eGFR decline (Campbell *et al.,* 2009), proximal tubular dysfunction (Horberg *et al.,* 2010; Labarga *et al.,* 2009), proteinuria (Gupta *et al.,* 2009), chronic kidney disease (CKD) (Scherzer *et al.,* 2012; Mocroft *et al.,* 2010) and increased mortality (Campbell *et al.,* 2012). On the other hand, ABC use has been associated with an increased risk of CVD, mainly myocardial infarction (Friis-Møller *et al.,* 2010; Hsue *et al.,* 2009). The issue is still discussed because recent studies showed no differences in the onset of CV events between ABC/3TC and TDF/FTC, and several meta-analyses of randomized clinical trials have not confirmed previous associations between ABC use and increased CV risk (Wohl *et al.,* 2014; Martin *et al.,* 2010; Ding *et al.,* 2012; Cruciani *et al.,* 2011).

From a pathogenetic perspective, several studies have focused on the biological mechanisms and on the biomarkers potentially involved in the cardiovascular dysfunction of patients receiving ABC. The first randomized controlled trial demonstrating a relationship between ABC and CVD biomarkers was the SMART study (INSIGHT/DAD Study Groups, 2008), where higher values of IL-6 and high-sensitivity CRP were reported with ABC compared to other NRTIs. Another study (BICOMBO) reported no differences between ABC/3TC and TDF/FTC in any of the biomarkers investigated (Martínez *et al.,* 2010). Different potential mechanisms, including endothelial dysfunction, have been investigated, but no clear biological cause has been recognized, and recent results seem to indicate that endothelial dysfunction, enhanced inflammation, and altered coagulation markers are unlikely to be mechanisms by which the drug could increase this risk (Hsue *et al.,* 2009; Wohl *et al.,* 2014). Moreover, although available data are not always consistent, HIV-1 infection *per se* has been associated, both in naïve and in cART-treated subjects, with increased levels of inflammation and coagulation markers (Deeks, 2009). HIV-1 induced activation of inflammatory and coagulation pathways, with elevated levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), and D-dimer might therefore increase the risk of cardiovascular diseases and mortality, as suggested by recent studies (Nordell *et al.,* 2014).

A global evaluation of current regimens that include metabolic, inflammation and coagulation markers may therefore provide relevant information for therapeutic decisions. Current treatment guidelines suggest optimizing cART in virologically suppressed patients with simplification strategies that reduce the pill burden and increase adherence and with switching strategies that prevent/reduce long-term drug toxicities and inflammation, without compromising stable viral suppression (DHHS HIV/AIDS Guidelines, 2014; Italian HIV/AIDS Guidelines, 2014). Within this scenario, the aim of our study was to perform a comprehensive evaluation of safety and efficacy markers in patients switching to the ABC/3TC fixed-dose combination from different NRTI backbones, represented by ZDV-based regimens (strategy: simplification) and TDF-based backbone (strategy: prevention or minimization of long-term drug-related toxicities).

METHODS

Patients

This study was an open-label, observational, non-randomized, prospective trial to compare the safety and efficacy of switching from ZDV or TDF containing regimens to a fixed-dose backbone of ABC/3TC 600/300 mg daily. Inclusion criteria were: documented HIV-1 infection with undetectable HIV-1 RNA load (<37 copies/mL) with current regimen from at least 24 months, and ZDV/3TC (arm 1), or TDF/FTC (arm 2) as ongoing NRTI backbones from more than 24 months. Exclusion criteria were prior use of ABC, diabetes mellitus, untreated hypertension, pregnancy, alcohol abuse, or positivity for the HLA-B5701 allele upon screening. Demographic and clinical information (smoking habit, CD4+ T cell nadir, HIV-1 RNA load, duration of HIV-1 infection and previous cART exposure) was retrieved from the patients' records.

According to current Italian guidelines, a treatment optimization strategy was applied in both

arms in order to improve adherence (mainly in the ZDV/3TC recipients) and to prevent or minimize long-term toxicities (i.e., referred/observed lipodystrophy, dyslipidemia, renal and bone impairment) (Italian HIV/AIDS Guidelines, 2014). All patients maintained the same anchor drug they were taking before the enrollment in the study. The study took place at the Department of Clinical Medicine, "Sapienza" - University of Rome, Italy. Patients were followed up clinically until 48 weeks from the enrollment. The study was approved by the local Ethics Committee (approval number 2687-216/13). Written informed consent was obtained from each patient before enrollment. The investigation was conducted in adherence to the declaration of Helsinki's guidelines.

Efficacy and safety parameters

Main endpoints of the study were efficacy and safety profiles after 48 weeks from the switch. Efficacy profile was evaluated monitoring HIV-1 RNA levels and CD4+ T cell counts and percentages at enrollment and after 48 weeks. Virologic failures were defined as the inability to maintain suppression of viral replication to an HIV RNA level <37 copies/mL in two consecutive determinations taken one month apart, whereas virologic blips were isolated detectable HIV RNA values (>37 copies</mL) that are followed by a return to virologic suppression.

Safety was investigated through the analysis of serum levels of fasting total cholesterol (TC), high density lipoprotein cholesterol (cHDL), low density lipoprotein cholesterol (cLDL), fasting glucose and triglycerides. Renal function was monitored through serum creatinine levels, serum phosphate, and eGFR using the Cockcroft-Gault formula and the MDRD (Modification of Diet in Renal Disease) Study equation formula.

Bone metabolism was investigated in a subset of patients of both arms evaluating bone mass density (BMD) in hip and lumbar spine by dual energy x ray absorptiometry (DEXA) scans at switch time. Serum levels of 25-OH vitamin D were measured by electrochemiluminescence (ECLIA) with the Elecsys Vitamin D3 (25-OH) reactive (Roche Diagnostic GmbH, Mannheim, Germany) using the Roche/Hitachi COBAS E 601 clinical chemistry analyzer. BMI was calculated as the weight in kilograms divided by the square of the height in meters.

Biomarker measurements

Study biomarkers were evaluated in batch on plasma samples stored and maintained at -80°C until analysis. To identify changes in inflammation and metabolic/coagulation markers and cytokines, we analyzed plasma levels of tumor necrosis factor-α (TNF-α), IL-6, fibrinogen, D-dimer, adiponectin, and resistin at baseline and at week 48 from enrollment in the study. Commercial available enzyme-linked immunosorbent assays (ELISA) were used for plasma quantification of IL-6 (R&D Systems, Minneapolis, MN, USA), TNF-alpha (R&D Systems, Minneapolis, MN, USA), resistin (Enzo Life Sciences Inc., NY, USA), and adiponectin (Adipogen International, San Diego, CA, USA). All analyses were performed following the manufacturer's instructions. All measurements were performed in duplicate. Samples with undetectable levels were assigned the value of the lower detection limit.

Statistics

Results were summarized as proportions and as means with standard deviation (SD) or as medians with interquartile range (IQR), according to the characteristics of data distribution (normal or skewed, respectively). Groups were compared using the χ^2 test or the Fisher test for categorical variables and the T-test or the Mann-Whitney U test for quantitative variables. Multivariable linear regression analyses were used to evaluate the impact of multiple covariates on dependent quantitative variables (e.g. mean changes from baseline in cholesterol levels or CD4+ T cell counts). P values below 0.05 were considered statistically significant. All statistical analyses were conducted using the SPSS software, version 22.0 (IBM, Somers, NY, USA).

RESULTS

Study participants

Between January and October 2012, forty HIV-1 infected patients, 17 on a ZDV/3TC backbone (arm 1) and 23 on a TDF/FTC backbone (arm

2), were included in the study. Two patients in arm 1 who withdrew shortly after enrollment (because of onset of diabetes mellitus, and alcohol abuse with adherence issues, respectively), and never received the ABC/3TC regimen, were excluded from all analyses. All the remaining subjects (n=38) completed the study follow up and were included in all analyses. None of the study participants had been receiving systemic corticosteroids, bisphosphonates, vitamin D, calcium or other therapies known to affect bone metabolism at enrolment.

Baseline general characteristics were similar in the two arms, with a low number of females enrolled, a low percentage of active smokers and low rate of hepatitis C virus (HCV) co-infection (Table 1). Route of transmission, stage of disease and HIV-related parameters (including current and nadir CD4+ T cell levels) were also similar in the two groups, with a trend for a more frequent use of NNRTIs in arm 2, due to the prescription of efavirenz-based co-formulated triple combination regimens.

Baseline metabolic evaluation (Table 2) showed no significant differences between the two arms in fasting glucose, triglycerides, cholesterol (including HDLc and LDLc), serum phosphate or creatinine levels. Patients in arm 2 (TDF/FTC) had however significantly lower values of estimated glomerular filtration rate with both the MDRD and the Cockcroft-Gault equations. Levels of vitamin D, measured in a subset of patients, were slightly higher in arm 1, although not significantly. However, these levels were below the normal ranges in the majority of evaluated patients, without increased values of parathyroid hormone. The markers of inflammation and coagulation (ESR, CRP, fibrinogen and D-dimer) were substantially identical in the two groups, and the overall baseline cytokine profile was also similar, except for higher values of resistin in patients on the TDF/FTC backbone (Table 2).

Efficacy and safety evaluations

Mean changes from switch in CD4+ T cell counts, lipid profiles, and renal parameters

TABLE 1 - *Demographics and main clinical characteristics. Values are reported as mean ± SD or proportion (%).*

	ALL (n=38)	*ZDV/3TC (n=15)*	*TDF/FTC (n=23)*	*P value*
Male sex, n (%)	26 (68.4)	12 (80)	14 (60.9)	0.294
Mean age (years)	45.0±8.4	43.7±9.2	45.9±8.0	0.443
Active smokers, n (%)	12 (31.6)	4 (26.7)	8 (34.8)	0.599
BMI (kg/m2)	22.9±3.1	23.5±2.7	22.4±3.3	0.289
HCV-coinfected, n (%)	7 (18.4)	2 (13.3)	5 (21.7)	0.681
HIV-1 transmission, n (%)				
Heterosexual contacts	18 (47.4)	7 (46.7)	11 (47.8)	0.456
MSM	12 (31.6)	5 (33.3)	7 (30.4)	0.980
Drug injection	8 (21.1)	3 (20)	5 (21.7)	0.896
Time since HIV-1 diagnosis (years)	16.2±6.2	15.2±6.9	16.9±5.8	0.427
Time of cART exposure (years)	13.6±5.9	14.6±6.8	12.9±5.3	0.397
NNRTIs exposure at baseline, n (%)	24 (63.2)	7 (46.7)	17 (73.9)	0.089
PIs exposure at baseline, n (%)	11 (28.9)	7 (46.7)	4 (17.4)	0.073
INIs exposure at baseline, n (%)	3 (7.9)	1 (6.7)	2 (8.7)	
HIV-1 disease stage, n (%)				
CDC-A	22 (57.9)	10 (66.7)	12 (52.2)	
CDC-B	12 (31.6)	4 (26.7)	8 (34.8)	
CDC-C	4 (10.5)	1 (6.6)	3 (13)	
CD4+ T cell nadir (cells/ml)	263±102	274±101	256±105	0.605
CD4+ T cells, %	34.7±10.1	33.0±10.6	35.9±9.8	0.392
CD4+ T cells (cells/ml)	781±324	786±343	778±319	0.942

SD: standard deviation; ZDV: zidovudine; 3TC: lamivudine; TDF: tenofovir difumarate; FTC: emtricitabine; BMI: body mass index; HCV: hepatitis C virus; cART: combined antiretroviral treatment; MSM: men who have sex with men; NNRTIs: non-nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors; INIs: integrase inhibitors; CDC: Centers for Disease Control and Prevention.

TABLE 2 - *Baseline profiles.*

	ALL (n=38)	*ZDV/3TC (n=15)*	*TDF/FTC (n=23)*	*P value*
A) Lipid and renal markers. Values are reported as mean ± SD.				
Fasting glucose (mg/dl)	84.9±8.6	85.0±8.4	84.9±8.9	0.964
Total fasting cholesterol (mg/dl)	199.6±44.5	197.5±35.8	201.0±50.1	0.817
Fasting cLDL (mg/dl)	122.6±33.6	127.1±31.5	119.7±35.4	0.517
Fasting cHDL (mg/dl)	50.2±13.3	48.7±13.7	51.2±13.2	0.587
Fasting triglycerides (mg/dl)	168.3±128.2	184.3±147.5	157.9±116.2	0.542
Serum creatinine (mg/dl)	0.87±0.14	0.85±0.13	0.88±0.14	0.439
Estimated creatinine clearance:				
MDRD (mL/min)	91.0±16.2	99.9±16.1	85.2±13.8	**0.005**
Cockcroft-Gault (mL/min)	102.3±26.4	112.9±25.2	95.5±25.3	**0.045**
25-OH D2/D3 vitamin D (ng/ml)	21.7±6.8	25.2±5.4	19.7±7.1	0.214
Serum phosphate (mg/dL)	3.1±0.6	3.1±0.7	3.0±0.6	0.735
B) Inflammation and coagulation markers. Values are reported as mean ± SD.				
ESR (mm/h)	11.7±7.5	12.3±8.0	11.3±7.4	0.694
CRP (mg/dL)	2101±3283	1788±3098	2373±3521	0.647
Fibrinogen (g/L)	2.63±0.76	2.69±0.86	2.58±0.69	0.688
D-dimer (ng/ml)	270.1±184.2	225.2±74.4	311.8±242.5	0.212
C) Serum cytokines. Values are reported as median (IQR).				
IL-6 (pg/mL): Median values (IQR)	7.8 (7.8-11.7)	7.8 (7.8-11.7)	7.8 (7.8-16.2)	0.697
TNF-α (mg/mL) Median values (IQR)	15.6 (15.6-15.6)	15.6 (15.6-15.6)	15.6 (15.6-18.9)	0.525
Adiponectin (mg/mL) Median values (IQR)	10.1 (5.95-19.4)	10.1 (5.9-16.8)	10.2 (6.1-24.5)	0.637
Resistin (ng/mL) Median values (IQR)	7.3 (4.0-10.5)	4.9 (2.6-7.9)	10.0 (5.5-27.5)	**0.031**

SD: standard deviation; ZDV: zidovudine; 3TC: lamivudine; TDF: tenofovir difumarate; FTC: emtricitabine; cLDL: low density lipoprotein cholesterol; cHDL: high density lipoprotein cholesterol; MDRD: Modification of Diet in Renal Disease Study equation formula; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IQR: interquartile range; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

are shown in Table 3. CD4+ T cells rose in both groups, with a trend for a larger increase in patients switching from TDF/FTC. Patients in both arms remained virologically suppressed (HIV-1 RNA levels <37 copies/mL) after the switch to ABC/3TC throughout the study, with no virological failures or blips during the 48 weeks of follow up. No serious adverse events occurred throughout the observation time, and no grade 3 or 4 adverse events were reported during the 48 week follow-up.

Fasting glucose remained substantially unchanged, whilst lipid profile showed different trends, with a significant difference between the two groups for mean change from baseline in total cholesterol (+28.8 mg/dl in patients switching from ZDV/3TC vs. -1.0 mg/dl in patients switching from TDF/FTC; p=0.016). A similar but not significant trend was observed for triglycerides and LDLc, that tended to increase in patients switching from ZDV/3TC, remaining substantially unchanged in patients switching from TDF/FTC. HDLc levels showed a mild increase in both groups. Renal parameters also showed a mild worsening in patients switching from ZDV/3TC compared to no change in patients switching from TDF/FTC. The significant difference between the two groups in total cholesterol during follow up was further explored in multivariable analyses in order to evaluate the role of potential confounders and adjust for covariates. Data were analyzed in a multivariable linear regression model which used the difference in total cholesterol values between 0 and 48 weeks as the dependent variable and smoking, body mass index, protease inhibitor use and treatment group as independent variables. After adjusting for the above covariates, baseline treatment at switch remained the only significant predictor of the increase in cholesterol after switch, with an adjusted estimated difference between baseline treatment groups of 26.5 mg/dl (95%CI 0.8-52.1) (p=0.044). The full results of this multivariable analysis with

TABLE 3 - *Changes between baseline (switch time point) and week 48 in the main laboratory parameters.*

A) Metabolic markers (mean change ± SD)

	ALL	*ZDV/3TC*	*TDF/FTC*	*P value*
Fasting glucose (mg/dl)	-0.26±7.5	-1.4±6.6	-0.47±8.1	0.459
Fasting total cholesterol (mg/dl)	10.8±38.1	28.8±42.4	-1.0±30.5	**0.016**
Fasting LDLc (mg/dl)	5.1±26.8	11.7±26.8	0.83±26.5	0.228
Fasting HDLc (mg/dl)	5.2±14.5	6.3±16.0	4.4±13.8	0.700
Fasting triglycerides (mg/dl)	6.9±124.9	29.6±139.5	-7.9±115.1	0.373
Serum creatinine (mg/dl)	0.01±0.08	0.05±0.10	-0.01±0.06	**0.031**
MDRD (mL/min)	-1.42±10.6	-5.16±13.8	1.01±7.2	0.127
Cd4+ T (cells/ml)	52.9±153.6	16.6±151.9	76.6±153.4	0.245
CD4+ T (%)	-0.10±5.4	1.38±3.9	-1.06±6.09	0.177

B) Median changes in serum adiponectin and resistin levels (IQR).

	ALL	*ZDV/3TC*	*TDF/FTC*	*P value*
Serum adiponectin (mg/mL)	3.2 (-3.6-8.0)	6.4 (2.2-18.2)	2.0 (-8.6-3.9)	**0.030**
Serum resistin (ng/mL)	1.4 (-4.8-6.0)	2.7 (-1.3-8.0)	1.4 (-1.0-5.3)	0.313

SD: standard deviation; LDLc: low density lipoprotein cholesterol; HDLc: high density lipoprotein cholesterol; MDRD: Modification of Diet in Renal Disease Study equation formula; IQR: interquartile range). P values are determined by using Student T test (Section A) and Mann-Whitney U test (Section B).

the estimate effect for all variables are shown in Table 4.

Similar multivariable linear regression analyses were performed using CD4+ T cell change from baseline as dependent variable and duration of cART treatment, CD4+ T cell nadir, HCV coinfection, treatment with protease inhibitors, history of toxicity and baseline treatment group as covariates, with no significant associations found.

Vitamin D measurements were available at baseline for 11 patients (4 ZDV/3TC, 7 TDF/FTC). Mean value was 21.7 ng/ml (SD 6.8). No statistically significant differences between treatment groups were present (25.2 vs. 19.7 ng/ml, respectively, p=0.214). Due to the generalized low vitamin D levels, according to HIV-1 treatment guidelines patients received a *per os* colecalciferol replacement.

Baseline data on bone mineral density were available for 22 subjects. Overall, a reduced bone mineral density was observed in nine subjects of the entire group (40.9%), 3/6 (50%) of subjects switching from ZDV/3TC and 6/16 subjects (37.5%) switching from TDF/FTC (p=0.655).

Inflammation/coagulation biomarkers and cytokines

No significant differences were observed in the values of erythrocyte sedimentation rate, CRP, fibrinogen, and d-dimer between study groups at baseline (Table 2) or at 48 weeks follow-up (data not shown).

TABLE 4 - *Multivariable regression analysis of variables independently associated with cholesterol change (mg/dl) between baseline and week 48.*

Variable	*Coefficient (B)*	*B 95% Confidence limits*		*P value*
		lower	*upper*	
Body Mass Index (per unitary increase)	-2.266	-6.193	1.662	0.249
Status of current smoker	-4.654	-29.539	20.231	0.706
Ritonavir-boosted protease inhibitors in the regimen	18.629	-9.088	46.347	0.181
ZDV/3TC group	26.493	0.795	52.190	**0.044**

Coefficient (B) indicates the estimated adjusted difference in change (in mg/dl) between baseline and week 48 in total cholesterol levels (dependent variable) between subjects with/without the relevant characteristic for dichotomic independent variables (status of current smoker, ritonavir-boosted protease inhibitors in the regimen, ZDV/3TC group) or the estimated adjusted change attributable to any unitary increase in the quantitative independent variable (Body Mass Index).

Baseline information for cytokine levels was available for 30 patients (ZDV/3TC 14, TDF/FTC 16) and is summarized in Table 2. The majority of samples showed non-detectable values of IL-6 and TNF-α in both arms. Median values of adiponectin levels were substantially identical in the two groups, while resistin levels were significantly higher in patients in TDF/FTC: median 10.0 ng/ml (IQR 5.5-27.5); ZDV/3TC: median 4.9 ng/ml (IQR 2.6-7.9), p=0.031 (Table 2).
Information on cytokine levels at 48 weeks was available for 23 patients (ZDV/3TC: 10; TDF/FTC: 13). As for baseline, most of the patients showed undetectable levels of IL-6 (60.9%) and TNF-α (82.6%), with no differences between treatment groups (data not shown). Changes from baseline in adiponectin and resistin levels are shown in Table 3. For resistin, both median changes between baseline and 48 weeks (+2.7 ng/ml vs. +1.4 ng/ml, p=0.313), and median levels at 48 weeks (6.5 vs. 8.4 ng/ml, p=0.410) were similar in the two groups.
Adiponectin values, conversely, showed a significantly higher increase during follow up in patients switching from ZDV/3TC compared to patients switching from TDF/FTC (median: 6.4 mg/ml vs. 2.0 mg/ml, p=0.030). Final levels were higher in patients who switched from ZDV/3TC (median 14.0 vs. 10.4 mg/ml, p=0.021), with 4/10 patients in this group (40%) showing levels above the upper normal limit of 19 mg/ml compared to 1/13 (7.7%) among patients who switched from TDF/FTC (p=0.127). No correlations were found between adiponectin levels and the metabolic and inflammation/coagulation parameters (i.e., ESR, CRP, fibrinogen, d-dimer, IL-6, TNF-a) evaluated in the study.

DISCUSSION

Current HIV/AIDS treatment guidelines recommend cART optimization in virologically suppressed subjects for the following reasons: documented toxicity or side effects; prevention of long-term toxicity (pre-emptive switch); therapy in place that might aggravate concomitant comorbidities; interactions with other drugs; need to treat coinfections (i.e., TB, HBV, HCV); need to improve adherence; planning of pregnancy; patient's request, and being on an antiretroviral regimen which is no longer recommended. Optimization may be conducted reducing the number/dosing of antiretroviral drugs or through other switching strategies (DHHS HIV/AIDS Guidelines, 2014; Italian HIV/AIDS Guidelines, 2014). In this study based on common clinical practice, the main reasons for optimizing the N(t)RTI backbone to ABC/3TC fixed dose combination were different: simplification for better adherence in the ZDV/3TC group, and presence or prevention of long term toxicities, including renal function/bone metabolism deterioration, in patients taking TDF/FTC.
In terms of treatment efficacy, all patients remained virologically suppressed during the study time, no blips of viremia were detected, and CD4+ T cell counts increased in both groups, with a trend for better response in patients switching from TDF/FTC. Overall, the findings support the strategy as effective in both groups. The significant effect of baseline treatment group on subsequent CD4+ response was confirmed in a multivariable analysis that adjusted for duration of cART treatment, CD4+ T cell nadir, HCV coinfection, treatment with protease inhibitors, and history of toxicity. The increase observed in both groups may be due to distinct reasons, represented by removal of ZDV-induced myelotoxicity and better adherence with QD regimens in patients previously receiving ZDV/3TC and by T-cell redistribution or effects on precursor cells for patients previously taking TDF/FTC, as suggested by other comparative trials of the two backbones (Eron *et al.,* 2006; *Sax et al.,* 2011).
In terms of lipid profile, this remained substantially unchanged in patients switching from TDF/FTC to ABC/3TC, while patients who switched from ZDV/3TC to ABC/3TC experienced a significant increase in total cholesterol, accompanied by non-significant increases in all the other lipid parameters evaluated. The significant role of baseline treatment group in determining cholesterol changes after switch was confirmed by a multivariable analysis that adjusted for smoking, body mass index and protease inhibitor use, and requires further evaluations in order to define its clinical significance. It is important to note that we were unable to control for other cofactors potentially involved,

such as lifestyle modifications, diet, and possible introduction of lowering lipid agents (i.e. statins) not monitored during the study. Patients on TDF/FTC had lower eGFR values at entry, as expected, given the well-known toxicity profile of TDF. However, this group had better changes in renal function parameters during follow up, thus suggesting that switching to ABC/3TC may produce positive effects on renal function.

With respect to inflammation and coagulation markers, our data showed no significant differences between the two groups and no significant changes from baseline, suggesting a limited impact of switching on the existing individual patient profile. It has however to be considered that the entire population studied was characterized by undetectable viral load throughout the study, and that therefore HIV-induced inflammation in this context is likely to be substantially reduced. Similar considerations may be valid for the profile of pro-inflammatory cytokines: serum levels of both IL-6 e TNFα were below the threshold of detection in the majority of patients of both groups before and after switching, probably reflecting a status of low activation of HIV-induced inflammation.

One of the adipocytokines is resistin, a protein hormone that seems to be involved in the process of blood glucose regulation, although its biological function in humans has not been fully identified yet (Bienek *et al.,* 2012; Cieslak *et al.,* 2011). Although resistin values were significantly higher at baseline in patients on TDF/FTC, changes from baseline were similar in the two groups and the final levels at 48 weeks were also similar, suggesting limited impact of switching to ABC/3TC on this parameter. The data on adiponectin (an anti-inflammatory hormone also correlated with the presence of lipodystrophy), that indicate a significantly higher increase for switching from ZDV/3TC, although based on a limited number of cases, may warrant further investigations, particularly to define the mechanisms that linked this particular group to a common increase in adiponectin levels and lipid parameters. Such investigations may also be useful to define the potential mechanisms responsible for increased cardiovascular risk in patients taking ABC. The results should however be interpreted cautiously, given the low number of cases and the absence of any correlation observed between adiponectin values and the main metabolic parameters studied.

This study has some limitations, represented by low number of cases, the absence of detailed immunological evaluations (e.g. additional lymphocyte subsets or cytokines), and lack of information on more directly relevant measures of cardiovascular risk, such as intima media thickness or flow mediated dilation. The short period of follow-up and the limited sample size also precluded evaluation of clinical cardiovascular events, but most of these evaluations were beyond the objectives of this pilot study.

In conclusion, the findings of this study suggest that switching the N(t)RTI backbone to ABC/3TC fixed-dose combination was overall effective, safe and well tolerated in virologically suppressed HIV-1 patients on either ZDV/3TC or TDF/FTC. Levels of inflammatory markers were low and were not influenced by switching to ABC/3TC, in either group. Some changes in metabolic, kidney and cytokine profiles were apparently specific for baseline treatment group, but further evaluations are needed to define their clinical significance. Overall, these preliminary results should be further investigated in larger studies.

ACKNOWLEDGMENTS

This work was supported in part by unrestricted educational grants from ViiV Healthcare and Gilead Sciences.

REFERENCES

Albrecht H. (2008). Abacavir/3TC vs. tenofovir/FTC: interim results from ACTG 5202. *AIDS Clin. Care*. **20**, 28.

Bienek R., Marek B., Kajdaniuk D., Borgiel-Marek H., Piecha T., Nowak M., Siemińska L., Głogowska-Szeląg J., Foltyn W., Kos-Kudła B. (2012). Adiponectin, leptin, resistin and insulin blood concentrations in patients with ischaemic cerebral stroke. *Endokrynol. Pol.* **63**, 338-345.

Campbell L.J., Ibrahim F., Fisher M., Holt S.G., Hendry B.M., Post F.A. (2009). Spectrum of chronic kidney disease in HIV-infected patients. *HIV Med.* **10**, 329-336.

Campbell L.J., Dew T., Salota R., Cheserem E., Hamzah L., Ibrahim F., Sarafidis P.A., Moniz C.F., Hendry B.M., Poulton M., Sherwood R.A., Post

F.A. (2012). Total protein, albumin and low-molecular-weight protein excretion in HIV-positive patients. *BMC Nephrol.* **13**, 85.

Cieslak J., Skorczyk A., Stachowiak M., Szydlowski M., Grzes M., Paczynska P., Skowronska B., Majewska K., Stankiewicz W., Fichna P., Switonski M. (2011). Polymorphism in 5'-flanking regions of genes encoding adiponectin, leptin, and resistin are not associated with obesity of Polish children and adolescents. *Mol. Biol. Rep.* **38**, 1793-1798.

Cooper R.D., Wiebe N., Smith N., Keiser P., Naicker S., Tonelli M. (2010). Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-1infected patients. *Clin. Infect. Dis.* **51**, 496-505.

Cruciani M., Zanichelli V., Serpelloni G., Bosco O., Malena M., Mazzi R., Mengoli C., Parisi S.G., Moyle G. (2011). Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. *AIDS.* **25**, 1993-1904.

Deeks S.G. (2009). Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. *Top HIV Med.* **17**, 118-123.

DeJesus E., Herrera G., Teofilo E., Gerstoft J., Buendia C.B., Brand J.D., Brothers C.H., Hernandez J., Castillo S.A., Bonny T., Lanier E.R., Scott T.R.; CNA30024 Study Team. (2004). Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral- naive HIV-infected adults. *Clin. Infect. Dis.* **39**, 1038-1046.

Ding X., Andraca-Carrera E., Cooper C., Miele P., Kornegay C., Soukup M., Marcus K.A. (2012). No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis. *J. Acquir. Immune Defic. Syndr.* **61**, 441-447.

Eron J. Jr, Yeni P., Gathe J. Jr, Estrada V., DeJesus E., Staszewski S., Lackey P., Katlama C., Young B., Yau L., Sutherland-Phillips D., Wannamaker P., Vavro C, Patel L., Yeo J., Shaefer M.; KLEAN study team. (2006). The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* **368**, 476-482.

Friis-Møller N., Thiébaut R., Reiss P., Weber R., Monforte A.D., De Wit S., El-Sadr W., Fontas E., Worm S., Kirk O., Phillips A., Sabin C.A., Lundgren J.D., Law M.G.; DAD study group. (2010). Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. *Eur. J. Cardiovasc. Prev. Rehabil.* **17**, 491-501.

Fux C.A., Simcock M., Wolbers M., Bucher H.C., Hirschel B., Opravil M., Vernazza P., Cavassini M., Bernasconi E., Elzi L., Furrer H.; Swiss HIV Cohort Study. (2007). Tenofovir use is associated with a reduction in calculated glomerular filtration rates in the Swiss HIV Cohort Study. *Antivir. Ther.* **12**, 1165-1173.

Gallant J.E., DeJesus E., Arribas J.R., Pozniak A.L., Gazzard B., Campo R.E., Lu B., McColl D., Chuck S., Enejosa J., Toole J.J., Cheng A.K.; Study 934 Group. (2006). Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N. Engl. J. Med.* **354**, 251-260

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents DHHS (2014). Downloaded from http://aidsinfo.nih.gov/guidelines on 10/21/2014

Gupta S.K., Smurzynski M., Franceschini N., Bosch R.J., Szczech L.A., Kalayjian R.C.; AIDS Clinical Trials Group Longitudinal Linked Randomized Trials Study Team. (2009). The effects of HIV type-1 viral suppression and non viral factors on quantitative proteinuria in the highly active antiretroviral therapy era. *Antivir. Ther.* **14**, 543-549.

Hogg R.S., Heath K.V., Yip B., Craib K.J., O'Shaughnessy M.V., Schechter M.T., Montaner J.S. (1998). Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA.* **279**, 450-454.

Horberg M., Tang B., Towner W., Silverberg M., Bersoff-Matcha S., Hurley L., Chang J., Blank J., Quesenberry C. Jr, Klein D. (2010). Impact of tenofovir on renal function in HIV-infected, antiretroviral naive patients. *J. Acquir. Immune Defic. Syndr.* **53**, 62-69.

Hsue P.Y., Hunt P.W., Wu Y., Schnell A., Ho J.E., Hatano H., Xie Y., Martin J.N., Ganz P., Deeks S.G. (2009). Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. *AIDS.* **23**, 2021-2027.

Labarga P., Barreiro P., Martin-Carbonero L., Rodriguez-Novoa S., Solera C., Medrano J., Rivas P., Albalater M., Blanco F., Moreno V, Vispo E., Soriano V. (2009). Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir. *AIDS.* **23**, 689-696.

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1 (18 dicembre 2014). Downloaded from http://www.salute.gov.it/portale/ news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=1876

Martin A., Amin J., Cooper D.A., Carr A., Kelleher A.D., Bloch M., Baker D., Woolley I., Emery S.; STEAL study group. (2010). Abacavir does not affect circulating levels of inflammatory or coagulopathic biomarkers in suppressed HIV: a randomized clinical trial. *AIDS.* **24**, 2657-2663.

Martínez E., Larrousse M., Podzamczer D., Pérez I., Gutiérrez F., Loncá M., Barragán P., Deulofeu R., Casamitjana R., Mallolas J., Pich J., Gatell J.M.; BICOMBO Study Team. (2010). Abacavir based

therapy does not affect biological mechanisms associated with cardiovascular dysfunction. *AIDS.* **24**, F1-F9.

Mocroft A., Ledergerber B., Katlama C., Kirk O., Reiss P., d'Arminio Monforte A., Knysz B., Dietrich M., Phillips A.N., Lundgren J.D.; EuroSIDA study group. (2003). Decline in AIDS and death rates in the EuroSIDA study: an observational study. *Lancet.* **362**, 22-29.

Mocroft A., Kirk O., Reiss P., De Wit S., Sedlacek D., Beniowski M., Gatell J., Phillips A.N., Ledergerber B., Lundgren J.D.; EuroSIDA Study Group. (2010). Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV positive patients. *AIDS.* **24**, 1667-1678.

Nordell A.D., McKenna M., Borges Á.H., Duprez D., Neuhaus J., Neaton J.D.; INSIGHT SMART, ESPRIT Study Groups; SILCAAT Scientific Committee. (2014). Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. *J. Am. Heart Assoc.* **3**, e000844.

Sax P.E., Tierney C., Collier A.C., Daar E.S., Mollan K., Budhathoki C., Godfrey C., Jahed N.C., Myers L., Katzenstein D., Farajallah A., Rooney J.F., Ha B., Woodward W.C., Feinberg J., Tashima K., Murphy R.L., Fischl M.A.; AIDS Clinical Trials Group Study A5202 Team. (2011). Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J. Infect. Dis.* **204**, 1191-1201.

Scherzer R., Estrella M., Li Y., Choi A.I., Deeks S.G., Grunfeld C., Shlipak M.G. (2012). Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS.* **26**, 867-875.

Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. (2008). Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS.* **22**, F17-F24.

Wohl D.A., Arnoczy G., Fichtenbaum C.J., Campbell T., Taiwo B., Hicks C., McComsey G.A., Koletar S., Sax P., Tebas P., Ha B., Massengale K., Walsh K., Stein J.H. (2014). Comparison of cardiovascular disease risk markers in HIV-infected patients receiving abacavir and tenofovir: the nucleoside inflammation, coagulation and endothelial function (NICE) study. *Antivir. Ther.* **19**, 141-147.