REPORT FROM 8TH IAS CONFERENCE ON HIV PATHOGENESIS, VANCOUVER, CANADA 19–22 JULY 2015

Tenofovir-related renal and bone toxicity

LISA HAMZAH

Introduction

This report aims to cover tenofovir-related renal and bone toxicity presented at the 8th IAS Conference on HIV Pathogenesis, Vancouver, Canada in 2015. Much of the data on tenofovir described the effect of tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) on renal and bone parameters, either directly or through regimen strategy. Not all renal and bone data are reported here; this report focuses on studies attempting to provide novel insight.

Tenofovir-related renal and bone safety

Improved renal and bone safety profiles with TAF

Three oral abstracts presented findings on TAF and TDF integrase inhibitor-containing single-tablet regimens. Two were switch studies (in adults with and without renal impairment) and one a naïve study in adolescents. TAF is the novel pro-drug of TDF which passes directly to the HIV target cells without cleavage to the active moiety tenofovir (TFV), reducing TFV levels in the plasma by 91%. Data were presented earlier this year, demonstrating limited bone and renal toxicity in naïve patients while maintaining good viral suppression [1].

The first abstract was the 48-week data from the Gilead 0109 open-label switch study in which 1,436 virologically suppressed subjects on TDF-containing antiretroviral therapy (ART) were randomised to either remain on their TDF-containing regimen, or switch to single tablet elvitegravir/cobicistat/emcitritabine (E/C/F) TAF [2]. In the comparator arm, TDF was in combination with emcitritabine (FTC) and either elvitegravir and cobicisitat, efavirenz or boosted atazanavir.

Renal adverse events leading to discontinuation were greater numerically in the TDF arm. Although the two renal events in the TAF arm (acute renal failure and interstitial nephritis) were not related to study drug, it was unclear how many were related to TDF in the TDF arm.

BMD hip and spine improved in the TAF arm (1.6–2% difference between arms at week 48) (**Error! Reference source not found.**). Renal safety results demonstrated improvements in urinary protein–creatinine ratio (PCR), albumin creatinine ratio (ACR) and specific markers of renal tubular dysfunction, including urinary retinol binding protein–creatinine ratio (RBP) and β-2 microglobulin–creatinine ratio (B2M) in the TAF arm (**Error! Reference source not found.**). These results support a favourable renal and bone profile with TAF vs TDF in terms of renal biomarkers and BMD, though the direct contribution of TAF is hard to determine due to the number of individual drug changes.

Table 1: Percentage (%) change from baseline to week 48 in renal biomarkers and bone mineral density in HIV-positive adults randomised to remain on TDF-based ART or switch to E/C/F/TAF

	Summary statistic*	**% Change from baseline to week 48 for subjects**		***p*-value for comparison**
		E/C/F/TAF	**FTC/TDF + 3rd agent**	
PCR mg/g	Median	-21	+10	$p<0.001$
ACR mg/g	Median	-18	+9	$p<0.001$
RBP µg/g	Median	-33	+18	$p<0.001$
B2M µg/g	Median	-52	+19	$p<0.001$

Spine BMD g/cm^2	Mean	+1.79	-0.28	p<0.001
Hip BMD g/cm^2	Mean	+1.37	-0.26	p<0.001

*Variability around the summary statistic is presented where data were available.

PCR: urinary protein-creatinine ratio, ACR: albumin creatinine ratio, RBP: urinary retinol binding protein creatinine ratio, B2M: β-2 microglobulin creatinine ratio, BMD: bone mineral density

The Gilead 0112 48-week study was an open-label switch study of TAF in renal impairment (Cockcroft-Gault creatinine clearance eGFR$_{CG}$ between 30–69 mL/min) in which all 242 subjects were switched to E/C/F/TAF [3]. 158 (65%) were on TDF-containing ART at the time of switch and these were compared to the non-TDF group.

The primary outcome of actual GFR measured by iohexol clearance was unaffected by switch to TAF, regardless of previous regimen, as expected given this is a marker of glomerular function. eGFR change measured differed according to estimating equation, but these changes were small and clinically not significant. Proteinuria significantly decreased at 48 weeks overall, and this was primarily driven by changes in the TDF group, where PCR, ACR, RBP and B2M all decreased. BMD also significantly increased overall, again primarily driven by increases in the TDF group (Table 2).

Table 2: % change from baseline to week 48 for subjects switching from a TDF-containing regimen to E/C/F/TAF in HIV-positive adults

	Summary statistic*	**% Change from baseline to week 48 for subjects *on a TDF-containing regimen* pre-switch**	***p*-value**
$CrCl_{CG}$ mL/min	Median [IQR]	+0.2 [-5.8, 6.3]	0.81
eGFR CKD-Epi mL/min/1.73m^2	Median	-1.5	>0.05
eGFR cystatin C mL/min/1.73m^2	Median [IQR]	+2.7 [-6.2, 14.1]	0.003
PCR mg/g	Median [IQR]	-55 [-70, -28]	<0.05

ACR mg/g	Median [IQR]	-61 [-81, -27]	<0.05
RBP µg/g	Median [IQR]	-82 [-95, -55]	<0.05
B2M µg/g	Median [IQR]	-89 [-97, -61]	<0.05
Spine BMD g/cm^2	Mean	+2.95	<0.05
Hip BMD g/cm^2	Mean	+1.85	<0.05

*Variability around the summary statistic is presented where data were available.
$CrCl_{CG}$: creatinine clearance measured using Cockcroft-Gault, eGFR CKD-Epi: estimated glomerular filtration rate measured using CKD-Epi equation, PCR: urinary protein-creatinine ratio, ACR: albumin creatinine ratio, RBP: urinary retinol binding protein creatinine ratio, B2M: β-2 microglobulin creatinine ratio, BMD: bone mineral density

Again, the relative contribution of TAF to the changes seen was difficult to determine; this study appeared to be more a proof of strategy. The author also conceded that the clinical relevance of the renal tubular biomarkers is unclear as there are few longitudinal data to support the association with renal tubular biomarkers and clinical outcomes. Nonetheless there was a convincing argument for the safety of this fixed dose combination in patients with existing renal impairment, identifying a new option for this single-tablet regimen in a sub-group of patients.

The third oral presentation compared the week 24 renal and bone outcomes of two ongoing single-arm, open-label studies of 100 ART-naive HIV-infected adolescents between 12 and 18 years commencing either E/C/F/TAF or E/C/F/TDF [4]. The TAF group was younger, more likely to be female, with 60% recruited from Uganda and had lower baseline BMD.

There was no difference between groups in creatinine or eGFR outcomes at week 24; both experienced decreased eGFR as would be consistent with MATE-1 inhibition of tubular creatinine secretion [5]. Although there was a trend for TAF to show a decrease in urinary protein (PCR, RBP or B2M) and TDF to show an increase, none of these changes reached statistical significance and this was suggested to be due to the small sample size (Table 3).

Table 3: % change in renal and bone markers from baseline to week 24 in HIV-positive adolescents starting TDF- or TAF-based ART

	Summary	**% Change from baseline to week 24 for**	***p*-value for**

	statistic*	subjects		comparison
		E/C/F/TAF	E/C/F/TDF	
eGFR CKD-Epi mL/min/1.73m^2	Median	-15	-14	-
PCR mg/g	Median	-7	-5	>0.05
RBP µg/g	Median	-2	+10	>0.05
B2M µg/g	Median	-34	+4	>0.05
Spine BMD g/cm^2 **ACTUAL**	Mean (SD)	+1.25 (-0.96, 4.11)	-0.99 (-3.57, 0.95)	0.009 for predicted to actual change
Spine BMD **PREDICTED**	Mean (SD)	+2.55 (1.11, 4.54)	+2.95 (2.2, 6.08)	

*Variability around the summary statistic is presented where data were available.

eGFR CKD-Epi: estimated glomerular filtration rate measured using CKD-Epi equation, PCR: urinary protein-creatinine ratio, RBP: urinary retinol binding protein creatinine ratio, B2M: β-2 microglobulin creatinine ratio, BMD: bone mineral density

At week 24, neither group showed a significant increase in BMD, but by week 48 the TAF group had shown an increase, albeit not as great as predicted according to age and gender [median (Q1, Q3) actual % change +3.25 (2.07, 6.47) vs +5.09 (2.23, 9.23) predicted].

Again, it is hard to draw a firm conclusion on the clinical relevance of these results; for example they compare two trials with baseline imbalances, the BMD result is influenced by a number of confounders and it was not clear if these were accounted for and one would expect a drop of 2–3% in BMD for naïve patients starting ART [6]. However the upward trend of BMD in the TAF group was reassuring and again highlights a further group of patients who would perhaps particularly benefit from TAF containing regimens.

Maternal TDF use not associated with bone toxicity

Two studies examined the impact of maternal TDF use. The first suggesting increased duration of *in utero* TDF exposure was not associated with decreased foetal long bone growth on ultrasound [7]. Even after adjustment for potential confounders, foetuses who were TDF exposed from conception or after 14 weeks gestation did not differ in femur or humeral length

scores, compared to those exposed for or less than 4 weeks or unexposed. Lack of repeated bone measurements limited the ability of the study to assess long-term foetal bone growth; nonetheless the results were reassuring.

Postnatal bone growth was assessed in the prevention of mother-to-child transmission (PMCT)-MCH survey 2013 in Kenya [8]. Growth outcomes, including age and sex-adjusted z-scores for weight, weight-for-length, length, and head circumference were no different between HIV-uninfected infants with and without prenatal TDF, again supporting the safety of TDF use in PMCT.

Improved bone parameters in TDF-sparing regimens

Two studies presented data suggesting favourable bone profiles in patients on TDF-sparing regimens. The MODERN [Maraviroc (MVC) Once-daily with Darunavir Enhanced by Ritonavir (DRV/r)] study randomised naïve patients to either MVC/DRV/r or TDF/FTC/DRV/r [9]. A sub-study of 143 patients favoured MVC and demonstrated lesser BMD decreases in the hip [mean (SD) % change BMD -1.4 (2.2) vs -2.6 (2.3) for MVC vs TDF)], but not the femoral neck or spine at 48 weeks and lesser bone turnover [Mean (SD) C-terminal telopeptide (CTX) 121 (243) vs 222 (288) pg/mL for MVC vs TDF].

The MIDAS (Metabolic impact of DRV/r maintenance monotherapy after successful viral suppression with Atripla) study randomised patients on Atripla to switch to DRV/r monotherapy [10] and demonstrated improvements in vitamin D, bone mineral density at hip, spine and femoral neck and bone turnover (Table 4). This suggested DRV/r may be an attractive strategy for those at high risk of osteoporosis, but the high rate of virological failure (one subject with HIV viral CNS escape and three with virological rebound) limited generalised use.

Table 4: Mean difference from baseline to week 48 in patients switching from Atripla to DRV/r monotherapy

	Adjusted mean difference [95% CI] between arms from baseline to week 48*	*p*-value
25(OH)D (ng/mL)	3.6 [0.6, 6.6]	0.02
1,25(OH) D (pmol/L)	12.1 [5.9, 18.3]	<0.001
PTH (ng/L)	-7.7 [-19.1, 3.8]	0.2
Bone specific ALP (IU/L)	-5.5 [-8.4, -2.6]	<0.001
CTX (µg/L)	-0.1 [-0.2, -0.06]	<0.001
P1NP (µg/L)	-9.5 [-18.5, -0.5]	0.04
BMD total hip	0.02 [0.0005, 0.03]	0.04
BMD neck of femur	0.03 [0.005, 0.05]	0.02
BMD spine	0.03 [0.003, 0.05]	0.02

25(OH)D: 25-hydroxy vitamin D 1,25(OH), D: 1,25-hydroxy vitamin D, PTH: parathyroid hormone, ALP: Alkaline phosphatase, CTX: type 1 collagen cross-linked C-telopeptide, P1NP: procollagen type 1 N-terminal propeptide, BMD: bone mineral density

Other renal and bone studies of interest

ABCC2 single nucleotide polymorphisms not associated with eGFR outcomes

One study assessed the association between the two most consistent genetic polymorphisms (24C→T and 1249G→A) associated with renal tubular dysfunction and three renal endpoints: 1) decrement in eGFR of >10 mL/min/1.73 m^2, 2) >25% decrement in eGFR, and 3) eGFR <60 in 703 patients initiating and continuing a TDF containing regimen [11].

Despite reasonable renal function at entry into the cohort (median eGFR 96 mL/min/1.73 m^2 (IQR 84.6–109.2), a large proportion of the cohort experienced an eGFR endpoint; >10 mL/min decrement in 89%, >25% decrement in 17%, and eGFR <60 in 18% of the patients. There was no association between the frequencies of the ABCC2 genotypes with those with and without the endpoint, or any association in logistic regression of the SNPs with the three endpoints. The

authors conclude that these SNPs are not considered a risk factor for clinically relevant renal dysfunction. Although this study is interesting in its attempt to determine if these SNPs have potential value to identify clinically relevant glomerular dysfunction, the authors' conclusion is somewhat overstated, as they did not look for an association with tubular dysfunction. It could be argued that reduced eGFR is a proxy marker for severe tubulopathy but the reduction in eGFR is not always a prominent feature of the phenotype.

HIV-related factors not associated with late BMD loss in those on ART

The AIDS clinical trial group (ACTG) anlaysed BMD in subjects enrolled in the 5202/5224s studies and compared them to uninfected individuals in the BACH/Bone and WIHS cohorts [12]. HIV infection remained significantly associated with greater adjusted BMD decline at the spine (-0.29%/year; 95% CI: -0.49, -0.09; p=0.005) but not at hip (p=0.63). Interestingly, in the first 2 years of ART, HIV-related characteristics were associated with bone loss; however, after 2 years, only lower total lean body mass (not BMI) was associated with BMD loss, suggesting a potential area for prevention of osteopenia.

Conclusion

The data presented supported the favourable renal and bone profile of E/C/F/TAF in comparison to TDF-containing regimens, but was unable to determine the relative contribution of TAF to changes seen. The changes in glomerular function were small in magnitude and of questionable clinical significance. The renal tubular changes, although more impressive, were harder to quantify in terms of clinical significance as little to date is understood regarding the long-term implications of tubular biomarkers. Most TAF studies, along with the TDF-sparing studies demonstrated BMD changes in the magnitude of 2–3%. Arguably this does represent a meaningful difference, as vitamin D supplementation may increase BMD by 1% and bisphosphonates 2–4%. In summary, although the data lack generalisability to the entire HIV population, they do provide expansion of bone and renal protection strategies for sub-groups of patients with co-morbidities.

Acknowledgements

I would like to thank the British HIV Association and Janssen for the Janssen Travel Bursary Scholarships in collaboration with BHIVA to attend the IAS Conference 19–22 July 2015, Vancouver, Canada.

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