

# Assessment of Renal Findings of Abacavir/Lamivudine (ABC/3TC) Compared to Tenofovir/Emtricitabine (TDF/FTC) in Combination with QD Lopinavir/Ritonavir (LPV/r) Over 96 Weeks in the HEAT Study

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## Introduction

- HAART has resulted in dramatic improvements in morbidity and mortality shifting the focus to long-term management of HIV and co-morbid conditions such as renal dysfunction.
- HIV infection, host factors, specific antiretrovirals, and concomitant nephrotoxic drugs all may contribute to the increasing prevalence of renal disease in the U.S.
- We compared the effect of the renal effects of ABC/3TC vs. TDF/FTC each with LPV/r in HIV-1 infected, antiretroviral-naïve subjects enrolled in the HEAT study over 96 weeks.

## Renal Disease and HIV Infection

- Renal function is estimated to be abnormal in up to 30% of HIV-infected patients, however, patients are usually asymptomatic unless in advanced stages.<sup>1</sup>
- Risk factors for kidney disease in the HIV-infected population include: hypertension, diabetes, black race, host factors, hepatitis C infection, lower CD4+ count and higher VL.<sup>1</sup>
- Baseline assessment of risk factors for chronic kidney disease, urine analysis (for proteinuria) and serum creatinine (for estimate of Clcr or GFR) is recommended for all HIV-1 infected patients.<sup>1</sup>
- Drug-induced renal dysfunction has been reported with the use of certain antiretrovirals, notably tenofovir and indinavir.<sup>2</sup>
- Tenofovir has been variably associated with a range of renal disturbances from decreased creatinine clearance to proximal renal tubule damage.
  - Zimmermann et al. found tenofovir-associated acute renal failure to be commonly associated with use of the boosted PI, LPV/r.<sup>3</sup>
  - Kiser et al. reported a 17.5% decrease in TFV clearance when co-administered with LPV/r after adjustment for renal function.<sup>4</sup>
- In contrast with tenofovir, abacavir has been rarely associated with renal dysfunction likely due to its negligible renal elimination (<2%).<sup>5</sup>

## Methods

- HEAT was a large, randomized, double-blind, placebo-matched, 96 week study that demonstrated the non-inferiority of ABC/3TC to TDF/FTC when each was combined with QD LPV/r in 688 ARV-naïve subjects.
- In addition to routine chemistries, the following markers of renal function were assessed at each study visit: phosphorus, serum cystatin C, urinalysis for albumin, total protein, and creatinine, quantified urine glucose, and estimates of renal clearance using Cockcroft-Gault creatinine clearance (CrCl) and the 4-variable modification of diet in renal disease (MDRD or eGFR) equations.
- Subjects with confirmed reduction of CrCl<50 mL/min were not permitted to dose reduce their blinded NRTI.
- The criteria for development of proximal renal tubule dysfunction (PRTD) was based on early studies of adefovir and expert opinion from the study nephrologist.<sup>6</sup>
  - PRTD definition: serum creatinine rise of ≥0.5 mg/dL from BL and serum phosphate <2 mg/dL or either of the former plus any 2 of the following: proteinuria ≥100 mg/dL, glycosuria ≥250 g/dL, low serum potassium <3 meq/L, or low serum bicarbonate <19 meq/L.
- All cases of PRTD were reviewed by the medical monitor and study nephrologist.
- Descriptive summaries of the baseline demographics and relevant laboratory parameters were provided.

## Results

Table 1. Baseline Demographics and Characteristics

	ABC/3TC N = 343	TDF/FTC N = 345
Mean Age, yrs (range)	38 (18-74)	39 (18-69)
Female, n (%)	56 (16%)	69 (20%)
Race, n (%)		
White	176 (51%)	173 (50%)
African-American	122 (36%)	124 (36%)
Other	45 (13%)	48 (14%)
Hispanic/Latino Ethnicity, n (%)	73 (21%)	62 (18%)
Plasma HIV-1 RNA (log <sub>10</sub> c/mL), median	4.90	4.84
≥100,000 c/mL, n (%)	155 (45%)	140 (41%)
CD4+ count (cells/mm <sup>3</sup> ), median	214	193
<50 cells/mm <sup>3</sup> , n (%)	61 (18%)	70 (20%)
50-200 cells/mm <sup>3</sup> , n (%)	99 (29%)	110 (32%)
≥ 200 cells/mm <sup>3</sup> , n (%)	183 (53%)	165 (48%)
CDC Class C, n (%)	55 (16%)	57 (17%)
Hepatitis B Positive, n (%)	19 (6%)	9 (3%)
Hepatitis C Positive, n (%)	27 (8%)	24 (7%)
Relevant Medical Conditions		
Any Condition	116 (34%)	115 (33%)
Hypertension	50 (15%)	50 (14%)
Hypercholesterolemia	42 (12%)	33 (10%)
Diabetes Mellitus	8 (2%)	16 (5%)
Drug abuse	23 (7%)	20 (6%)
Cardiomyopathy	7 (2%)	9 (3%)
Nephropathy	1 (<1%)	5 (1%)
Congenital renal disorder	1 (<1%)	0
Selected Concomitant Medications		
Trimethoprim-Sulfamethoxazole	119 (35%)	127 (37%)
Ibuprofen	67 (20%)	79 (23%)
Acetylsalicylic acid	18 (5%)	19 (6%)
Naproxen	23 (7%)	20 (6%)
Diuretics	28 (8%)	25 (7%)
Median Weight (kg) (range)	77 (44-145)	75 (46-136)
Median BMI (for those with height data) (range)	25 (17-48)	25 (16-43)

Figure 1. Change in Renal Clearance

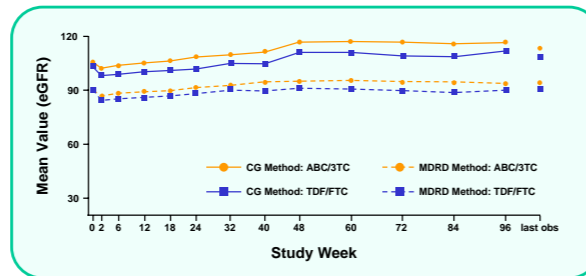


Table 2. Changes in Renal Function

	n BL, Last Obs	ABC/3TC N = 343			n BL, Last Obs	TDF/FTC N = 345		
		BL	Last Obs <sup>1</sup>	Last Obs Δ BL		BL	Last Obs <sup>1</sup>	Last Obs Δ BL
Mean (SD)								
Phosphorus (mg/dL)	343, 325	3.63 (0.694)	3.20 (0.646)	-0.43 (0.820)	344, 335	3.71 (0.732)	3.22 (0.673)	-0.49 (0.832)
Serum Creatinine (mg/dL)	343, 325	1.05 (0.219)	1.01 (0.211)	-0.04 (0.180)	345, 335	1.04 (0.217)	1.05 (0.236)	0 (0.199)
MDRD (eGFR) (mL/min/1.73 <sup>2</sup> )	339, 325	90 (19.2)	93.7 (19.2)	+3.4 (16.7)	340, 333	90.4 (20.5)	90.6 (21.7)	+0.7 (18.7)
C-G CrCl (mL/min)	339, 325	105.4 (26.6)	113.4 (29.6)	+7.8 (19.7)	340, 333	103.3 (26.1)	108.2 (32.4)	+5 (19.4)
Urine glucose ≥15 mg/dL <sup>2</sup>	224, 247	5/224 (2%)	10/247 (4%)	NA	235, 261	10/235 (4%)	11/261 (4%)	NA

<sup>1</sup> Last obs was based on the last available assessment when subject was still on randomized treatment.  
<sup>2</sup> Excluded subjects with known diabetes, fasting glucose > 126, or glucose >140 at any timepoint.

Table 3. Renal Adverse Events Reported in HEAT

Treatment-Related Renal AEs, n (AEs leading to withdrawal from study)	ABC/3TC N = 343	TDF/FTC N = 345
Subjects with any event, n	26	32
GFR decreased	25 (0)	22 (0)
Grade 2	18	9
Grade 3	7	12
Grade 4	0	1
Creatinine increased	0	3 (0)
Grade 2	0	2
Grade 3	0	1
Creatinine clearance decreased (Grade 3)	0	1 (0)
Nephropathy (Grade 3)	0	1 (0)
Renal failure	0	4 (2)
Grade 2	0	2 (1)
Grade 3	0	2 (1)
Acute renal failure (Grade 4)	0	1 (0)
Renal impairment (Grade 3)	1 (0)	0
Renal tubular disorder (Grade 2)	0	1 (0)
Proximal Renal Tubule Dysfunction (not graded)	0	5 (0)

- Subjects receiving TDF/FTC experienced greater number of renal adverse events over 96 weeks and resulted in either early treatment or study discontinuation.

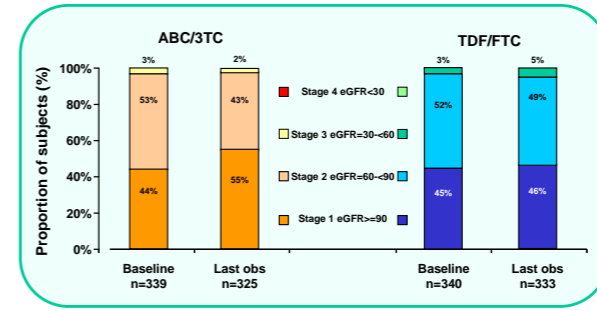
## Proximal Renal Tubule Dysfunction (PRTD)

- 5 subjects (4 male, 1 female) met laboratory defined criteria for PRTD. All 5 cases were reported in the TDF/FTC + LPV/r treatment group.
- Each subject had a confirmed increase in serum creatinine ≥0.5 mg/dL from baseline (except subject 3) with the addition of the following criteria: A) low serum phosphate (Subjects 1,2,5); B) proteinuria and glycosuria (Subject 4); and C) low serum phosphate, glycosuria, and low bicarbonate (Subject 3).
- The median time to PRTD development was 128 days (range 43-425).

Table 4. Description of PRTD Cases

PRTD Criteria Study Wk	Demographics, Past Medical History, Selected ConMeds	Abnormal lab changes from baseline	Comments
Subject 1 A (60)	35yo, Caucasian male None, none	Scr: 0.9 -> 1.4 Phos: 4.8 -> 1.9	Clinically asymptomatic but found to be taking up to 8 Vicodin tabs/day. Completed study on TDF/FTC.
Subject 2 A (18)	48yo, Japanese female None, none	Scr: 0.8 -> 1.4 Phos: 3.5 -> 1.9	Subject denied diarrhea/vomiting but appeared pre-renal. Subject decided to prematurely withdraw from study.
Subject 3 C (18)	37yo, Native American male None TMP-SMX	Phos: 4.3 -> 2.8 Ugic: <8 to 101 CO <sub>2</sub> : 19 -> 15	Received multiple medications for MAC and had adverse GI effects possibly contributing to worsening renal function. Subject switched to 3TC/ZDV and completed study.
Subject 4 B (12)	52yo, Caucasian male None, none	Scr: 1 -> 1.6 Ugic: <8 to 572 Uprot: 29 -> 137	Subject stopped study meds after developing bronchial candidiasis and started TMP-SMX 19 days after BL visit. Subject switched to ABC/3TC + ATV but prematurely withdrew from study due to AE (diarrhea).
Subject 5 A (40)	60yo, African-American male History of latent syphilis, Hepatitis C None	Scr: 0.6 -> 1.2 Phos: 4.4 -> 1.9	Subject was hospitalized for community-acquired pneumonia and resumed study meds after serum phosphate normalized. Subject was lost to follow-up.

Figure 2. Graph of CKD Progression by MDRD



- Progression to a more advanced CKD stage occurred in a slightly greater number of subjects in the TDF/FTC arm compared to the ABC/3TC arm (49 [15%] vs 31 [10%], respectively).
- More subjects in the TDF/FTC arm progressed to stage 3 CKD; (4 ABC/3TC, 11 TDF/FTC).

## Discussion

- Renal disease and its complications are important to consider and likely to increase due to increasing life expectancy afforded by HAART and the ageing of HIV-infected patients.
- Limited data are available to help practitioners determine which patients are at highest risk for antiretroviral-induced renal toxicity and how often to assess for toxicity.
- Results showed that improvement in renal function, as measured by eGFR and CrCl, was slightly greater, though small in absolute terms, with ABC/3TC compared to TDF/FTC over 96 weeks.
- More subjects in the TDF/FTC arm had treatment-related renal adverse events over 96 weeks including 5 subjects with PRTD. In most subjects with adverse renal events, confounding medical history or use of nephrotoxic concomitant meds was not a contributing factor thus complicating the identification of patients at highest risk.
- Progression to a more advanced stage of CKD (eGFR <60mL/min/1.73<sup>2</sup>) occurred more often in subjects receiving TDF/FTC.
- As HIV-infected patients advance into older age and exhibit declines in renal function, selection of antiretroviral therapy may become more complicated.
- All subjects experiencing renal dysfunction required closer follow-up and repeat laboratory testing. Early consult with a nephrologist is suggested for patients with changing renal function.

## Conclusions

- Absolute differences in renal function as estimated by eGFR and eCrCl were small between ABC/3TC and TDF/FTC each co-administered with LPV/r over 96 weeks.
- TDF/FTC-treated subjects were more likely to experience any renal adverse event compared to ABC/3TC-treated subjects.
- Progression to CKD stage 3 (eGFR <60mL/min/1.73<sup>2</sup>) occurred more often in TDF/FTC-treated subjects.
- Routine renal monitoring can detect overt or antiretroviral-induced kidney disease earlier and should be considered in all patients commencing antiretroviral therapy.

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