

# Tenofovir Effect on Renal Function Factoring in Both MDRD-Calculated Glomerular Filtration Rate (GFR) and Spot Urine Protein-to-Creatinine (UPC) Ratio

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## Background

- Spot urine protein/creatinine ratio (UPC) is considered a useful marker for most diagnostic and surveillance purposes of proteinuria.
- UPC has also been reported to predict progression of renal disease in patients without diabetes entering a ramipril trial reported by Ruggenenti et al.
- In the study, Ruggenenti reported that UPC significantly correlated with 24-hour urinary protein values and had high predictive value for rate of decline of glomerular filtration rate: UPC < 1.7 g/moH had 3% rate of renal failure compared with 21.2% for UPC > 2.7 g/moH.
- Although proteinuria has been shown to be a marker for progressive HIV-related chronic kidney disease (CKD), predictors of proteinuria in the HAART era are unknown. A study by Palella et al suggest that proteinuria was:
  - more sensitive sign of early renal disease in HIV+ persons than GFR declines;
  - 5 times more common in HIV+ men on HAART than HIV- men;
  - strongly associated with GFR declines regardless of HIV serostatus;
  - not associated with ARV use, including tenofovir; and
  - more common in men with classic risks for renal disease (e.g., AIDS, HCV)
- A study by Gupta et al evaluated UPC in a large HIV-infected cohort, ALLRT. The study reported that:
  - UPC decreased over time;
  - viral suppression to <400 copies/mL reduced the likelihood of developing clinically significant proteinuria, an effect that was more pronounced with lower baseline CD4 counts;
  - several non-HIV factors also predicted those who were more likely to have proteinuria and who should be treated aggressively to prevent progressive kidney disease
- The definition of CKD from National Kidney Disease (NKF) emphasizes proteinuria as a marker for CKD regardless of GFR.
- Tenofovir (TDF) is renally excreted via a combination of glomerular filtration and active tubular secretion. Renal impairment (including acute renal failure and Fanconi Syndrome) has been associated with TDF use in some cohort studies. Most cases have occurred in patients with underlying systemic or renal disease or in patients taking nephrotoxic agents. Despite the apparent renal safety of TDF in placebo-controlled clinical trials, these reports raise concerns about nephrotoxicity with long-term TDF use.
- We investigated whether proteinuria assessed by UPC may predict early renal disease in the clinical setting in HIV+ patients treated with HAART.

## Methods

- This retrospective analysis compared patients on tenofovir (TDF) vs non-TDF-containing HAART.
- All clinic patients who had at least one UPC measurement from March 2006 through December 2007 were included in the analysis.
- UPC was evaluated every 6 months and some patients were followed for at least one year.
- Data included demographics, history of co-morbidities, current ARV regimen, serum creatinine, UPC, CD4 count, and HIV-1 RNA at start and end of study period.

### Definitions

- TDF group: patients receiving TDF as part of initial or subsequent ART
- Non-TDF group: patients who never received TDF as part of initial or subsequent ART or patients who switched from TDF based on renal toxicity as per provider's discretion
- Baseline: this is a study-defined point which is the time of the first UPC measurement and is not a "true" baseline when ART is first initiated. (In this study, most of the patients were treatment-experienced, and there were a few treatment-naïve patients for whom the baseline is a "true" baseline.)
- GFR determined by modification-of-diet-in-renal-disease (MDRD) equation and by Cockcroft-Gault equation
- Stage 3+ renal impairment defined as GFR <60 mL/min/1.73m<sup>2</sup> by NKF guidelines
- Proteinuria defined as UPC >200 mg/g by NKF guidelines
- CKD defined as GFR <60 mL/min/1.73m<sup>2</sup> or UPC >200 mg/g ([www.kidney.org/professionals/kdoqi/guidelines\\_ckd](http://www.kidney.org/professionals/kdoqi/guidelines_ckd))

### Analyses

- Descriptive statistics are provided for baseline characteristics and change in renal parameters
- Time to proteinuria, time to ≥Stage 3 renal impairment, and time to CKD were analyzed by Kaplan-Meier method
- Cox Proportional Hazards model was performed to identify predictors of CKD, proteinuria, and moderate renal impairment. We report hazard ratios (HR). Predictors included age, comorbidities (diabetes, hypertension), gender, PI use, TDF use, and use of ace inhibitors.

## Results

Table 1. Baseline Characteristics  
 Values are number (%) or median (range)

Characteristic	TDF (n=253)	Non-TDF (n=122)
Age (years)	44 (22-68)	46 (29-66)
Sex:		
male	239 (94%)	115 (94%)
Race:		
Non African-American	242 (96%)	118 (97%)
African-American	11 (4%)	4 (3%)
Diabetes Mellitus	20 (8%)	11 (9%)
Hypertension	60 (24%)	29 (23%)
History of Kidney Disease	3 (1%)	6 (5%)
Hepatitis B/C Co-infection	36 (14%)	12 (10%)
CD4 (cells/mm <sup>3</sup> )	440 (116-1287)	554 (66-1587)
HIV-1 RNA, log copies/mL	1.69 (1.69-5.88)	1.69 (1.69-5.62)
% HIV-1 <50 copies/mL	68%	88%
On ACE Inhibitors	46 (18%)	23 (19%)
HAART Regimen:		
Naïve or Initial	41 (16%)	21 (17%)
Second or later	212 (84%)	101 (83%)
Median time on HAART* prior to baseline (days)	551 (11-3226)	854 (5-4437)

\*Sample sizes for patients included were n=221 (TDF) and n=110 (Non-TDF)

Table 2. Summary of All Antiretrovirals Received During the Study

Characteristic	TDF (n=253)	Non-TDF (n=122)
<b>NNRTIs</b>		
NVP	84 (33%)	50 (41%)
EFV	43 (17%)	25 (20%)
ABC	41 (16%)	24 (20%)
<b>Nucleosides</b>		
Truvada	230 (91%)	116 (95%)
Epilcom	124 (91%)	0
Epicom	35 (14%)	51 (42%)
Combivir	16 (6%)	23 (19%)
Trizivir	5 (2%)	22 (18%)
TDF	105 (42%)	0
FTC	20 (8%)	0
3TC	19 (8%)	13 (11%)
ABC	11 (4%)	8 (7%)
d4T	8 (3%)	8 (7%)
ZDV	3 (1%)	1 (<1%)
ddl	24 (9%)	10 (8%)
<b>Protease Inhibitors</b>		
RTV	155 (61%)	79 (65%)
SQV	85 (34%)	30 (25%)
LPV/RTV	63 (25%)	35 (29%)
ATV	48 (19%)	22 (18%)
FPV	26 (10%)	9 (7%)
NFV	12 (5%)	11 (9%)
TPV	9 (4%)	8 (7%)
DRV	5 (2%)	0
IDV	2 (<1%)	1 (<1%)

Table 3. Renal Parameters at Baseline  
 Values are mean ± SD or median (range)

	TDF*	Non-TDF**
Creatinine, mg/dL	1 ± 0.21	1 ± 0.21
GFR (by MDRD), mL/min/1.73m <sup>2</sup>	85.9 ± 19.7	90.4 ± 21.8
GFR (by Cockcroft-Gault), mL/min	94.7 ± 21.6	97.5 ± 23.1
UPC, mg/g	131	98.5
% with Stage 1 GFR <sup>†</sup>	91 (36%)	57 (47%)
% with Stage 2 GFR <sup>†</sup>	141 (56%)	59 (48%)
% with Stage 3+ GFR <sup>†</sup>	21 (8%)	6 (5%)
% with UPC Ratio >200 mg/g	69 (27%)	12 (10%)

\*n=253 except for GFR (by Cockcroft-Gault) where n=252  
 \*\*n=122 except for GFR (by Cockcroft-Gault) where n=119  
<sup>†</sup>Staging by NKF (MDRD): Stage 1 (≥90 mL/min/1.73m<sup>2</sup>), Stage 2 (60-89 mL/min/1.73m<sup>2</sup>), Stage 3+ (<60 mL/min/1.73m<sup>2</sup>)

Figure 1. Mean Change from Baseline in GFR (by MDRD)

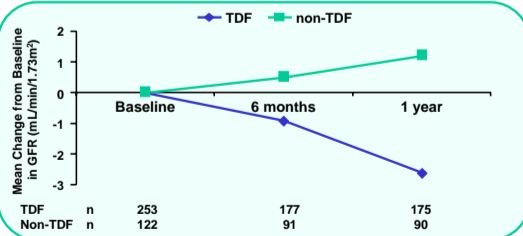
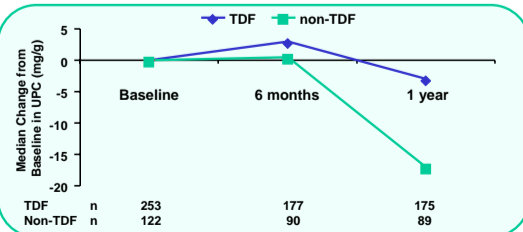


Figure 2. Median Change from Baseline in UPC



## References

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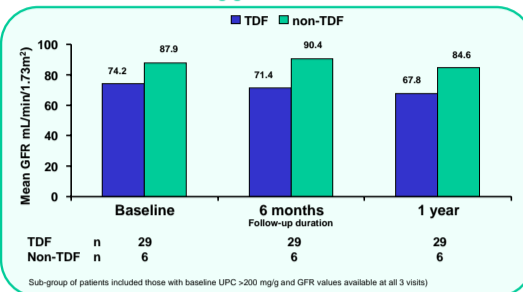
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Figure 3. Mean GFR (by MDRD) in Sub-group of Patients with Baseline UPC ratio >200 mg/g



- Among subjects who switched from TDF (n=16), improvements were noted in mean GFR (by MDRD) and UPC. The last means before switch versus after switch was for GFR – 56 mL/min/1.73m<sup>2</sup> vs. 60 mL/min/1.73m<sup>2</sup> – and for UPC – 666 mg/g vs. 230 mg/g.

Table 4. Comparison of Kaplan-Meier Analyses

	TDF	Non-TDF
Time to UPC ratio >200 mg/g – see Figure 4		
% survival* at 48 weeks	66%	86%
% survival – without proteinuria		
Time to chronic kidney disease – see Figure 5		
% survival* at 48 weeks	62%	83%
% survival – without CKD		

- When using both MDRD and UPC combined to define CKD, 62% (TDF) vs. 83% (non-TDF) did not experience CKD by 48 weeks. These values are similar to values obtained in the analysis with UPC alone.

Figure 4. Kaplan-Meier Survival Curve of Time to UPC >200 mg/g

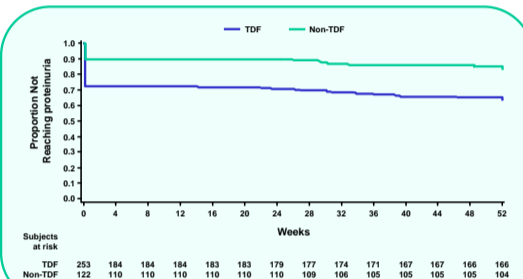


Figure 5. Kaplan-Meier Survival Curve of Time to CKD

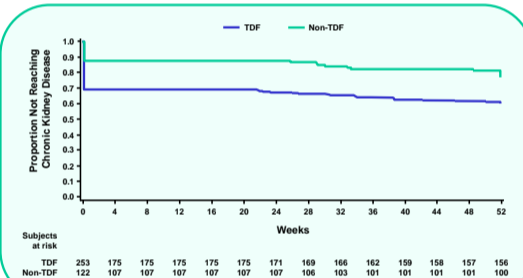


Table 5. Multivariate Analyses

Variable	Hazard Ratios (95% Confidence Intervals)	P-value
<b>Predictors of UPC &gt; 200 mg/g</b>		
TDF use	2.13 (1.22-3.72)	0.008
Diabetes	2.20 (1.25-3.88)	0.006
Age	1.04 (1.02-1.07)	0.001
Hypertension	1.26 (0.73-2.16)	0.40
Ace inhibitor use	1.07 (0.58-1.97)	0.82
PI use	1.32 (0.85-2.03)	0.21
Male	0.84 (0.39-1.83)	0.66
<b>Predictors of chronic kidney disease (UPC &gt;200 mg/g or GFR &lt;60mL/min/1.73m<sup>2</sup>)</b>		
TDF use	1.83 (1.11-3.02)	0.02
Diabetes	1.83 (1.06-3.16)	0.03
Age	1.05 (1.03-1.07)	<0.0001
Hypertension	1.14 (0.68-1.91)	0.62
Ace inhibitor use	1.14 (0.64-2.04)	0.65
PI use	1.27 (0.84-1.91)	0.26
Male	0.71 (0.36-1.41)	0.32

- Multivariate analyses:
  - Both TDF use (HR=2.13, p=0.008) and diabetes (HR=2.2, p=0.006) were associated with time to UPC ratio >200 mg/g.
  - Predictor of CKD:
    - Both TDF use (HR=1.83, p=0.02) and diabetes (HR=1.83, p=0.03) were also associated with time to CKD.
    - Age was a predictor for both UPC >200 and CKD.

## Discussion

- The differences at the start of the Kaplan-Meier survival curves reflect the differences in renal status of each study group at the time the study baseline was defined. This difference likely reflects the impact of a number of contributing factors up to that defined time-point, including ART treatment, presence of any primary renal disease, HIV disease characteristics, concomitant medications, and comorbidities.
- The baseline renal function characteristics of this cohort have some similarities with other HIV cohorts with varying degrees of differences in patient demographics, HAART use, or disease characteristics among the cohorts.
- In our analysis, 8% in the TDF group had Stage 3+ GFR, similar to the nearly 10% of patients with Stage 3+ GFR noted in the CHORUS observational database study of 1298 TDF-treated patients. In the MACS cohort of 2163 men, 4.4% had Stage 3+ GFR, which is comparable to the 5% noted for the non-TDF group in our study. In a CDC analysis by Heflinger et al of 9535 HIV-infected patients in the Adult/Adolescent Spectrum of Disease (ASD) project, 8.5% of patients had Stage 3+ GFR.
- Our analysis indicates a higher % of patients with proteinuria in the TDF group (27%) compared with other HIV cohorts, that did not delineate specific ARVs. The ALLRT cohort of 2827 patients had 20% with proteinuria whereas the MACS cohort of 1800 men with data had 13% with proteinuria.
- This analysis indicates that TDF use was associated with chronic kidney disease as defined using NKF guidelines. Our results appear consistent with a CDC analysis by Heflinger et al who reported that taking a TDF-containing regimen increased the odds of any renal impairment by 60% compared with patients not taking TDF (odds ratio 1.6, 95% CI 1.4-1.7) after controlling for other factors associated with decreased renal function.
- However, our results are in contrast to those reported by Palella et al who did not find any association between ARV use, including TDF, with proteinuria or with GFR declines in his analysis of the MACS cohort.
- Baseline characteristics were generally similar between study groups; however, the non-TDF group had higher median CD4+, greater % of patients with HIV-1 RNA >50 copies/mL, and longer follow-up.
- The better virologic/immunologic responses in the non-TDF group may explain lower UPC values at baseline, consistent with observations reported by Gupta et al.
- Of the 253 subjects in TDF group, 16 (6%) switched by the time of the 6-month visit to the non-TDF group. This may partially explain why we do not see more dramatic worsening in GFR or UPC values in the TDF group because those patients stopped TDF and their data were not included in 6-month and 12-month follow-up visits.

## Limitations

- This analysis did not account for possible primary renal disease that may be present at the start of ART treatment nor the variable follow-up duration prior to analysis baseline, other nephrotoxic drugs, differences in patient demographics, and HIV disease characteristics.
- Adherence to study medications is unknown.
- This analysis included a mixture of ART-naïve and ART-experienced patients, including some on salvage therapies.
- Current study population is predominantly white & further evaluation should be conducted in an ethnically and racially diverse population.

## Conclusions

- In this analysis, TDF use and diabetes in addition to age, were associated with decline in renal function as defined by reduced GFR or proteinuria measured by spot urine protein-to-creatinine ratio.
- Measurement of proteinuria by spot urine protein-to-creatinine ratio may add additional benefit when monitoring renal function in HIV patients.

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