Poster H-383

Comparing Renal Function Declines in Tenofovir and Abacavir Based Regimens in a Predominately African-American Cohort of Men

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Abstract

Background: Tenofovir (TDF) use has been associated with a decrease in calculated glomerular filtration rates (cGFR). Consideration of TDF associated cGFR decline may be especially important in individuals at elevated risk of renal disease such as HIV-infected African-Americans (AA).

Methods: Changes in cGFR were examined in a retrospective study of all HIV-infected men initiating TDF (n=150) or Abacavir (ABC, n=68) therapy since July 2003 at the Baltimore VA Medical Center. Patients on dialysis or with prior TDF or ABC exposure were excluded. Medication history, demographic, and laboratory data were collected from the electronic medical record through September 2006. cGFR was calculated by the simplified modification of diet in renal disease equation (MDRD) at baseline, 6 months, and end of therapy or time of data censure. TDF effects on cGFR were investigated with nonparametric tests of means and regression analysis.

Results: Study subjects were 89% AA race, 28% treatment naïve, and had a mean drug exposure of 16 months. TDF treated patients were younger (mean (SD), 49 (7) vs. 53 (9) years, p<.05) and had higher baseline cGFR (103 (26) vs. 92 (27) mL/min/1.73m2, p<0.01). TDF treated patients experienced a greater cGFR decline at 6 months (11 (19) vs. 2 (16) mL/min/1.73m2, p<.05) and end of treatment (12 (21) vs. 4 (18) mL/min/1.73m2, p=.05). TDF effects remained significant at 6 months (p<.05) and at end of therapy (p= 0.05) after adjustment for age and baseline cGFR in regression models. At the end of therapy 17% of TDF (n=25) and 9 % of ABC (n=6) treated subjects had a cGFR decline >30 mL/min/1.73m2 (p=0.1). Ritonavir treatment did not impact TDF associated cGFR decline (p=.9).

Conclusions: In a predominately AA cohort of men, TDF use was associated with an 8-10% decline in cGFR compared with ABC. This decline occurred in the first 6 months of therapy.

Background

Tenofovir disoproxil fumarate (TDF) was approved by the US Food and Drug Administration in 2001 and is the first nucleotide reverse- transcriptase inhibitor (NRTI) approved for the treatment of HIV disease. TDF is renally excreted via a combination of glomerular filtration and active tubular secretion (1) Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of TDF (2). Dosing interval adjustment of TDF and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min. Potential benefit of TDF therapy should be assessed against the potential risk of renal toxicity. TDF should be avoided with concurrent or recent use of a nephrotoxic agent (2).

Abacavir sulfate (ABC) was approved by the US Food and Drug Administration in 1998 and is a carbocyclic synthetic nucleoside reverse transcriptase inhibitor (NRTI) (3). ABC is primarily metabolized by carboxylation and glucoronidation, with 1% of the parent drug excreted in the urine in subjects with normal renal function (3). Therefore, no dose modifications are recommended in renal failure or with impaired renal function (4,5). To our knowledge, there is only one case report of a reversible Fanconi syndrome associated with abacavir in the published literature (6).

A number of investigators from a variety of cohorts have reported that Tenofovir (TDF) use is associated with a 5 – 19 % decline in calculated glomerular filtration rates (cGFR) (7-12). A significant decrease in cGFR is typically seen by 24 weeks of therapy and deemed to be of minimal clinical significance because of the high baseline cGFR of subjects when they initiated therapy. There is a paucity of data with regard to cGFR in individuals with mild baseline Chronic Kidney Disease (CKD) initiating TDF based regimens. Furthermore, there is little data with regard to cGFR in populations at high risk for CKD and whether duration of treatment is important with regard to populations at high risk for CKD.

Objectives

- **To characterize and compare renal function declines in tenofovir and abacavir based regimens in a predominately African-American cohort of men**
- **To Explore potential predictors for decline in renal function**

Methods

- Changes in cGFR were examined in a retrospective study of all HIV-infected men initiating TDF (n=150) or Abacavir (ABC, n=68) therapy since July 2003 at the Baltimore VA Medical Center.
- Patients on dialysis or with prior TDF or ABC exposure were excluded.
- Medication history, demographic, and laboratory data were collected from the electronic medical record through September 2006. Co-Morbid Conditions are based on ICD-9 diagnoses made by members of the patient care team in the patient's computerized record.
- cGFR was calculated by the simplified modification of diet in renal disease equation (MDRD) at baseline, 6 months, and end of therapy or time of data censure. Analysis is based upon only 3 time points – Baseline, 6 months, and End of Treatment
- TDF effects on cGFR were investigated with nonparametric tests of means and regression analysis.
- Multivariate Logistic Regression was performed comparing change in cGFR from baseline to 6 months and change from baseline to end of treatment to assess potential predictors of change in cGFR

Results

Table 1 Cohort Characteristics

	Tenofovir (n=149)	Abacavir (n = 68)	Total (217)	Comparing TDF to ABC T-test - P Value
Mean Age	49	53	50.6	0.002
Mean Baseline CD4	298	292	296	NS
Mean Baseline CD4 %	16	17	16.3	NS
Mean Baseline HIV RNA	94456	113924	100525	NS
Mean Baseline log HIV RNA	3.73	3.96	3.80	NS
Mean Baseline creatinine	1.02	1.22	1.08	0.014
Mean Baseline cGFR	103	91.3	99.3	0.005
Mean duration of follow-up (months)	16.3	16.7	16.4	NS

Table 2 Cohort Characteristics (continued)

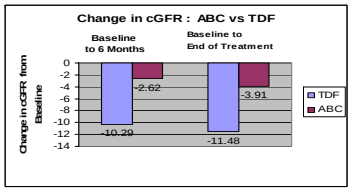
	Tenofovir (n=149)	Abacavir (n = 68)	Total (217)	Comparing TDF to ABC (Chi-Square - P Value)
African American	126 (85%)	65 (96%)	191 (88%)	NS
Treatment naïve	38 (26%)	24 (35%)	62 (29%)	NS
Diabetes	32 (21%)	14 (21%)	46 (21%)	NS
Hypertension	78 (52%)	49 (72%)	127 (59%)	0.006
Hyperlipidemia	38 (26%)	16 (24%)	54 (26%)	NS
Ace-inhibitor use	42 (28%)	33 (49%)	75 (35%)	0.004
Statin use	32 (21%)	19 (28%)	51 (24%)	NS
Ritonavir use (Boosted Pi)	106 (70%)	40 (59%)	146 (67%)	NS
HCV Co-infection	90 (60%)	36 (53%)	126 (58%)	NS

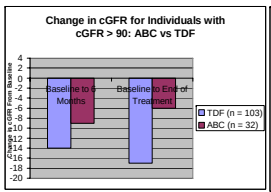
Table 3 cGFR Results

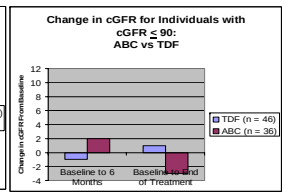
	TDF (n=149)	ABC (n=68)	T – Test or Fisher's Exact Test
Baseline cGFR	103	91.31	P = 0.005
6 month cGFR	92.71	88.69	P = NS
End of Treatment cGFR	91.52	87.40	P = NS
Patients who discontinued TDF or ABC due to decline in cGFR	4 (3%)	0 (0%)	P = NS

Table 4 Subjects Experiencing >30 mL/min/1.73m2 Declines

	Tenofovir (n=149)	Abacavir (n = 68)	Total (217)	Comparing TDF to ABC Fisher's Exact Test
cGFR decline > 30 mL/min/1.73m2 at 6 months	13 (9%)	4 (6%)	17 (8%)	NS
cGFR decline > 30 mL/min/1.73m2 at End of Treatment	25 (17%)	6 (9%)	31 (14%)	NS







Multivariate Regression Model 1
Change in GFR from Baseline to 6 Months

	Beta Coefficient	P – value
TDF	-7.73	0.004
Hyperlipidemia	-6.26	0.029

Multivariate Regression Model 2
Change in GFR from Baseline to End of Treatment

	Beta Coefficient	P – value
TDF	-7.85	0.009
Dbt	-7.88	0.010
Hyperlipidemia	-8.77	0.005
Duration of tx (months)	-0.28	0.027

Potential predictors for changes in GFR from Baseline to 6 months were assessed using Stepwise Regression Analysis. The following potential factors were included in the model: TDF, Dbt, Hyperlipidemia, Duration of treatment, Race, Diagnosis of Hypertension, Ace-inhibitor use, Statin use, HCV co-infection, Treatment experience, or Ritonavir (boosted Pi).

Conclusions

- **Patients prescribed TDF were younger, had lower prevalence of HTN, and had better baseline renal function than patients prescribed ABC**
- **8 – 10% decline in cGFR associated with TDF use compared to ABC**
- **4 /149 (3%) of Patients in the TDF group discontinued therapy due to decreased cGFR while 0/68 (0%) in the ABC group discontinued therapy due to decreased cGFR**
- **Decline due to TDF occurred primarily during the first 6 months of therapy**
- **Decline in cGFR is more pronounced in patients with cGFR > 90**
- **TDF use predicted change in cGFR at 6 months and at End of Treatment. In our cohort, DM and Hyperlipidemia appear to be important predictors of change in cGFR as well.**

Discussion

- **Prospective studies are needed to assess functionality differences in the proximal tubule in the setting of ABC and TDF Therapy.**
- **Genetic predisposition may account for a significant portion of the decrease in cGFR seen in TDF patients.**
- **There is a great need to prospectively collect changes in cGFR in a systematic fashion in the developing world to determine whether the renal risk in diverse populations are similar to renal risks seen in various US cohorts.**
- **Wide spread introduction of TDF in countries with increased rates of CKD and decreased access to hemodialysis warrants appropriate caution.**

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