

## Abstract

**Background:** Recent reports of renal insufficiency associated with the NRTIs have included elevations in serum creatinine, proximal tubular dysfunction, nephrogenic diabetes insipidus, renal failure, Fanconi-like syndrome and death. Monitoring of renal function by GFR has been suggested and the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) has been recommended as an appropriate method for calculating GFR in patients.

**Methods:** GFR was calculated from baseline through study completion using the abbreviated MDRD equation on data from two completed randomized clinical trials of antiretroviral therapy in naïve subjects. The first study, ESS40013, had an induction-maintenance design with subjects induced with Trizivir (TZV) and EFV for 48 weeks. The second study, CNA30024, randomized subjects to either 3TC+ZDV or ABC+3TC both with EFV in a double-blinded design. GFR was categorized according to National Kidney Foundation (NKF) guidelines: Stage 1-2, GFR ≥ 60 mL/min; Stage 3, GFR 30-59 mL/min; Stage 4-5, GFR < 30 mL/min.

GFR and NKF Stage	N(BL)	TZV+EFV	3TC+ZDV+EFV	ABC+3TC+EFV
Mean (SD)		111 (26)	111 (24)	111 (24)
% Stage 1-2		98	>99	99
% Stage 3		2	<1	1
	N(48wks)	309	261	269
Mean (SD)		112 (24)	113 (21)	111 (22)
% Stage 1-2		>99	100	99
% Stage 3		<1	0	1

No Stage 4-5 GFR was observed.

**Conclusions:** These results illustrate that regimens containing ABC, ZDV, 3TC and EFV in various combinations to treat HIV naïve subjects do not appear to adversely affect GFR.

## Introduction

Kidney disease is an important complication of infection with HIV-1. Patients infected with HIV-1 may develop HIV associated nephropathy (HIVAN), membranous nephropathy, membranoproliferative glomerulonephritis, diabetic and hypertensive nephropathy and immune complex glomerulonephritis. In addition some of the antiretroviral agents used for treatment of HIV-1 infection may lead to drug induced nephrotoxicity. Drugs most commonly reported to cause nephrotoxic effects include: indinavir, adefovir and tenofovir disoproxil fumarate.

Recently the HIV Medicine Association of the Infectious Disease Society of America published guidelines for management of chronic kidney disease in HIV infected patients. As part of the guidelines it has been recommended that renal function be followed in patients infected with HIV by monitoring either creatinine clearance which can be calculated by the Cockcroft-Gault equation or by following glomerular filtration rate as calculated by the simplified modification of diet in renal disease equation (MDRD). The simplified MDRD equation lends itself to use in population databases as the parameters in the equation are typically collected and easily retrieved.

This study was conducted to ascertain the GFR of subjects using different reverse transcriptase (NRTI) backbones in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz. GFR was categorized according to National Kidney Foundation (NKF) guidelines.

## Methods

GFR was calculated on retrospective data from two completed clinical trials by using the simplified MDRD equation:

$$\text{GFR (mL/min/1.73mm}^2\text{)} = 186 \times \text{serum creatinine (mg/dL)}^{-1.154} \times [\text{age (years)}]^{-2.03} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]$$

Trial 1: ESS40013 (n=448) – an induction-maintenance trial with all HIV-1 positive, therapy naïve subjects treated with a regimen of Trizivir® BID (TZV) [abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg] + efavirenz (EFV) 600 mg QD for 48 weeks followed by a randomization to either remain on the four drug regimen or switch to a simplified regimen of TZV alone. This analysis only includes assessment of renal function for the 48 week induction period.

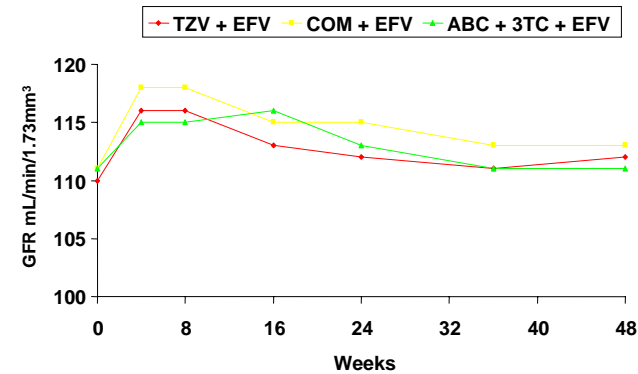
Trial 2: CNA30024 (n=650) – a randomized double-blind trial in therapy naïve HIV-1 infected subjects comparing either Combivir® [lamivudine (3TC) 150 mg/zidovudine (ZDV) 300 mg] or abacavir (ABC) 300 mg + 3TC 150 mg both in combination with EFV 600 mg for 48 weeks.

GFR was calculated for each of the three regimens in the studies by the simplified MDRD equation at baseline and at 48 weeks. GFR was categorized according to NKF guidelines for assessment of chronic kidney disease:

- Stage 1 GFR ≥ 90 mL/min
- Stage 2 GFR 60-89 mL/min
- Stage 3 GFR 30-59 mL/min
- Stage 4 GFR 15-29 mL/min
- Stage 5 GFR < 15 mL/min or dialysis

## Results

Figure 1. Mean Glomerular Filtration Rate



- TZV + EFV arm; n = 448 at baseline and 309 at week 48. At baseline and week 48 mean (±SD) GFR was 111 (26) mL/min and 112 (24) mL/min, median (range) GFR at baseline and week 48 was 109 (33-190) mL/min and 111 (45-236) mL/min.
- COM + EFV arm; n = 326 at baseline and 261 at week 48. At baseline and week 48 mean (±SD) GFR was 111 (24) mL/min and 113 (21) mL/min, median (range) GFR at baseline and week 48 was 109 (48-194) mL/min and 112 (62-203) mL/min.
- ABC + 3TC + EFV arm; n = 324 at baseline and 269 at week 48. At baseline and week 48 mean (±SD) GFR was 111 (24) mL/min and 111 (22) mL/min, median (range) GFR at baseline and week 48 was 109 (50-215) mL/min and 109 (44-214) mL/min.

Figure 2. GFR by NKF Category TZV + EFV

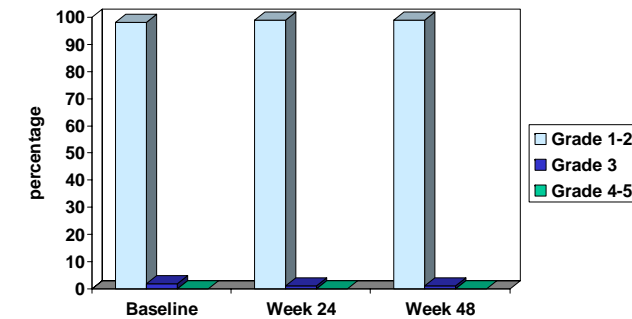


Figure 3. GFR by NKF Category COM + EFV

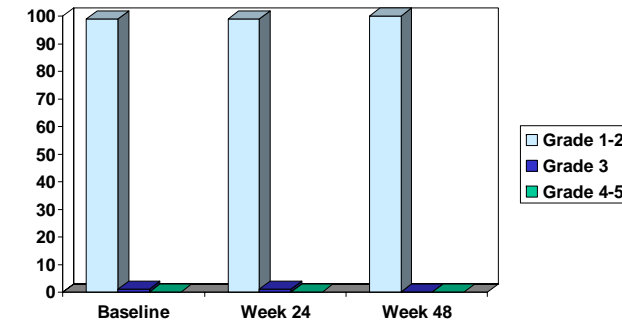
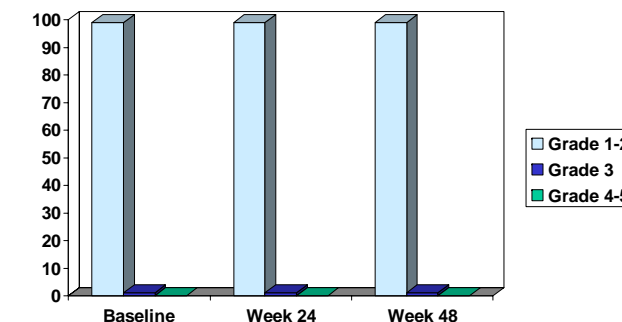


Figure 4. GFR by NKF Category ABC + 3TC + EFV



## Discussion

- Kidney disease is an important complication of infection with HIV. Abnormal kidney function may be present in as many as 30% of HIV infected patients. Causes of kidney disease in patients infected with HIV include HIV associated nephropathy (HIVAN), diabetes, hypertension and drug therapy including some antiretroviral agents.
- Effective antiretroviral therapy has led to a decreased incidence of HIVAN.
- Reports of antiretroviral therapy associated renal disorders have increased over the past few years.
- Antiretrovirals most commonly associated with reports of nephrotoxicity include indinavir, adefovir and tenofovir disoproxil fumarate.
- Glomerular filtration rates should be followed in patients at risk for chronic kidney disease and in those on antiretroviral therapy with higher risk of causing nephrotoxicity. GFR should be routinely monitored in clinical trials of antiretroviral therapy and results which include GFR grouped by NKF category should be reported for regimens in clinical trials.

## Conclusion

- Of 1098 subjects studied in this retrospective analysis of clinical trial data none progressed to NKF stage 4 or 5
- Overall the incidence of NKF stage 3 GFR was very low (≤2%) at baseline and either remained the same or decreased with antiretroviral treatment over 48 weeks
- HIV-1 infected subjects, naïve to therapy, treated over 48 weeks with regimens of efavirenz with either Trizivir®, Combivir® or abacavir + lamivudine did not exhibit clinically significant changes in GFR

## References

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