

Tenofovir use and urinary biomarkers among HIV-infected women in the Women's Interagency HIV Study (WIHS)

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Abstract

Background: Tenofovir (TDF), a nucleotide reverse transcriptase inhibitor, has been associated with renal tubular injury. However, because rises in creatinine lag behind tenofovir-associated kidney dysfunction, biomarkers that signal early tubular injury are needed. Several urinary biomarkers precede creatinine changes in detection of acute kidney injury.

Methods: Three urinary biomarkers of tubular reabsorption impairment and damage - neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and β-2-microglobulin (β2MG) - were measured across three time points in one hundred and thirty two (132) HIV-positive women from the Women's Interagency HIV Study (WIHS). Women initiating HAART containing tenofovir were propensity score matched to women initiating HAART without tenofovir, and women not on HAART.

Results: There were no differences between groups for NGAL or NAG but β2MG was 19 times more likely to be elevated among TDF users at the 3rd time point compared to non-TDF users at the 1st time point (p<0.01). History of proteinuria was associated with higher NGAL (p<0.01). Additional factors associated with elevated NAG were GFR<60 ml/min, history of proteinuria, hepatitis C (p<0.01 for all) and history of diabetes mellitus (p=0.05). Factors associated with increased odds of elevated β2MG were CD4 ≤200 cells/ml, HIV RNA plasma level >100,000 copies/ml, hepatitis C, boosted protease inhibitor (PI) use, and GFR<60 ml/min (p≤0.05 for all).

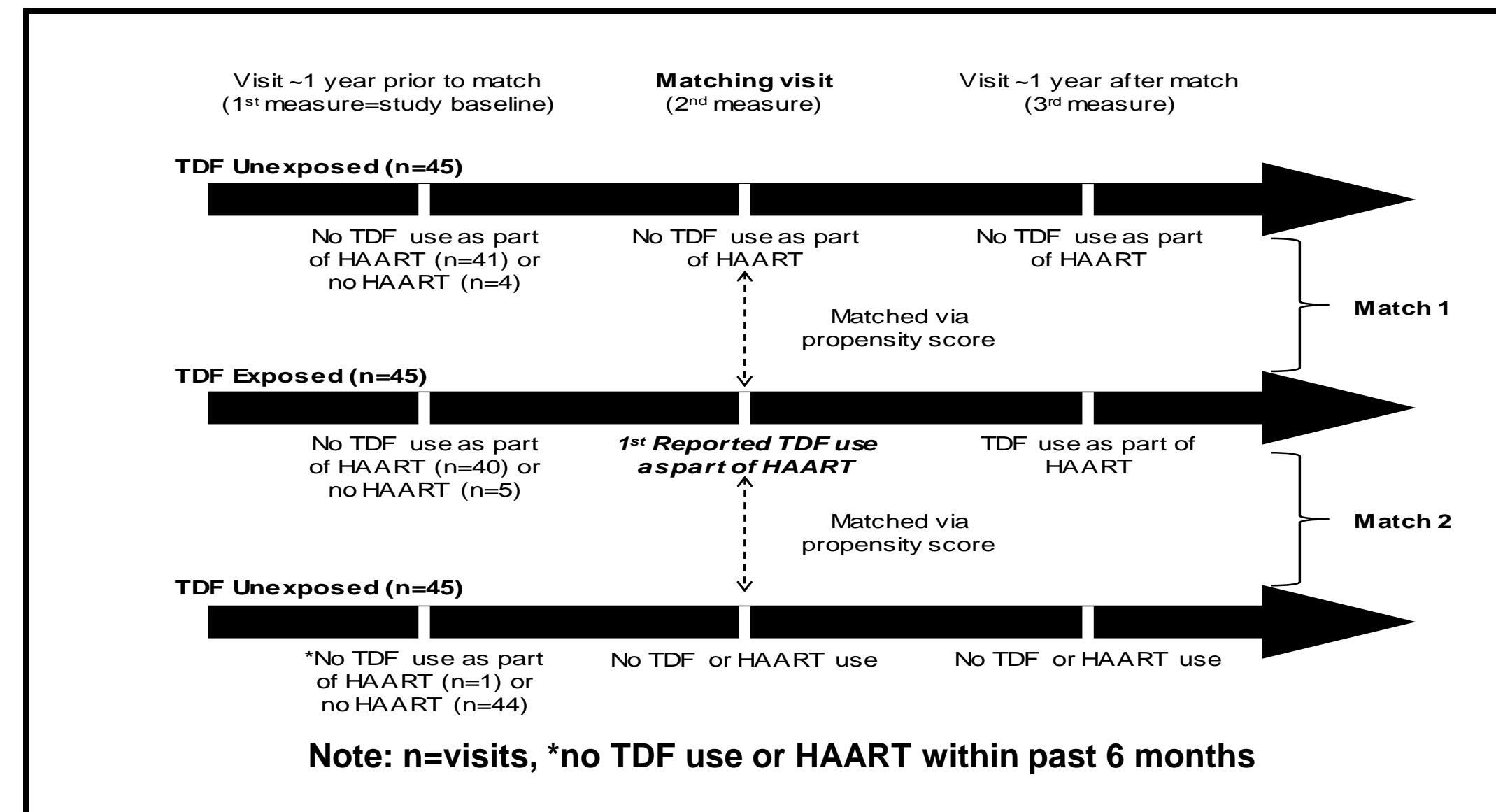
Conclusions: β2MG levels are elevated in women on tenofovir indicating probable early renal dysfunction. Biomarker elevation is additionally associated with baseline chronic kidney disease, uncontrolled viremia, and boosted PI use. Future studies are needed to explore urinary biomarker thresholds and their clinical utility in identifying treated HIV-infected individuals at high risk for renal injury.

Introduction

•Tenofovir (TDF) has been implicated as a source of impaired kidney function in HIV-infected individuals.

•Urine biomarkers, neutrophil gelatinase-associated lipocalin (NGAL), a marker of epithelial injury, N-acetyl-β-D-glucosaminidase (NAG), a proximal tubule lysosomal enzyme whose presence in the urine suggests proximal tubular damage, and β-2-microglobulin (β2MG) a low molecular weight protein, catabolized by the proximal tubules, provide an earlier indication of renal impairment

Methods



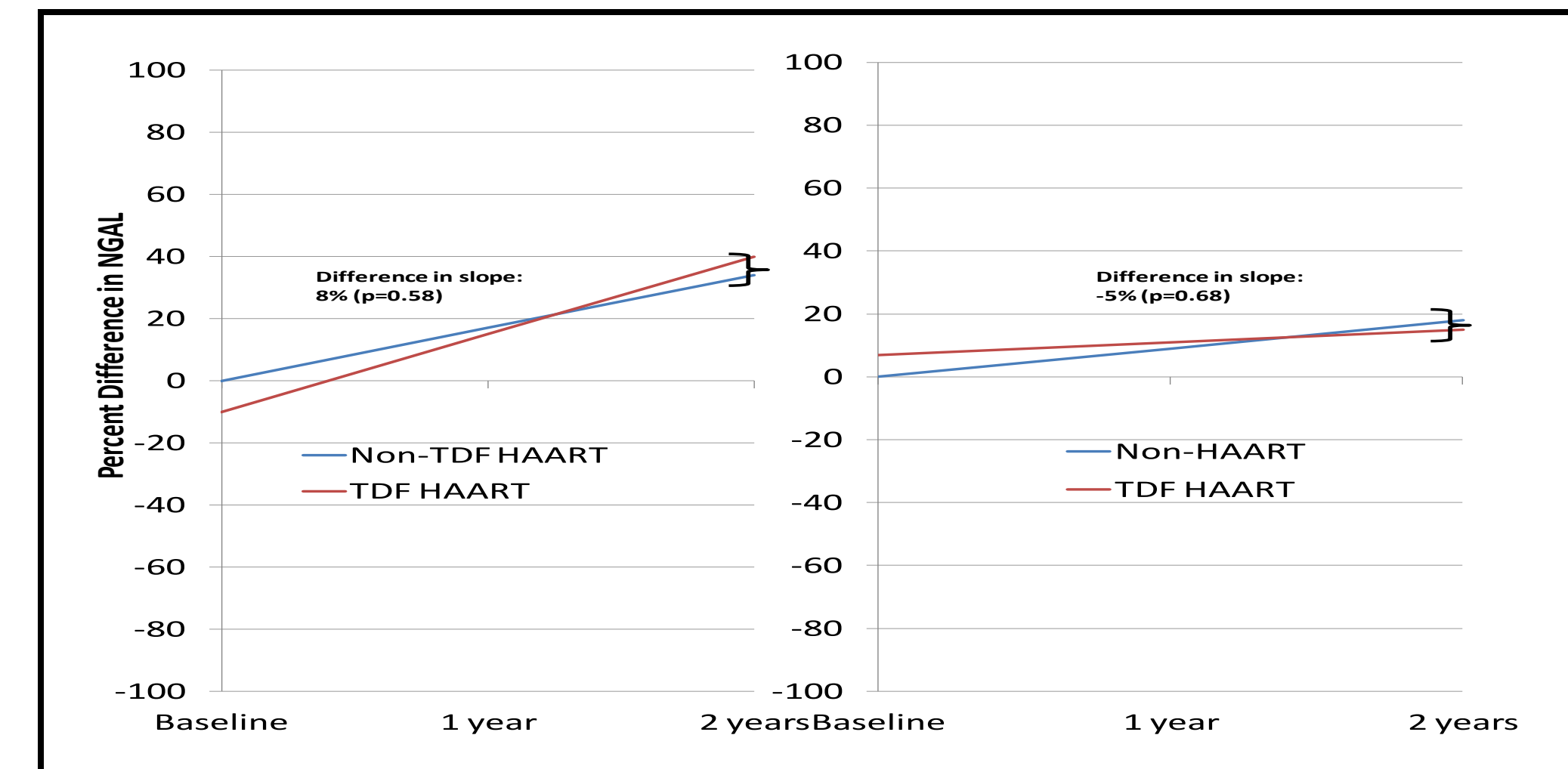
Results

Characteristics at study baseline

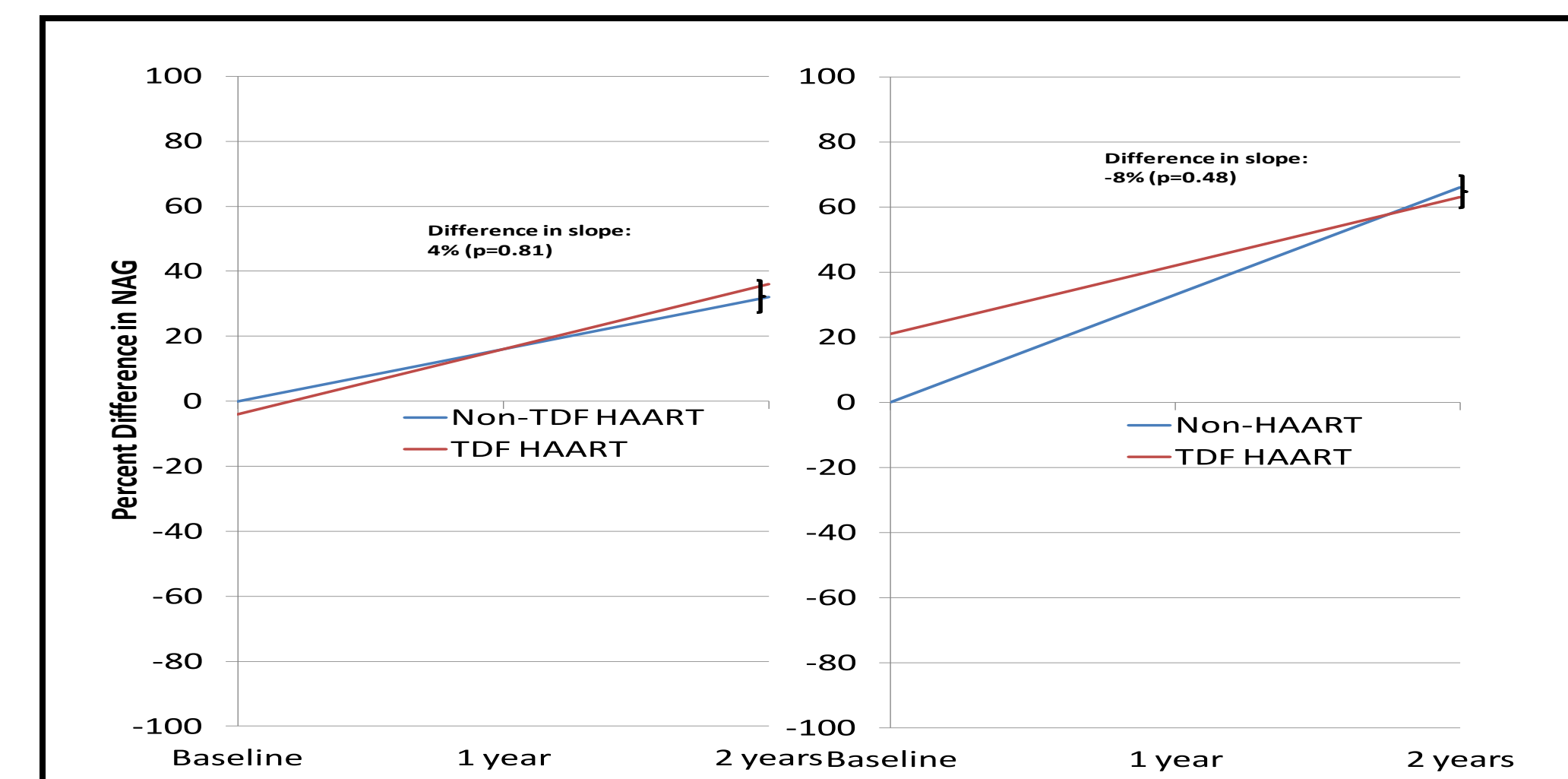
	TDF HAART n=45	Non-TDF HAART n=45	Non-HAART n=43
Characteristic	% or Med (IQR)	% or Med (IQR)	% or Med (IQR)
Age	42 (39-47)	40 (36-45)	41 (37-47)
African-American	49	60	53
CKD-EPI-estimated GFR	98 (86-114)	91 (78-114)	103 (82-112)
<60	4	4	2
Hx Proteinuria	18	14	16
HCV Ab+ @ BL	38	40	22
Hx DM	11	16	4
SBP≥140 or DBP≥90	13	7	22
CD4	411 (292-587)	324 (237-579)	465 (315-581)
<200	18	18	11
200-500	49	47	44
>500	33	33	40
HIV RNA (copies/ml)			
<500	31†	62†	36
500-5,000	27	13	36
5,000-50,000	24	18	22
>50,000	18	4	7
Years since HAART initiation	4.0 (2.9-5.0)	4.5 (3.6-5.0)	N/A
Boosted PI use	22	29	N/A

†p-values<0.05

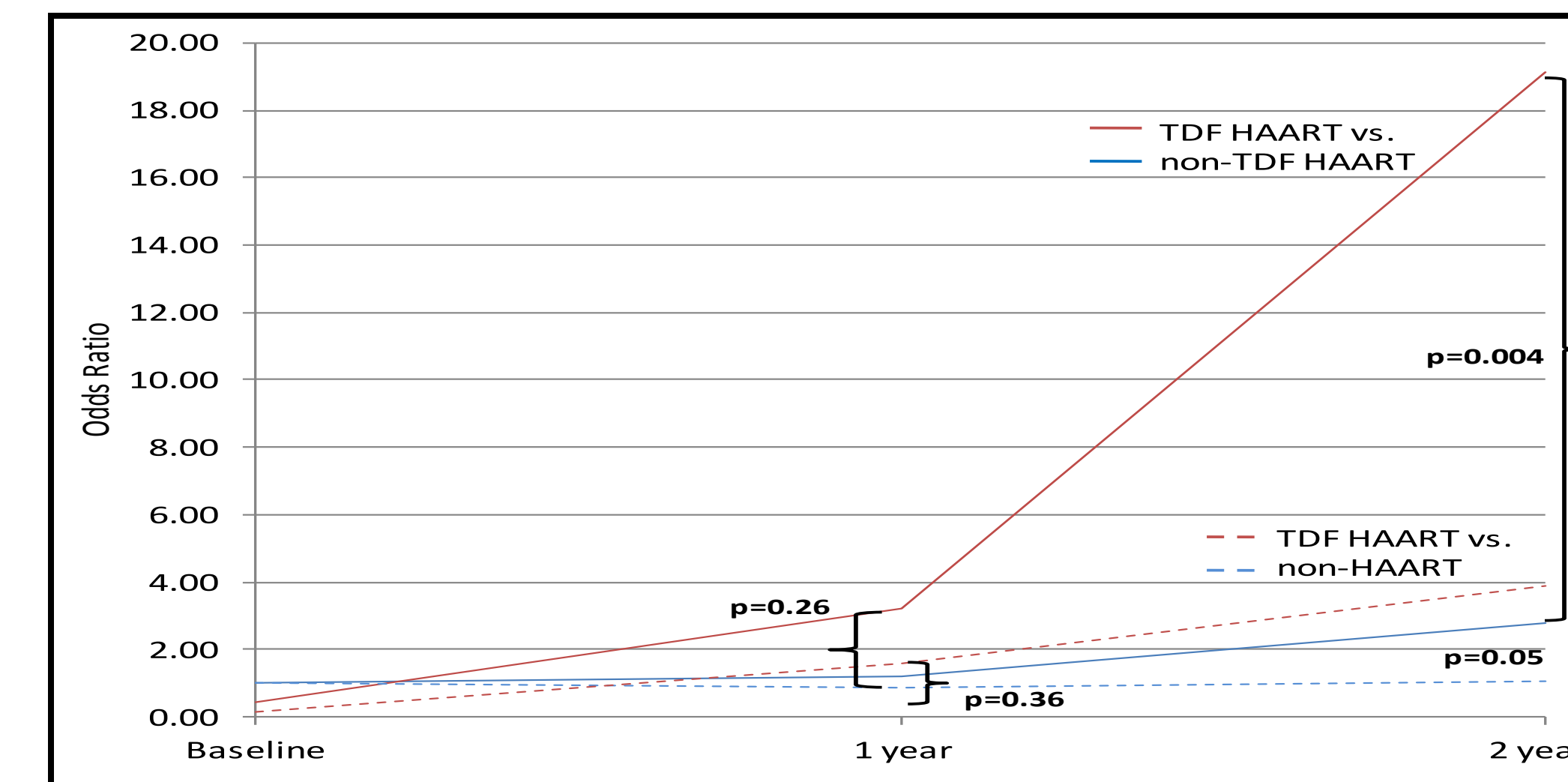
NGAL level change



NAG level change



β2MG level change



Factors associated with β2MG

Factor	Controls: Non-TDF HAART users		Controls: Non-HAART users	
	OR	95% CI	OR	95% CI
History of proteinuria	2.36	(0.6,9.34)	1.76	(0.44,7.12)
Hepatitis C antibody positive at WIHS baseline	9.33	(2.81,31.01)†	5.83	(1.84,18.47)†
History of diabetes mellitus	1.21	(0.34,4.31)	0.73	(0.17,3.23)
Estimated GFR<60	5.67	(1.48,21.69)†	9.96	(1.32,75.06)†
High blood pressure (systolic>140 or diastolic >90)	1.51	(0.52,4.4)	1.65	(0.64,4.24)
Current smoker	0.27	(0.08,0.92) †	0.41	(0.13,1.35)
Obese (>30)	0.54	(0.16,1.76)	0.22	(0.06,0.87)†
CD4 cell count ≤200 cell/mm ³	2.58	(0.68,9.74)	8.99	(2.91,27.82)†
HIV-1 viral load >100,000 copies/ml	23.89	(2.89,197.87)†	1.39	(0.28,6.82)
Years since HAART initiation	0.62	(0.39,0.99)*	N/A	
Boosted PI use	8.97	(3.56,22.59)†		

†p-values <0.05, * p-values=0.05, other p-values >0.05

Summary

- NGAL and NAG levels did not differ across treatment groups.
- β2MG levels were elevated in women on TDF.
- Advanced immunosuppression, uncontrolled viremia, and boosted PI use were associated with elevated β2MG .
- Chronic Kidney Disease is also associated with elevated β2MG.

Acknowledgement

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