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Renal and Metabolic Safety of Initial HIV-1 Therapy in Resource-limited Settings

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Abstract

BACKGROUND: Convenient dosing, potency, and low toxicity profile support use of tenofovir disoproxil fumarate (TDF) as preferred nucleotide reverse transcriptase inhibitor (NRTI) in combination regimens for HIV-1 treatment. However, renal and metabolic safety of TDF compared to other NRTI has not been well described in resource-limited settings.
METHODOLOGY: Secondary analysis within the ACTG A5175/PEARLS trial, examining the renal and metabolic safety outcomes between participants randomized to zidovudine/lamivudine plus efavirenz (ZDV/3TC + EFV) and TDF/emtricitabine plus EFV treatment arms. Adverse event analysis included occurrence of renal abnormalities, and renal and metabolic serious non-AIDS defining events (SNADEs) during study follow up. Logistic regression explored associations between baseline covariates and renal abnormality. Wilcoxon tests compared serum creatinine with urine dipsticks, and response profile longitudinal analysis compared creatinine clearance (CrCl) levels over time between NRTI groups.
RESULTS: Twenty-one of 1045 participants developed renal abnormalities through 192 weeks of follow-up; 15 (71%) were in TDF arm (p=0.08). Age ≥ 41 years (OR=3.35, 95% CI: 1.1 – 13.1), history of diabetes (OR: 10.7, 95% CI: 2.1-55), and a lower baseline CrCl (OR: 3.1 per 25 ml/min lower, 95% CI: 1.7-5.8) were each significantly associated with development of renal abnormality. Renal SNADEs occurred in 42 participants (19 in ZDV arm and 23 in TDF arm), the majority (79%) were urinary tract infections. Renal failure was recorded in 4/42 patients and only one event was attributed to TDF use. Serum creatinine levels did not significantly differ by summary urine dipstick results (normal versus abnormal) at any time point. Significantly lower CrCl values were maintained in patients receiving TDF compared to ZDV (medians ranging from 98 vs. 106 ml/min at 24 weeks; p < 0.001, to 103 vs. 106 ml/min at 96 weeks; p=0.06; repeated measures analysis over time p=0.05), however worsening CrCl from baseline was not observed with TDF exposure. Serious metabolic diagnoses were rare, but significantly higher in the ZDV arm compared to the TDF arm (20 vs. 3 ; p< 0.001).
CONCLUSIONS: TDF was not associated with a significantly higher risk of renal abnormalities or serious renal events compared to ZDV in this randomized, multinational study. Laboratory monitoring of TDF nephrotoxicity in resource limited settings could be reserved for older individuals, with history of diabetes and lower baseline CrCl.

Background

- Early antiretroviral therapy effectively prevents HIV transmission and improves survival related to non-AIDS defining diseases.[1]
- Based on efficacy, low toxicity and convenient dosing Tenofovir disoproxil fumarate (TDF) has been upgraded to the preferred 1st line nucleotide reverse transcriptase inhibitor (NRTI) in rich and poor-resource settings, leaving zidovudine (ZDV) as alternative.[2, 3]
- Data from middle and low-income countries supporting the superiority of TDF compared to ZDV are limited.
- Mitochondrial toxicity leading to metabolic abnormalities has been linked to long term NRTI use, whereas kidney injury and potential bone toxicity has been associated particularly with TDF use.[4, 5, 7, 8]
- We evaluate the occurrence of metabolic and renal adverse events associated with ZDV and TDF based regimens among participants of the A5175 trial.

Methods

- Secondary analysis focusing on the renal and metabolic safety outcomes among participants randomized only to ZDV/3TC + EFV and TDF/FTC + EFV treatment arms within A5175/PEARLS.[6]
- Clinical and laboratory evaluations were scheduled at screening, study entry, weeks 2, 4, 8, 12, 16, 20, 24, and then every 8 weeks until closeout visits. Urine dipstick was recorded every 24 weeks.
- Adverse event outcomes included:

Renal Abnormalities
- **Serum creatinine ≥ 1.9 mg/dl** (Grade 3 or 4 serum DAIDS) **OR**
- **Calculated creatinine clearance (CrCl) by Crockcoft-Gault < 50 ml/min.**

Renal serious non-AIDS defining events (SNADEs)
- Nephrolithiasis, proximal renal tubular dysfunction, HIV nephropathy, drug-induced nephropathy, **AND**
- Renal insufficiency/failure, acute renal insufficiency, cystitis/urinary tract infection, calculus of ureter, hydronephrosis, pyelonephritis, renal cyst, unspecified urethral and urethritis (if approved by blinded central medical review)

Metabolic SNADEs
- Diabetes/glucose intolerance, diabetic ketoacidosis, lipoatrophy/fat loss, fat accumulation, hypogonadism, pancreatitis, lactic acidosis, **AND** thyroid disease (if approved by blinded central medical review)

- Logistic regression modeling explored the association between baseline covariates and renal abnormality outcome.
- Comparisons of distributions of serum creatinine between normal versus abnormal urine dipstick (protein ≥ 2+ or glucose ≥ 1+ results used Wilcoxon Rank-Sum tests.
- Response profile repeated measures compared changes in CrCl over time by randomized treatment group.

Results

- From a total of 1571 recruited individuals, 1045 HIV were randomized to the EFV-containing arms; 519 participants to **arm A: ZDV/3TC + EFV** and 526 to arm **C: TDF/FTC + EFV**.
- Baseline clinical and demographic characteristics were comparable in both treatment arms as expected by randomization. Follow up was completed in 84% of arm A participants and in 80.5% of arm C with median follow-up of 184 wks.
- 21 participants developed a renal abnormality during study follow up (10 with grade 3 or 4 serum creatinine and 16 with CrCl < 50ml/min; 71% belonged to the TDF arm (p=0.08).
- Persons with renal abnormality post-baseline were significantly older and started with a lower CrCl (median 77 ml/min) compared to those that did not develop renal abnormality (median 99 ml/min).
- Logistic regression analysis demonstrated that older age, a 25 ml/min lower baseline CrCl and a history of diabetes were associated with higher odds of developing a renal abnormality (Table 1).

Table 1. Logistic Regression Analysis: Association between pre-treatment covariates and Renal Abnormality during Follow up (N=21).

Variable	Univariate analysis OR (95% CI)	P value
Age (vs. < 29 years)		0.008
29 – < 34 years	0.97 (0.2 – 4.6)	
34 – < 41 years	0.81 (0.2 – 3.8)	
≥ 41 years	3.35 (1.1 – 13.1)	
Assigned treatment arm (C vs. A)[1]	2.51 (0.91 – 8)	0.08
Body mass index (kg/m^2)	0.94 (0.84 – 1.05)	0.25
Country (versus USA)		0.072
Brazil	0.45 (0.04 – 5)	
Haiti	1.03 (0.09 – 11.6)	
India	2.1 (0.4 – 11)	
Malawi	3.97 (0.83 – 19)	
Peru	NONE***	
South Africa	0.5 (0.04 – 5.5)	
Thailand	1.05 (0.09 – 11.7)	
Plasma HIV-1 viral load (log_{10} copies/ml)	1.68 (0.79 – 3.57)	0.15
CD4 cell count (per 50 cells/uL)	1 (0.99 – 1)	0.46
Creatinine clearance by CG (per 25 ml/min lower)	3.1 (1.7 – 5.8)	< 0.001
History of hypertension (n=2)	1.05 (0.03 – 6.9)	0.93
History of diabetes (n=2)	10.7 (2.1 – 55)	0.045
History of AIDS event (n=5)	2.7 (0.95 – 57.4)	0.13
History of tuberculosis (n=6)	1.8 (0.57 – 5.0)	0.25
Significant urine dipstick[2] (n=2)	3.0 (0.32 – 13.5)	0.17

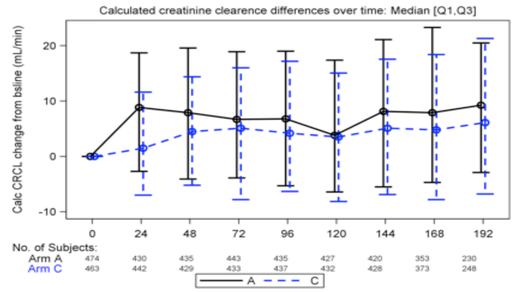
[1]Assigned treatment arm A: ZDV/3TC + EFV; arm C: TDF/FTC + EFV
[2]Urine dipstick positive for protein (≥ 2+) or glucose (≥ 1+); 3 missing values.
**** No estimate – Peru had no events; model excluding 86 participants from Peru resulted in very similar odds ratios.*

- 42 incident renal SNADEs were recorded (19 in ZDV/3TC + EFV arm vs. 23 in TDF/FTC + EFV arm). Urinary tract infections was the most common diagnoses (79%).
- Rates of urine dipstick protein were comparable between both treatment arms and no significant association was found between serum creatinine and abnormal urine dipstick at any time point.
- Incident metabolic SNADEs were rare occurring in 23 participants (20 in ZDV/3TC + EFV arm vs. 3 in TDF/FTC + EFV arm). Lipoatrophy was the most common diagnosis in this category, seen mostly in women after the second year of treatment.

Results

- Significantly lower CrCl values were maintained in treatment arm C compared to arm A (medians at 24 wks = 98 vs.106 ml/min, p < 0.001; medians at 96 wks = 103 vs. 106 ml/min, p=0.06; repeated measures analysis p=0.05). However, the CrCl over time did not decline from baseline in any treatment arm (Figure 1).

Figure 1. Changes in CrCl over time compared to baseline by treatment arm.



Conclusions

- Our analysis suggest that TDF associated renal toxicity in resource limited settings is low and not significantly higher to ZDV-based regimen, whereas metabolic safety of TDF is superior to ZDV and stavudine.
- Laboratory monitoring for TDF renal toxicity in resource-limited areas could be reserved for older individuals (age > 40 yrs), or with history of diabetes or with relatively lower baseline CrCl.
- Lower CrCl values observed in TDF-based treatment arm over time were of small magnitude and are likely related to a lower baseline CrCl in this group. TDF exposure was not associated with worsening CrCl over time compared to baseline.
- The study is limited by the small number of renal abnormalities as a result of prescreening eligibility criteria.

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