29th ECCMID
Amsterdam, Netherlands
13 – 16 April 2019
The congress of ESCMID

O1194 Inosine-5′-triphosphatase activity is associated with TDF-associated nephrotoxicity in HIV

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Background: Nucleotide reverse transcriptase inhibitors play a pivotal role in HIV-treatment. The enzyme Inosine 5′-triphosphatase (ITPase) is involved in the nucleotide metabolism and has been associated with adverse drug events. We studied the association between ITPase-activity and tenofovir disoproxil fumarate (TDF)-associated nephrotoxicity.

Materials/methods: Single center 1:2 case control cohort study, including suppressed HIV-infected patients with (cases) and without (controls) TDF-associated nephrotoxicity. 26 cases (eGFR-decline >25% and/or ≥2 proximal tubular dysfunction (PTD)-markers during TDF use) were matched to 55 controls. ITPase-activity and *ITPA* genotype were measured in all patients. The primary endpoint was the proportion of patients with normal ITPase-activity (≥4 mmol IMP/mml Hb/hour) in cases versus controls. The eGFR-improvement 48 weeks after TDF-cessation was measured in cases. McNemar's test, conditional logistic regression, and paired T-tests were used.

Results: The eGFR in cases and controls at TDF-discontinuation was 78 and 85 ml/min. 19/26 cases (73.1%) versus 28/55 controls (50.9%) had normal ITPase activity, p=0.001 (OR 2.55, 95% CI 0.89-7.31, p=0.08). 23/26 cases (88.5%) versus 40/55 controls (72.7%) had wt/wt *ITPA* genotype, p=0.26 (OR 2.59, 95% CI 0.70-9.54, p=0.15). After TDF-cessation, the eGFR increased in cases with normal ITPase activity (-5.5 to +4.4 ml/min/year, p=0.008), but remained stable in cases with reduced activity (-4.3 to -4.0, p=0.97). In cases with wt/wt *ITPA* genotype, eGFR increased from –5.0 to +3.0 ml/min/year, p=0.021. 13/16 cases with PTD had normal ITPase activity. Of cases with available data, 50% with normal activity had PTD-recovery after TDF-cessation.

Conclusions: Normal ITPase-activity is associated with nephrotoxicity during TDF use and recovery after TDF-cessation. ITPase-activity might function as a screening-tool for probable occurrence and reversibility of TDF-toxicity.