Elevated Tenofovir Exposure via Intensive Pharmacokinetic Monitoring is Associated with Progressive Kidney Function Decline

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BACKGROUND

- Tenofovir disoproxil fumarate (TDF) is commonly used in HIV treatment and prevention.
- Acute toxicity is of concern, but longitudinal use of TDF is associated with decline in kidney function over time.
- Factors associated with elevated TFV blood levels are not well known[1,2], and drug concentration monitoring for tenofovir (TFV)-associated kidney disease is rarely performed.
- We hypothesized that greater TFV blood levels would be associated with reduced eGFR and faster eGFR decline in HIV-infected women.
- We performed 24 intensive pharmacokinetic (PK) evaluations of TDF in a cohort of HIV-infected women and evaluated the relationship between areas-under-the-time-concentration curves (AUC) with serially measured renal function over the succeeding 7 years.

MATERIALS AND METHODS

- **Study population:** The Women's Interagency HIV Study (WIHS) is a multicenter, prospective cohort of HIV-infected women and at-risk HIV uninfected women in the US; this substudy included 105 women on TDF-based ART for at least six months prior to intensive PK sampling.
- **Intensive PK protocol methods:** Plasma drawn over 24 hours for TFV concentration under conditions of real use at 0, 4, 8, 15, 18 and 24 hours after witnessed dosing.
- **Laboratory procedures:** Plasma levels of TFV determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS); validated from 10 to 1000 ng/mL of TFV.
- **Predictor**: Individual areas-under-the-time-concentration-curves (AUCs) from intensive PK studies of TDF over 24-hour dosing interval calculated by trapezoidal rule.
- **Covariates (baseline):** Age, race, body mass index (kg/m^2), diabetes, hypertension, ritonavir use (yes/no), prior TDF duration, CD4 cell count (log-transformed) & detectable viral load (yes/no).
- **Outcome:** CKD-EPI equation to estimate glomerular filtration rate using serum creatinine (eGFRcr) as change in ml/min/1·73m^2 per year over 7 years.
- **Statistical analysis:** Smoothed curves from **kernel density estimates,** compare TFV AUC tertiles with **multivariable linear mixed effect models** (tertile 1 as the reference category).

RESULTS

Figure 1. Higher Baseline TFV AUC is Associated with Reduced eGFRcr (mL/min/1.73 m^2) at Baseline in Women Living with HIV.

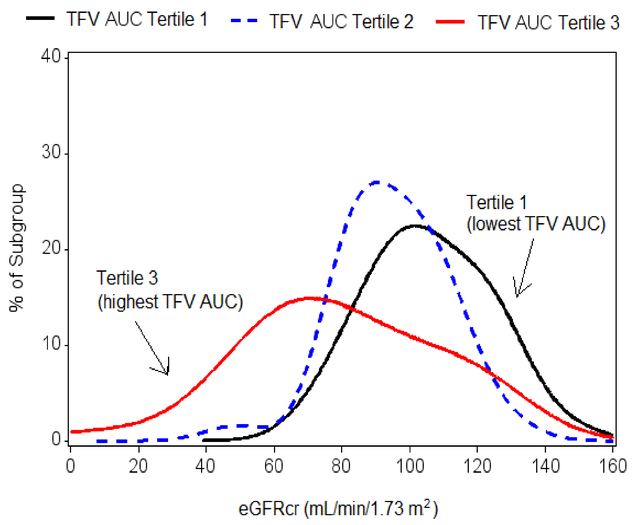
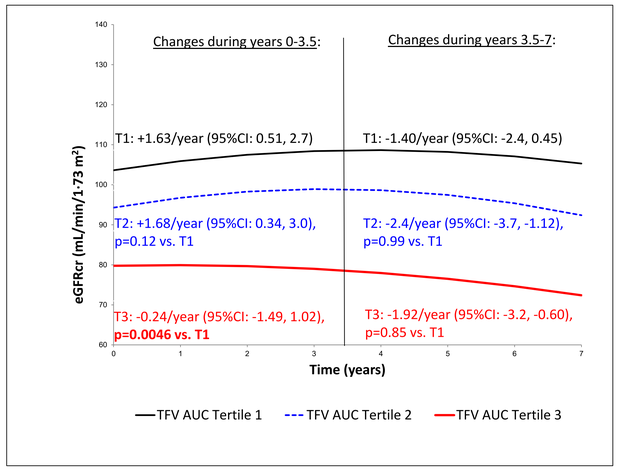
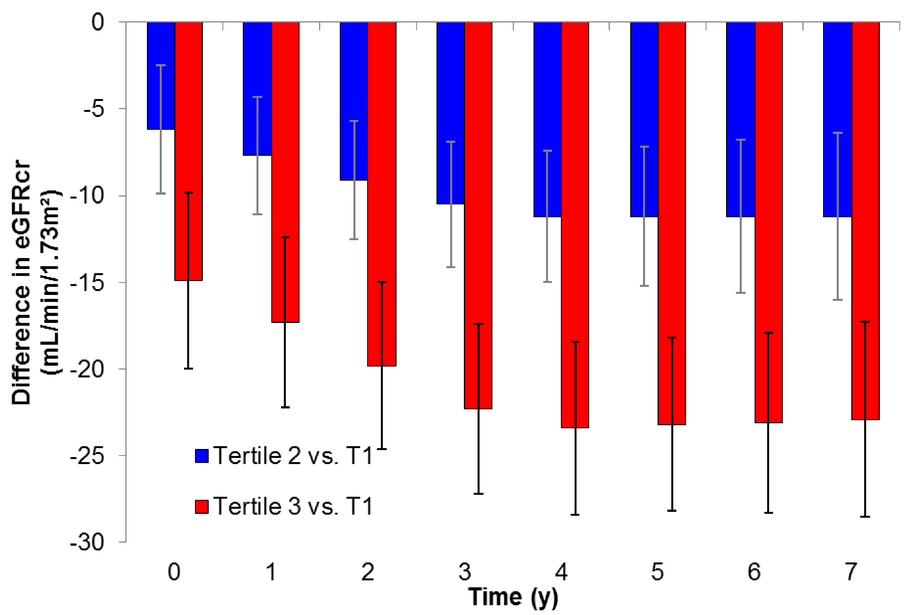


Figure 2. Higher baseline TFV AUC associated with lower eGFR (mL/min/1.73 m^2) over 7 years of follow-up



p-values compare eGFR change in tertiles 2 and 3 to tertile 1 (reference), from multivariable linear mixed models adjusted for age, race, body mass index, diabetes mellitus, hypertension, ritonavir use, duration of prior tenofovir exposure, CD4 cell count and HIV viral load.

Figure 3. Higher baseline TFV AUC is associated with sustained reductions in eGFR (mL/min/1.73 m^2) over 7 years of follow-up.



- Median age by TFV AUC tertile (IQR): 41 years (31-47) for T1, 42 years (34, 49) for T2 and 47 years (44, 51) for T3
- TFV AUC range in ng*h/mL: T1: 1031-2640, T2: 2646-3922 and T3: 4009-13911

CONCLUSION

- Higher tenofovir exposure (as measured in intensive PK studies) is strongly associated with decline in kidney function over time in a real-life cohort of HIV-infected women.
- Differences in eGFR trajectories were most pronounced in the initial follow-up period and higher baseline TFV AUC was associated with worse eGFR levels and changes, even after controlling for traditional and HIV-related characteristics.
- Assessing tenofovir drug exposure in HIV prevention and treatment settings may be important in predicting and potentially averting nephrotoxicity on tenofovir-based regimens.

REFERENCES

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