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Association of tenofovir level and discontinuation due to impaired renal function

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Background

Tenofovir (TFV) preparations are nucleotide reverse transcriptase inhibitors with highly anti-retroviral activity used as first-line treatment in HIV-1-infected patients. Long term TFV treatment, however, is associated with a risk of renal impairment[1)], especially cellular damage in renal tubules. Plasma trough concentrations of TFV are high in patients with renal impairment[2)], but the mechanism by which high trough concentration of TFV following its long-term administration affects renal function has not been clarified.

Patients & Methods

Participants

A regimen including TFV disoproxil fumarate (TDF) was administered to 136 HIV-1-infected patients aged ≥18 years treated at the National Hospital Organization Osaka National Hospital. The association between trough concentrations of TFV and discontinuation of its administration due to renal function-related adverse events within 288 weeks after the start of therapy was measured. This study was reviewed and approved by the institutional review board of the National Hospital Organization Osaka National Hospital (approval number: 13058).

TFV plasma trough concentrations

Blood samples were collected at 20–28 hours after its administration within 3 months after starting treatment. Plasma TFV concentration was measured by high-performance liquid chromatography.

Demographics of participants(Table)

	Discontinuation	Continuation	*p*
Participants (n, %)	34(25%)	102(75%)	
Age (years)	44 [39–57]	37 [33–44]	0.0032
Males (n, %)	34 (100%)	101 (99%)	0.26
Body weight (kg)	58 [63–69]	67 [59–74]	0.39
CD4 cell count (cells/μL)	252 [134–370]	271 [135–351]	0.93
Serum Creatinine(mg/dL)	0.79 [0.62–0.87]	0.71 [0.63–0.79]	0.30
Esitimated glomerular filtration rate [3)] (mL/min)	90.4 [77.3–109.7]	102.1 [87.9–112.9]	0.027
Participants with HIV-1-RNA level <50 at time of sampling (n, %)	2 (5%)	13 (13%)	0.22
AIDS(n, %)	16 (47%)	37 (36%)	0.18
HBV infection (n, %)	1(3%)	19(19%)	0.017
HCV infection (n, %)	1 (3%)	4(4%)	0.63
Treatment naïve(n, %)	31(91%)	99(97%)	0.16
Use of antiretroviral agents (n, %)			
Atazanavir/ritonavir	14 (41%)	36 (35%)	0.34
Lopinavir/ritonavir	8 (24%)	22 (22%)	0.49
Darunavir or Fosamprenavir/ritonavir	10(29%)	31(30%)	0.55
Raltegravir	2 (6%)	11(11%)	0.32
Efavirenz	0(0%)	2(2%)	0.56

IQR, interquartile range — Median [IQR]

Results

- TDF was discontinued due to renal function-related adverse events in 34 patients (25%), and the median time to discontinuation was 967 days (range: 183–1986 days).
- The median trough TFV concentration was significantly higher in discontinued than in continued patients (87.5 vs 73.0 ng/mL; p = 0.0033, Fig.1).
- Trough concentrations of TFV did not correlate with time to TDF discontinuation (p = 0.29, Fig.2).
- Trough TFV concentration was significantly correlated with TDF discontinuation due to renal function-related adverse events (p = 0.0022, Fig.4).
- Construction of a receiver operating characteristic (ROC) curve showed that the cut-off value of trough TFV concentration at TDF discontinuation was 98 ng/mL (area under the curve [AUC], 0.668; sensitivity, 0.471; specificity, 0.833).

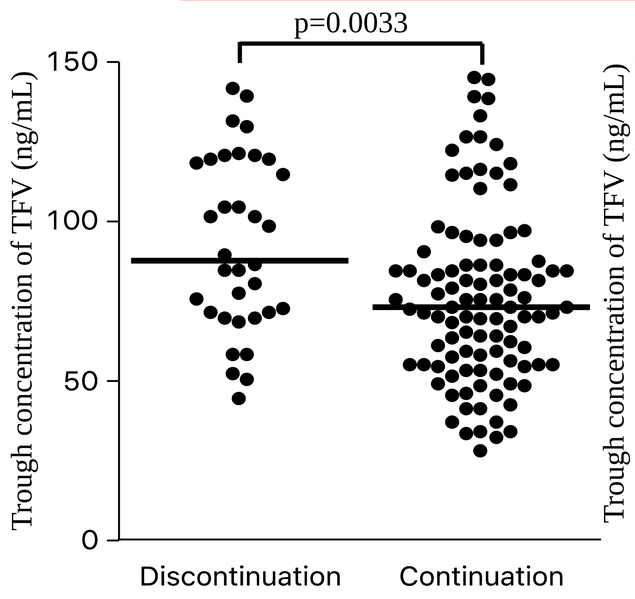

Fig.1 Comparison of Tenofovir plasma-trough concentrations and discontinuation due to impaired renal function

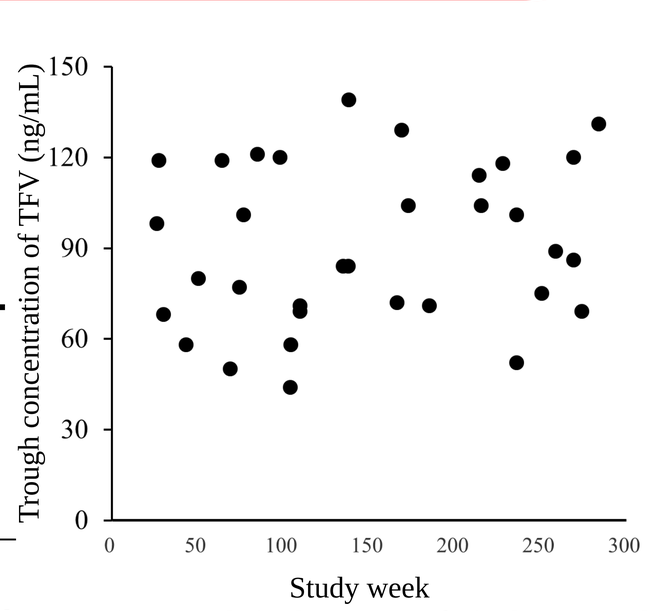

Fig.2 Correlation between tenofovir plasma trough concentration and TDF administration period in discontinuation patients

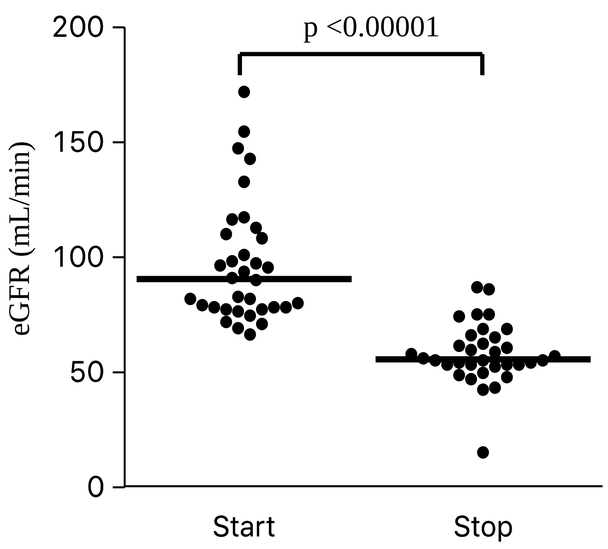

Fig.3 Change in estimate glomerular filtration rate at the start and stop of discontinuation patients

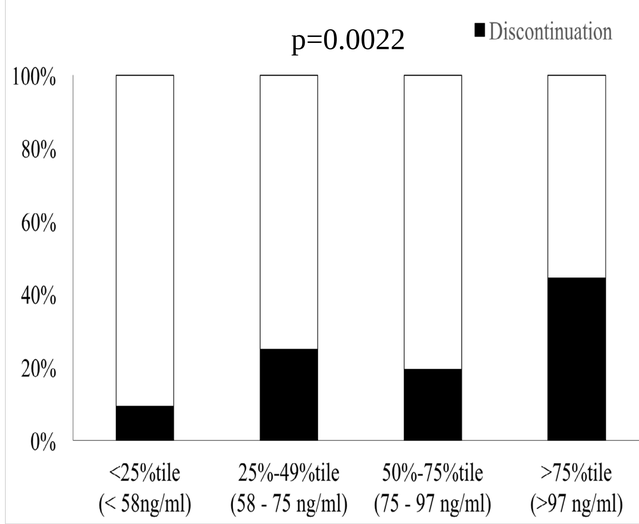

Fig.4 Association between trough Tenofovir concentration and discontnuation of TDF. P value by Cochran-Armitage test is shown

Conclusions

Discontinuation of long-term TDF administration due to renal function-related adverse events is associated with high trough TFV concentrations in Japanese patients infected with HIV-1.

This implied the importance of early after administration TFV concentration measurement for the risk assessment of renal dysfunction in long-term administration.

References

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3) Matsuo S, et al. Am J Kidney Dis, 2009;53:982-992