

## No change in calculated creatinine clearance after tenofovir initiation among Thai patients

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**Objectives:** Thai patients have a lower average body weight than patients from western Europe or the USA. Tenofovir is largely prescribed at the standard dosage of 300 mg once daily; therefore, the per kilogram dose is higher in Thailand than in the USA. We asked the question whether this higher per kilogram dose was associated with more nephrotoxicity.

**Methods:** Thai patients from the Staccato trial were treated with tenofovir/lamivudine combined with ritonavir-boosted saquinavir. Creatinine values were measured before the start of tenofovir and then every 12 weeks. Renal function was assessed using the Cockcroft–Gault formula and the MDRD formula. To compare CL<sub>CR</sub> before and after tenofovir, the *t*-paired or Wilcoxon signed rank tests were used. One-way analysis of variance and Spearman's correlation coefficient were used to study CL<sub>CR</sub> longitudinally.

**Results:** CL<sub>CR</sub> remained stable after a median of 21 weeks on tenofovir (difference of +1.06 mL/min; 95% CI –2.7–4.8, *P* = 0.58), even among patients with underlying diseases. The mean CL<sub>CR</sub> remained stable across time (*P* = 0.17).

**Conclusions:** We did not find renal dysfunction on tenofovir among Thai patients included in the Staccato trial. Tenofovir could be safely prescribed at a standard dosage of 300 mg once daily in the Thai population.

Keywords: antivirals, HIV/AIDS, safety, tolerance, nucleotide analogues, combination treatment, toxicity

### Introduction

Tenofovir disoproxil fumarate (Viread®; Gilead Sciences), a nucleotide reverse transcriptase inhibitor, has demonstrated an excellent safety profile in several controlled clinical trials<sup>1</sup> evaluating its use for the treatment of HIV infection in previously untreated patients. However, rare cases of nephrotoxicity have been reported, especially in patients with a past history of renal complications or other risk factors for the development of renal disease.<sup>2</sup> Small reductions in estimated CL<sub>CR</sub> without clinical sequelae have been reported in some studies,<sup>3–5</sup> but not in others.<sup>6,7</sup> The safety and efficacy of tenofovir disoproxil fumarate have not been

evaluated in Asian patients. A previous study showed that saquinavir concentration was significantly higher in Thai patients compared with UK patients, perhaps due to their lower body weight (BW) and genetic factors.<sup>8</sup> Here we evaluated the impact of standard tenofovir disoproxil fumarate therapy on renal function among Thai patients treated within the Staccato trial.<sup>9</sup>

### Methods

Staccato is a randomized trial of intermittent versus continuous antiretroviral treatment (HAART) in Thailand, Switzerland and

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**Unchanged renal function with tenofovir**

**Table 1.** Demographic characteristics in both subgroups

Variables	Before–after group <i>n</i> = 143	After-only group <i>n</i> = 121	<i>P</i> value
Female gender (%)	87 (60.8)	66 (54.5)	0.30
Mean age in years at tenofovir initiation (SD)	35.2 (± 7.2)	35.8 (± 6.9)	0.58
Route of infection (%)			0.001
heterosexual intercourse	129 (90.2)	92 (76.0)	
homo- or bisexual intercourse	5 (3.5)	22 (18.2)	
iv drug injection or blood products	1 (0.7)	2 (1.7)	
unknown	8 (5.6)	5 (4.1)	
Mean BW before tenofovir in kg (SD)	57.6 (± 9.8)	—	—
Mean BW after tenofovir in kg (SD)	57.7 (± 10.1)	57.2 (± 11.3)	0.73
CDC staging at baseline (%)			0.49
A	78 (54.5)	73 (60.3)	
B	49 (34.3)	37 (30.6)	
C	11 (7.7)	6 (4.9)	
Treatment-naïve status (%)	99 (69.2)	69 (57.0)	0.03
Mean time on tenofovir in weeks (SD)	27.6 (± 17.5)	27.1 (± 15.1)	0.77
Mean CD4 count before treatment (SD)	263.5 (± 95)	235.0 (± 109)	0.015
Patients with underlying disease (%)			
chronic hepatitis B	6 (4.2)	9 (7.4)	0.26
chronic hepatitis C	4 (2.8)	3 (2.5)	0.67
both chronic hepatitis B and C	1 (0.7)	0	0.99
diabetes mellitus	1 (0.7)	2 (1.7)	0.40
high blood pressure	4 (2.8)	1 (0.8)	0.23
diabetes mellitus and high blood pressure	0	1 (0.8)	0.99
STI/continuous treatment ratio	87/54 <sup>a</sup>	65/52	0.32

BW, body weight; STI, scheduled treatment interruption.

<sup>a</sup>Two non-randomized.

Australia.<sup>9</sup> Patients with CD4 >350 cells/mm<sup>3</sup> and viral load (VL) <50 copies/mL were randomized 1:2 to either continuous HAART or scheduled treatment interruptions (STIs) (with treatment stops as long as CD4 counts exceeded 350 cells/mm<sup>3</sup>). During Staccato, Thai patients received ritonavir-boosted saquinavir; in addition, stavudine/didanosine was administered early during the trial and then switched to tenofovir/lamivudine in 2003. CL<sub>CR</sub> was used as a proxy of glomerular filtration ratio and was calculated using the Cockcroft–Gault formula and the Levey modification of diet in renal disease formula (MDRD).<sup>8</sup> Creatinine values (in mg/dL), BW (in kg) and age were available before tenofovir and then measured every 12 weeks after. In the ‘before–after group’, we compared CL<sub>CR</sub> before and after tenofovir using *t*-paired tests ( $\alpha = 5\%$ ) or the Wilcoxon signed rank test, when appropriate. Some patients only had creatinine values after tenofovir (‘after-only group’) and were thus compared with those in the before period using Student’s *t*-test for independent samples ( $\alpha = 5\%$ ). Finally, in order to study CL<sub>CR</sub> distribution longitudinally, we restricted our analyses to patients from the continuous treatment arm with several creatinine values (77.1% had at least three creatinine values after tenofovir initiation) after 12–84 weeks on tenofovir (*n* = 109) and used Spearman’s correlation coefficient. We compared the mean CL<sub>CR</sub> between different time periods (12–36, 36–60, 60–84 and 84–108 weeks) using one-way analysis of variance and tested the effect of gender on CL<sub>CR</sub> over time using two-way analysis of variance.

The Staccato protocol has been accepted by the local Ethics Committees from the different participating centres, and written informed consent was obtained from each participant. The Staccato study is registered at ClinicalTrials.gov with the identifier NCT00113126.

**Results**

One hundred and forty-three patients were included in the before–after group and 121 patients in the after-only group. The mean BW at baseline in Thai patients was significantly lower than that in Swiss and Australian patients (57.1 ± 10.4 versus 70.2 ± 12.1 kg,  $P < 10^{-3}$ ) (in women: mean weight 52.4 ± 7.7 kg and in men: 63.5 ± 10.3 kg). Patient characteristics are presented in Table 1.

In the before–after group, 11.2% of patients were antiretroviral-naïve at tenofovir initiation, whereas the others were receiving stavudine/didanosine/ritonavir-boosted saquinavir. The mean creatinine at baseline was 0.92 ± 0.36 mg/dL; it was 0.87 ± 0.23 mg/dL after a median of 21.4 weeks on tenofovir [interquartile range (IQR) 15–36.3] ( $P = 0.04$ ). After tenofovir, the mean CL<sub>CR</sub> was 89.5 mL/min ( $\Delta +1.06$  mL/min, 95% confidence interval –2.71 to +4.83, *t*-paired test  $P = 0.58$ ). Among patients with underlying disease (*n* = 15 with chronic hepatitis B/C, high blood pressure or diabetes), the mean CL<sub>CR</sub> remained stable (92.0 ± 24.9 mL/min before versus 87.5 ± 18.9 mL/min after tenofovir, Wilcoxon signed ranks test  $P = 0.30$ ). Four patients with baseline CL<sub>CR</sub> <50 mL/min did not worsen their renal function and even tended to improve it, after a median of 23.4 weeks on tenofovir (IQR 14.7–51.7) (median of 34.1 mL/min, IQR 23.5–40.9, before and 60.6 mL/min, IQR 31.1–79.2, after tenofovir,  $P = 0.15$ ).

Demographical and infection-related characteristics were similar in both subgroups, which allow us to compare them (Table 1). In the after-only group, tenofovir was used for a median of 23.4 weeks (IQR 16–36). The mean creatinine was

$0.91 \pm 0.17$  mg/dL, not statistically different from creatinine values before tenofovir in the before–after group ( $P = 0.79$ ). The mean  $CL_{CR}$  was also not statistically different at  $83.8 \pm 21.5$  mL/min ( $P = 0.13$ ).

Using the MDRD formula in the before–after group, we found a mean  $CL_{CR}$  of  $91.2 \pm 28.8$  mL/min before tenofovir and  $92.8 \pm 21.6$  mL/min after tenofovir, which were not significantly different (*t*-paired test  $P = 0.46$ ). In patients with underlying conditions ( $n = 15$ ), the mean MDRD did not change between both periods ( $92.3 \pm 24.9$  mL/min before tenofovir and  $88.2 \pm 16.3$  mL/min after tenofovir  $P = 0.40$ ). In the after-only group, the mean  $CL_{CR}$  using the MDRD formula was  $87.7 \pm 17.2$  mL/min and was also not significantly different from the  $CL_{CR}$  before tenofovir in the before–after group ( $P = 0.23$ ).

In a subset of 109 continuous arm patients with creatinine values on tenofovir at different time points (from 12 to 108 weeks), there was no correlation between  $CL_{CR}$  and time spent on tenofovir (Spearman's  $\rho = 0.064$ ,  $P = 0.18$ ). The mean  $CL_{CR}$  remained stable across time ( $P = 0.17$  in ANOVA). We found an interaction between gender and time spent on tenofovir, with a significantly lower  $CL_{CR}$  after 36 weeks on tenofovir in women ( $CL_{CR}$   $94.5 \pm 25.5$  mL/min in men and  $80.3 \pm 19.3$  mL/min in women), which tended to disappear after 60 weeks on tenofovir ( $92.3 \pm 25.1$  and  $84.5 \pm 18.7$  mL/min in the 60–84 week period and  $83.6 \pm 16.2$  and  $77.1 \pm 21.2$  mL/min in the 84–108 week period, in men and women, respectively). No patient discontinued Staccato because of renal adverse events.

## Discussion

We did not find renal dysfunction on tenofovir among Thai patients included in the Staccato trial.  $CL_{CR}$  remained stable when time spent on tenofovir increased. The transient dip in  $CL_{CR}$ , observed only at 36 weeks, and only in women, may be a statistical artefact due to multiple measurements, without clinical significance, as  $CL_{CR}$  at tenofovir initiation was significantly higher among women. Nonetheless, this transient dip could also be real in light of some other observational data, suggesting an initial drop in  $CL_{CR}$  on tenofovir, which does not progress with time.<sup>5,10,11</sup> We postulated that due to a lower BW on average, Thai patients should have a higher exposure to tenofovir and might be more likely to develop nephrotoxicity on the standard 300 mg daily dose. However, tenofovir disoproxil fumarate was well tolerated, and significant renal toxicity was not observed.

Our study had some limitations, including its retrospective nature, the lack of a control group and incomplete data on creatinine values at tenofovir initiation. We did not consider the relative short follow-up time of patients as a limitation. Most of the published works had shown early changes in renal function on tenofovir.<sup>10,11</sup> In addition, in the primary analysis, estimates of  $CL_R$  were made using the Cockcroft–Gault formula. The MDRD formula is considered by some to be more accurate, as the Cockcroft–Gault formula may overestimate renal function by as much as 16%,<sup>8</sup> but others considered that both formulas lacked precision.<sup>12</sup> Moreover, MDRD has not been validated in HIV-infected patients with normal renal function, but it was developed as an estimate of glomerular filtration ratio in patients with impaired renal function. The additional analyses using the MDRD formula showed consistent results using both estimations of glomerular filtration ratio.<sup>10</sup> Finally, our results might differ

from those of other observational studies due to the specificity of our study population, which was younger, with a higher CD4 count, mostly treatment-naïve, with a normal renal function at baseline and the absence of underlying diseases.<sup>9</sup>

In conclusion, Thai patients from our study treated with a tenofovir-containing regimen were safely treated at the 300 mg once daily standard dosage, despite their lower weight.

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