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A clinical prediction tool for targeted pre-antiretroviral therapy creatinine testing applied to the TREAT Asia HIV Observational Database cohort

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We read with interest the recent letter by van Griensven and colleagues published in the 1st April, 2014 edition of *JAIDS*.¹ Using routinely collected, cross-sectional data from HIV-infected patients attending the Sihanouk Hospital Center of HOPE, Phnom Penh, Cambodia the authors generated a clinical prediction tool (CPT) for targeted creatinine testing during pre-antiretroviral therapy (ART) evaluation. Such a tool may prevent superfluous renal function assessment prior to initiating the nephrotoxic antiretroviral, tenofovir. This will become increasingly important in coming years given the World Health Organisation's (WHO's) recommendation of tenofovir in first-line ART^{2,3} and expanding global use of tenofovir.⁴⁻⁷

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Details on the generation of the CPT can be found in van Griensven *et al*¹ and elsewhere.⁸⁻¹¹ The primary outcome was kidney dysfunction (KD) at pre-ART evaluation, defined as an estimated creatinine clearance <50mL/min based on the Cockcroft-Gault equation. The WHO recommends tenofovir avoidance or dose reduction at this level of renal impairment.^{2,3} A risk prediction score that included age, body weight and haemoglobin, hereafter referred to as the primary CPT, achieved an area under the ROC (AUROC) of 0.81 (95%CI 0.76 to 0.86) in their validation dataset. The probability of KD ranged from 1.0% in those with a score of 0 to 51.2% in those with a score of 5. With the cutoff score set at 2, sensitivity was 91.5%, specificity was 54.7%, and creatinine testing would have been avoided in 50.5% of patients. Replacing body weight with BMI, hereafter referred to as the BMI CPT, achieved an AUROC of 0.77 (95%CI 0.72 to 0.83) however sensitivities and specificities were not described. With an alternative risk prediction score including age, body weight, sex, and WHO stage, hereafter referred to as the alternate CPT, AUROC was 0.81 (95%CI 0.76 to 0.85). With a cutoff score of 2, sensitivity was 95.8%, specificity was 40.7%, and creatinine testing would have been avoided in 37.4% of patients.

We sought to provide further validation of van Griensven's CPT by evaluating its performance in the TREAT Asia HIV Observational Database (TAHOD) cohort. TAHOD and the TREAT Asia Studies to Evaluate Resistance-Monitoring (TASER-M) have been described previously.^{12, 13} Briefly, TAHOD is an observational study of patients with HIV involving 21 adult treatment centres in 12 countries and territories of varying income levels in Asia, which aims to assess HIV disease natural history in treated and untreated patients in the region. Retrospective and prospective data is collected at each site. Recruitment started in September 2003. TASER-M was a multi-centre, cohort study monitoring development of HIV drug resistance in patients taking ART. Patients eligible for first- or second-line ART initiation were enrolled sequentially. Data on previous antiretroviral use was collected retrospectively. Patient recruitment commenced in March 2007 and ceased in 2011. Follow-up data continues to be collected as TASER-M was merged with TAHOD in 2012. Currently, each TAHOD site has contributed data from 100-450 patients. Data is transferred to the data management centre at the Kirby Institute, Sydney, Australia twice annually in March and September.

For this analysis, we used data from the September 2013 TAHOD transfer and included patients started on ART that had creatinine, body weight and haemoglobin data recorded at the time of treatment initiation. A window period of 6 months before ART was allowed for creatinine and haemoglobin levels. The window period for body weight was within 3 months either side of ART initiation. Patients with any history of a WHO stage III/IV illness leading up to the date of ART start were considered to be in WHO stage III/IV. Those with no such history were categorised as WHO stage I/II. BMI was calculated for those patients with height data available.

Of 7993 patients with a record of ART use, 3200 (40.0%) had sufficient data available for inclusion in this analysis. The majority (68.5%) were male. Patients were receiving ART in Thailand (23.1%), Vietnam (12.5%), Malaysia (12.1%), Cambodia (11.7%), Hong Kong (11.5%), India (7.9%), Indonesia (7.6%), Singapore (3.7%), Taiwan (3.5%), China (3.0%), Japan (1.7%), Philippines (0.9%), and South Korea (0.9%). Median age was 35.8 years

[interquartile range (IQR) 30.6 to 42.3], median CD4 cell count was 115 cells/mm³ [IQR 38 to 217], median body weight was 55 kg [IQR 48.5 to 63.3], and median haemoglobin was 12.2 g/dL [IQR 10.9 to 13.8]. Height data was available for 2965 (92.7%) patients. KD, as defined by van Griensven *et al*¹ (creatinine clearance <50mL/min based on the Cockcroft-Gault equation), was documented in 141 (4.4%) patients. Table 1 shows the performance of all three abovementioned CPT versions when applied to the TAHOD cohort. For the primary CPT, an AUROC of 0.81 (95%CI 0.77 to 0.84) was achieved. The probability of KD ranged from 0.8% in those with a score of 0 to 50.0% in those with a score of 5. With the cutoff score set at 2, sensitivity was 85.1%, specificity was 59.3%, and creatinine testing would have been avoided in 57.3% of patients. For the BMI CPT, the AUROC was 0.80 (95%CI 0.76 to 0.84). When the cutoff score was 2, sensitivity was 87.6%, specificity was 54.4%, and creatinine testing would have been avoided in 52.6% of patients. Applying the alternate CPT, AUROC was 0.79 (95%CI 0.76 to 0.83). With the cutoff score at 2, sensitivity was 86.5%, specificity was 56.0%, and creatinine testing would have been avoided in 54.1% of patients. We also examined the alternate CPT with weight substituted for BMI. This yielded an AUROC of 0.79 (95%CI 0.76 to 0.83). With a cutoff score of 2, sensitivity was 88.4% and specificity was 50.2%.

We have shown that the utility of the CPT described by van Griensven *et al*¹ extends beyond the Cambodian clinic within which it was developed. Opinion on the most suitable of the CPT versions evaluated will vary with the perceived importance of various factors. We believe it is crucial to minimise the number of patients with pre-existing KD treated with tenofovir whilst avoiding unnecessary creatinine testing if possible. Therefore, a test with high sensitivity that does not substantially compromise specificity is most appropriate. Our results indicate the primary CPT had the highest sensitivity when the specificity threshold was arbitrarily set at >50% (sensitivity 90.8%, specificity 52.9% with cutoff score at 1). A cutoff score of 2 for the primary CPT also performed well in the TAHOD cohort (sensitivity 85.1%, specificity 59.3%) and was the pick of the CPTs in van Griensven's validation cohort (sensitivity 91.5%, specificity 54.7%). Nevertheless, since the aim of the CPT is to avert unnecessary creatinine testing, the primary CPT, which requires a blood test result (haemoglobin), may not be entirely logical. The alternate CPT only needs basic patient data and a medical history. With a cutoff score of 2, it performed reasonably well in our independent validation. Sensitivity was 86.5% and specificity was 56.0%, which translates to 54.1% of patients avoiding creatinine testing during their pre-ART evaluation and 13.5% of patients with KD being considered fit to initiate tenofovir. We believe this may be a clinically acceptable tool, however future investigation will need to confirm its cost-effectiveness. Serum creatinine testing is not particularly expensive in Asia (approximately \$US3 per test at one TAHOD centre in Thailand) whilst the cost of managing a patient with chronic renal failure may be substantial.

Using data from a large, multicentre cohort of HIV-infected patients in Asia, we have provided supportive evidence for a CPT that could limit unnecessary renal function testing prior to tenofovir initiation. Further validation and cost-effectiveness analysis is required and will need to consider the savings achievable with this tool as tenofovir use expands. Optimising resources is of the utmost importance to the sustained global scale-up of ART.

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Table 1
External validation of a clinical prediction tool to detect kidney dysfunction

CPT	AUROC (95%CI)	Score	N (%)	N (%) test avoided	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Primary (n=3200)	0.81 (0.77 to 0.84)	1	1569 (49.0%)	1631 (51.0%)	90.8%	52.9%	8.2%	99.2%	1.93	0.17
		2	1365 (42.7%)	1835 (57.3%)	85.1%	59.3%	8.8%	98.9%	2.09	0.25
		3	319 (10.0%)	2881 (90.0%)	49.7%	91.9%	21.9%	97.5%	6.10	0.55
		4	121 (3.8%)	3079 (96.2%)	30.5%	97.5%	35.5%	96.8%	11.96	0.71
BMI (n=2965)	0.80 (0.76 to 0.84)	1	1569 (52.9%)	1396 (47.1%)	91.5%	48.8%	7.5%	99.2%	1.79	0.17
		2	1406 (47.4%)	1559 (52.6%)	87.6%	54.4%	8.0%	99.0%	1.92	0.23
		3	361 (12.2%)	2604 (87.8%)	53.5%	89.7%	19.1%	97.7%	5.19	0.52
		4	154 (5.2%)	2811 (94.8%)	30.2%	95.9%	25.3%	96.8%	7.45	0.73
Alternate (n=3200)	0.79 (0.76 to 0.83)	1	2478 (77.4%)	722 (22.6%)	95.7%	23.4%	5.5%	99.2%	1.25	0.18
		2	1469 (45.9%)	1731 (54.1%)	86.5%	56.0%	8.3%	98.9%	1.97	0.24
		3	915 (28.6%)	2285 (71.4%)	72.3%	73.4%	11.2%	98.3%	2.72	0.38
		4	280 (8.8%)	2920 (91.3%)	40.4%	92.7%	20.4%	97.1%	5.55	0.64

CPT: clinical prediction tool, AUROC: area under the ROC, 95%CI: 95% confidence interval, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio; +: positive; -: negative. All CPT versions were defined by van Griensven *et al.*¹ The primary CPT included three items: age (score +2 if >40 years), body weight (score +1 if <10 g/dL). The BMI CPT included three items: age (score +2 if >40 years), BMI (score +2 if <18 kg/m²) and haemoglobin (score +1 if <10 g/dL). The alternate CPT included four items: age (score +2 if >40 years), body weight (score +2 if <45 kg), sex (score +1 if female), and WHO stage (score +1 if WHO stage III/IV).