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A Clinical Prediction Score for Targeted Creatinine Testing Before Initiating Tenofovir-Based Antiretroviral Treatment in Cambodia

To the Editors:

INTRODUCTION

Following World Health Organization (WHO) recommendations, many antiretroviral treatment (ART) programs are currently scaling up the use of tenofovir-based first line ART.[1] However, tenofovir can potentially be nephrotoxic, and chronic kidney disease has been found to be prevalent in HIV-infected individuals in many regions and settings, including Asia.[2,3] WHO recommends that tenofovir should be dose reduced or avoided in case of decreased kidney function defined as an estimated creatinine clearance of <50 mL/min, based on the Cockroft–Gault (CG) formula.[1] Evaluation of kidney function before and during ART is thus indicated.

The 2013 revised WHO guideline recommends targeted creatinine testing before initiation of tenofovir.[4] In contrast with routine creatinine testing, targeted testing in those with a higher probability of kidney dysfunction (KD) has the potential to save precious resources while still identifying those at risk with a high yield. Although the 2013 WHO guidelines put forward several risk factors for KD, practical guidance on how to use these and how to target testing is lacking. However, such approach should be explicit and evidence based, simple and easy to apply in the field. Clinical prediction tools (CPTs) are increasingly used for such purposes. CPTs are decision-making tools for clinicians, often relying on basic readily available clinical information.[5] Among adults undergoing pre-ART evaluation in an ART program in Cambodia, we developed a CPT for targeted creatinine testing.

METHODS

Study Design and Population

We conducted a cross-sectional evaluation using routinely collected clinical data between 2003 and 2011 in the Sihanouk Hospital Center of Hope, Phnom Penh, Cambodia. As previously reported, this nongovernmental hospital provides free ART since 2003, as part of the national program.[6–9] All ARV-naive adult patients undergoing creatinine testing as part of their pre-ART evaluation were included. Those with missing body weight were excluded because this precluded the calculation of the CG equation.

HIV Care Delivery and Antiretroviral Treatment

All newly unrolled patients underwent clinical staging and CD4 cell count determination (FACSCount; Becton Dickinson, Franklin Lakes, NJ). ART-eligibility criteria followed WHO and national guidelines. Over the study period, preferential first line treatment was stavudine based. However, tenofovir-based first line ART will be implemented nationally before the end of 2013. Before ART initiation, a set of baseline laboratory tests were performed, including hematology, liver function tests, hepatitis B surface antigen, hepatitis C serology, CD4 cell count determination, and serum creatinine measurement (using Jaffe's kinetic assay on a HITACHI 704 analyzer with Human reagents).

Data Collection and Statistical Analysis

Since the launch of the ART program, clinical and laboratory data were prospectively recorded using standardized data collection tools and electronically stored, with regular quality control by the data management team. All patients enrolling in the program were requested to give written informed consent to store and use the data.

The main outcome was KD, defined as an estimated creatinine clearance—based on the CG equation—of <50 mL/min. The methodology for the development of the clinical prediction score has been reported before. In brief, we used the Spiegelhalter and Knill-Jones method adapted by Berkley et al.[9–12] The potential predictors considered were age, baseline body weight, baseline hemoglobin, WHO clinical stage, gender, baseline CD4 cell count, hepatitis B, and hepatitis C coinfection. Continuous variables were dichotomized based on the receiver operating curves (ROCs), with the optimal cutoff at the point that maximized the sum of sensitivity and specificity. Cutoff values were rounded to obtain values that are easy to use in clinical practice. Crude likelihood ratios (LHRs) were calculated for all variables and those with a LHR ≥2 or ≤0.5 were selected for inclusion in the score building. To adjust for correlations between predictors, LHR were adjusted using multivariate logistic regression. Variables conditionally associated with KD with a LHR ≥1.5 or ≤0.67 were retained. To develop the scoring system, the predictor score for each predictor was obtained by calculating the natural logarithm of the adjusted LHR and rounding this result to the nearest integer. For simplification, the score was recoded by

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TABLE 1. Predictors and Associated LHRs for Factors Used to Develop a Scoring System to Detect Kidney Dysfunction (N = 2192; Derivation Data Set)

	n/N (%)	Crude LHR*	Adjusted LHR	Original Score†	Final Score
Age, yrs‡					
>40	131/592 (22.1)	2.66	3.08	+1	+2
≤40	80/1600 (5.0)	0.49	0.45	−1	0
Body weight, kg‡					
<45	146/692 (21.1)	2.51	2.47	+1	+2
≥45	65/1500 (4.3)	0.43	0.43	−1	0
Hemoglobin, g/dL‡					
<10	109/558 (19.5)	2.28	1.75	+1	+1
≥10	101/1626 (6.2)	0.62	0.73	0	0
WHO stage‡					
III/IV	190/1727 (11.0)	1.16	—	—	—
I/II	21/465 (4.5)	0.45	—	—	—
Gender					
Female	157/1141 (13.8)	1.5	—	—	—
Male	54/1051 (5.1)	0.51	—	—	—
CD4 count, cells/μL					
<150	145/1292 (11.2)	1.22	—	—	—
≥150	52/814 (6.4)	0.66	—	—	—
Hepatitis B/C (+)					
Yes	29/331 (8.8)	0.92	—	—	—
No	182/1861 (9.8)	1.01	—	—	—

*Data shown are positive (if predictor is present) and negative (if predictor is absent) LHR.

†The score was calculated as ln(LHR), rounded to the nearest integer. A constant of +1 was added to items with negative scores.

‡Based on the predefined criteria (positive LHR >2 or negative LHR <0.5), these factors were included in multivariate analysis. Based on the adjusted LHRs, only 3 factors were retained in the CPT.

setting the reference level for each predictor to zero. Summing the predictor scores of the individual's risk factors yielded the total predictor score for each patient. Next, alternative scoring systems were developed by using body mass index (BMI) instead of body weight and by removing hemoglobin. Finally, we repeated the analysis using less stringent cutoff values for the crude LHRs (LHR ≥1.5 or ≤0.67). Comparison of the performance of the different scores relative to the original score was based on the area under the ROC (AUROC) and 95% confidence intervals (CIs). The data set was split randomly in a derivation data set—containing 75% of the data—and a validation data set.

RESULTS

Over the study period, a total of 3316 ARV-naive adults initiated ART. With 353 individuals excluded for missing baseline data, 2963 were included in analysis, with a median age of 35 years [interquartile range (IQR), 30–41] and a median baseline CD4 count of 88 cells per microliter (IQR, 27–212). Forty-nine percent were male. The median body weight at baseline was 49 kg (IQR, 43–55). In total, 282 (9.5%) had KD pre-ART. A total of 2192 (75%) were randomly included in the derivation data set, the remainder were used for validation. Four factors were retained for inclusion in multivariate analysis, based on the predefined criteria for LHR (Table 1). Only 3 factors were retained in the risk score development process, resulting in a score ranging from 0 to 5. The probability of KD ranged from 1.0% for those with a score of 0 to 51.2% for a score of 5. Using a risk prediction score including age (score +2 if >40 years), body weight (score +2 if <45 kg), and hemoglobin (score +1 if <10 g/dL) achieved an AUROC of 0.83 (95% CI: 0.80 to 0.85) in derivation and 0.81 (95% CI: 0.76 to 0.86) in the validation data set. With a cutoff of the score at 2 (score ≥2), sensitivity for KD was 91.5% in validation, while avoiding testing in 50.5%. Using a higher cutoff (score ≥4) increased specificity with only 7.3% of individuals requiring creatinine testing, but with a significant loss in sensitivity (see **Table S1, Supplemental Digital Content,** http://links.lww.com/QAI/A476). Using BMI (cutoff <18 kg/m^2) instead of body weight, a validated AUROC of 0.77 (95% CI: 0.72 to 0.83) was obtained. If hemoglobin measurement would be removed as item from the original score (eg, if this test would not be available), the AUROC was 0.79 (95% CI: 0.74 to 0.83) in the validation data set. Recalculating the clinical prediction score with less restrictive cutoff values for the crude LHRs yielded a 4 item score including 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), with an AUROC of 0.81 (95% CI: 0.76 to 0.85) (see **Table S2, Supplemental Digital Content,** http://links.lww.com/QAI/A476).

DISCUSSION

Guidelines and practices, including for HIV care, should ideally be evidence based and make careful use of resources.

Procedures or interventions are to be prioritized to those with the highest benefit and avoided in those with no or minimal gain. Doing routine laboratory testing is often costly and might result in additional delays, especially if the test cannot be performed on site. Targeted evaluation using evidence-based tools might be a rational way to optimize the use of often scarce resources available for health delivery in resource-constrained settings.[13] Moreover, patient populations are not homogeneous, but consist of different "risk groups." Risk-based patient management, relying on CPTs, is increasingly used to guide decision making.

The 2013 revised WHO guidelines recommend against routine and in favor of targeted creatinine testing before initiation of tenofovir.[4] The CPT in this study is an example of a tool for such a strategy, which is evidence based and relies on basic clinical information. It is simple and easy to apply in the field. Testing those with a score value of 2 or more would cut the amount of tests by half, with clear cost-saving implications, and would reduce unnecessary delays. Other examples of such CPTs exist within the HIV field, for example, the development of clinical scoring systems combined with targeted viral load testing.[14]

CPTs need to undergo extensive validation before being implemented and the same applies to ours. How its performance would vary across settings remains to be evaluated. Especially the cutoff of body weight might critically depend on the physical constitution in the general population. Possibly, the BMI cutoff might be more stable across populations. Importantly, traditional risk factors such as diabetes and hypertension should be integrated as well. Screening for these factors is, however, not yet integrated in many (vertical) HIV care programs. In this regard, this study essentially provides the proof of concept from the HIV program perspective. Adding additional non-HIV factors might lead to further model improvement. Finally, we only assessed targeted creatine testing before ART initiation. Future studies evaluating such an approach while on ART merit further study.

In conclusion, we developed and internally validated a CPT for targeted creatinine testing. Further validation is needed before routine clinical use. Similar approaches could be useful for other components of HIV care.

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World Health Organization's Stage 4 Conditions Among Adults Accessing Outpatient HIV Care: A Retrospective Cohort Study in Kisumu, Kenya

To the Editors:

INTRODUCTION

Opportunistic infections (OIs) are the main cause of morbidity and mortality in patients with HIV-1 infection throughout the world, particularly among patients who have not had access to anti-retroviral therapy (ART) and other HIV care services.[1–3] Among patients taking ART, OIs can present when the immune system starts to recover, also known as immune reconstitution inflammatory syndrome.[4,5] Also, some patients do not have a sustained response to ART due to the lack of adherence to medications, development of drug resistance, or suboptimal therapeutic regimens.[1] Therefore, OIs continue to cause substantial morbidity and mortality even after the initiation of ART.

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