

Clinic-based evaluation of a point-of-care creatinine assay to screen for renal impairment amongst HIV-positive patients receiving tenofovir disoproxil fumarate

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Background

Tenofovir disoproxil fumarate (TDF) is a key component of World Health Organization recommended first-line antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP),¹ with 20 million people predicted to use TDF by 2020.² TDF is only recommended for patients with normal renal function, meaning serum creatinine and estimated glomerular filtration rate (eGFR) should be assessed before initiation, and during follow-up.¹ However, limited access to laboratory testing in low- and middle-income countries (LMICs) can restrict compliance with these guidelines, delay receipt of results and impede ART uptake. Point-of-care (POC) creatinine devices could overcome these barriers and enable 'same-day' ART/PrEP initiation and subsequent 'same-day' monitoring. This could be particularly useful in home and community-based programmes that enhance test and treat efforts in high prevalence settings.^{3,4}

The Statsensor® Xpress-i™ (Nova Biomedical, Waltham, MA, US) is a battery powered, hand-held POC device that measures creatinine concentration in 30 seconds from capillary, venous or arterial whole blood. While evaluations of the analytical performance of this assay have shown mixed results,⁵⁻⁷ several ART trials in Southern Africa are currently using the assay to screen for renal impairment.^{3,8,9} However, no clinical evaluations have yet been published in this setting. Here, we evaluate the implementation of the Statsensor® Xpress-i™ for renal function assessment amongst HIV-positive patients receiving first-line ART in a primary care setting in South Africa.

Methods

We conducted a prospective, clinic-based evaluation of the POC Statsensor® Xpress-i™ compared to a laboratory-based reference method, as part of the STREAM (Simplifying HIV TREATment and Monitoring) study. STREAM is a randomised controlled implementation trial of POC viral load testing and task shifting being conducted in Durban, South Africa. Consenting participants were randomized in a 1:1 ratio to receive either POC monitoring (viral load, CD4 and creatinine) versus standard laboratory monitoring only.⁹ Eligible participants were clinically stable, non-pregnant, HIV-positive adults who initiated first-line ART within the past 6 months.

One patient with an eGFR of <30 mL/min in the 3 months prior to screening was deemed clinically unstable and excluded from the trial. The primary outcome is virological suppression and retention in care after one year.

In this sub-study, we only include participants allocated to POC monitoring, as they had both finger-prick capillary blood sampling and venepuncture performed by a study nurse at enrolment. Finger-prick capillary whole blood creatinine was measured immediately using the factory calibrated Statsensor® Xpress-i™. Venous plasma samples were transported to the central laboratory, where creatinine was measured using the Dimension® EXL™ 200 (Siemens Healthcare, Erlangen, Germany) isotope dilution mass spectrometry aligned assay. Prior to use, each new lot of Statsensor® strips was tested using manufacturer supplied linearity controls, with all results within expected ranges. The vendor provided on-site training prior to study commencement, with internal quality assurance reviews performed thereafter.

POC Statsensor® Xpress-i™ and laboratory serum creatinine were compared using Spearman correlation and a Bland-Altman plot. eGFR was calculated from age, sex and creatinine values using the Modified Diet in Renal Disease equation (without ethnicity factor), which has been validated and is widely used in our setting.¹⁰ We calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the Statsensor® Xpress-i™ to detect an eGFR below internationally recognised thresholds, which define <60 mL/min as moderate to severe impairment, and 60-89 mL/min as potential mild renal impairment (in the presence of other indicators of kidney disease).¹⁰ The Statsensor® Xpress-i™ does not have functionality to provide eGFR results, and calculating eGFR by hand can be complex for primary care providers. Therefore, we also used a previously validated creatinine cut-off of 106 µmol/L (1.2 mg/dL), which approximates an eGFR of 60 mL/min depending on age and sex.⁷

This study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee and the University of Washington Institutional Review Board.

Results

Between February and August 2017 a total of 390 participants were enrolled into STREAM. 195 were randomised to laboratory monitoring alone and were excluded from this sub-study. 195 were randomised to receive POC monitoring, with laboratory reference samples drawn for comparison. Eight reference samples were excluded because they were either not processed during a laboratory strike, or processed more than 48 hours after sampling,

leaving 187 participants with paired creatinine samples for inclusion in this analysis. Median age was 31 years (interquartile range [IQR] 27-38), 61.5% (115/187) were female and median CD4 count was 459 cells/mm³ (IQR 289-658).

Correlation between the Statsensor[®] Xpress-i[™] and laboratory serum creatinine was modest (Spearman $\rho=0.58$, Figure 1a). Mean POC creatinine was 79.4 $\mu\text{mol/L}$ (range 50-128) compared to 69.0 $\mu\text{mol/L}$ (range 28-116) with the laboratory test (bias +10.4 $\mu\text{mol/L}$, 95% limits of agreement ± 27.9 $\mu\text{mol/L}$ [-17.6 to +38.3 $\mu\text{mol/L}$] Figure 1b). Results were unchanged in a sensitivity analysis restricted to the 167 patients who had laboratory reference samples performed on the same day as the POC test. The Statsensor[®] Xpress-i[™] had 87.1% sensitivity (95% confidence interval [CI] 76.2-94.3) and 52.0% specificity (95% CI 42.9-61.0) to detect an eGFR of <90 mL/min, and correctly identified the one patient with a laboratory eGFR of <60 mL/min. Using an abnormal creatinine cut-off of >106 $\mu\text{mol/L}$, the Statsensor[®] Xpress-i[™] had sensitivity of 100%, specificity of 95.1% (95% CI 90.9-97.7), NPV of 100% and PPV of 30.8% (95% CI 9.1-61.4).

Nurses reported the analyser was easy to use, and required minimal training due to similarity with other widely used POC tests (e.g. finger-prick glucose). However, a separate eGFR calculator was needed to facilitate eGFR assessment. Cost per POC test in our study, including analyser cost, staff time, controls and consumables, was estimated at 10 USD compared to approximately 4.5 USD per laboratory test.

Discussion

The Statsensor[®] Xpress-i[™] demonstrated modest agreement with the laboratory reference assay and generally overestimated creatinine levels, with limits of agreement just outside the Clinical Laboratory Improvement Amendments (CLIA) acceptable test performance criteria of ± 27 $\mu\text{mol/L}$.⁵ However, this POC assay detected the few patients with potential renal impairment, suggesting it could be used to rapidly screen for renal impairment in HIV care programmes.

Previous evaluations have indicated that the Statsensor[®] Xpress-i[™] is negatively biased at higher creatinine levels, but positively biased at lower levels. Two studies from the Netherlands of 60 and 133 patients, with higher laboratory creatinine values than our study (up to 1000 $\mu\text{mol/L}$), demonstrated a negative bias of -10.7 and -12.38 $\mu\text{mol/L}$, and correlation coefficients of 0.97 and 0.95, respectively.^{5,6} However, when restricted to patients with normal creatinine levels, there was a small positive bias of 3 $\mu\text{mol/L}$, and a correlation coefficient of 0.69, which was more similar to our results.⁵ Overall, sensitivity and specificity to detect a creatinine >115 $\mu\text{mol/L}$ was 100% and 91%, respectively.⁵ In an evaluation from

Nicaragua of 100 patients with creatinine levels between 44-320 $\mu\text{mol/L}$, the Statsensor[®] Xpress-i[™] was positively biased with a median creatinine of 92 $\mu\text{mol/L}$ compared to 64 $\mu\text{mol/L}$ with the laboratory method. As in our analysis, the POC assay had a high sensitivity (100%) and acceptable specificity (84%) to detect a creatinine $>106 \mu\text{mol/L}$.⁷

Strengths of our analysis include the relatively large sample size, and the novel implementation of the Statsensor[®] Xpress-i[™] amongst HIV-positive patients. Patients in our analysis had generally lower creatinine values than in the above studies, which corresponds with low rates of renal disease seen in other HIV-positive cohorts on TDF in Southern Africa.¹⁰ This limits the interpretation of our results. Firstly, the positive bias seen in our study likely reflects an inherent positive bias in the assay at these lower creatinine levels. Secondly, the modest correlation seen in this analysis may not reflect performance of the assay over a higher range of creatinine levels, as demonstrated in previous studies.^{5,6} Thirdly, our analysis is limited by having few participants with abnormally high creatinine, or eGFR $<60 \text{ mL/min}$. However, the Statsensor[®] Xpress-i[™] did identify all of these correctly.

Our findings have implications for HIV programmes in other LMICs, where the young age of HIV positive cohorts means prevalence of renal impairment is likely to be similarly low.¹⁰ Overall, the positive bias, wide limits of agreement and modest Spearman correlation mean that the Statsensor[®] Xpress-i[™] should not be used to determine exact creatinine levels, or monitor trends, within the normal range. Instead, as demonstrated in previous studies, the acceptable sensitivity and specificity to detect renal disease suggests that this assay could be used to rapidly rule out renal impairment, allowing patients with normal POC results to be safely initiated or continued on TDF during the same clinical visit. Those with abnormal POC results (7% in our study) will require a confirmatory laboratory creatinine to prevent misdiagnosis of renal impairment and unnecessary withholding of TDF. Nurses and lay healthcare workers could use this assay in clinics and community settings, although a separate eGFR calculator would be needed. In settings such as South Africa, where creatinine monitoring for TDF is mandatory, the relatively high cost per POC test may be offset by costs saved through earlier treatment initiation and reductions in clinical visits to review test results. While there is ongoing debate about the value of universal creatinine monitoring for TDF,¹⁰ this POC assay could still be useful to screen for renal impairment in patients at higher risk of kidney disease.

In conclusion, amongst HIV-positive, primary care patients with generally normal renal function, the Statsensor[®] Xpress-i[™] displayed modest agreement with laboratory references, but accurately detected the few patients with high creatinine or renal insufficiency. This assay has potential to facilitate rapid screening for renal impairment within HIV programmes,

which is particularly important given growing interest in ‘same-day’ ART initiation and community based ART delivery.^{3,4} However, further evaluations are warranted, including cost-effectiveness studies, particularly amongst populations with higher levels of renal impairment and those considered for PrEP initiation.

Abbreviations

95% CI – 95% confidence interval, ART – antiretroviral therapy, CLIA - Clinical Laboratory Improvement Amendments, eGFR – estimated glomerular filtration rate, IQR – interquartile range, LMIC – low- and middle- income country, NPV – negative predictive value, POC – point-of-care, PPV – positive predictive value, PrEP – pre-exposure prophylaxis, STREAM – Simplifying HIV TREATment and Monitoring study, TDF – tenofovir disoproxil fumarate

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Figure Legends

Figure 1: Point-of-care (POC) Statsensor® Xpress-i™ creatinine versus laboratory Dimension® EXL™ 200 creatinine (N=187) A) Spearman correlation B) Bland-Altman plot, mean difference (POC – laboratory creatinine) +10.35 µmol/L, 95% limits of agreement (mean ±1.96 standard deviations [SD]) -17.57 to +38.26 µmol/L.