Implementation of multiple point-of-care testing in two HIV antiretroviral treatment clinics in South Africa

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Running title: Multidisciplinary POCT implementation

Abstract:

Background: A plethora of point-of-care (POC) tests exist in the HIV and TB diagnostic pipeline which require rigorous evaluation to ensure performance in the field. The accuracy and feasibility of nurse-operated multidisciplinary-POC testing for HIV antiretroviral therapy (ART) initiation/monitoring was evaluated.

Methods: Random HIV-positive adult patients presenting at two treatment clinics in South Africa for ART initiation/monitoring, were consented and enrolled. POCT was performed by a dedicated nurse on a venepuncture specimen; Pima (CD4), HemoCue (haemoglobin), Reflotron (alanine aminotransferase, creatinine), Accutrend (lactate) and compared to laboratory testing. External quality assessment (EQA), training, workflow and errors were assessed.

Results: n=324 enrolled at site1; n=469 enrolled at site2. Clinical data on n=305 participants: 65% (n=198) female with a mean age of 39.8[21-61] years; mean age of males 43.2[26-61] years; 70% of patients required 3 or more POC tests/visit. EQA material was suitable for POCT. CD4, haemoglobin and alanine aminotransferase testing showed good agreement with predicate methodology; creatinine and lactate had increased variability. Pima CD4 misclassified up to 11.6% of patients at 500cells/µl and reported 4.3-6% error rate. A dedicated nurse could perform POCT on 7 patients/day; inclusion of Pima CD4 increased time for testing from 6-110minutes. Transcription error rate was 1%.

Conclusions: Nurses can accurately perform multi-disciplinary POCT for HIV ART initiation/monitoring. This will however, require a dedicated nurse as current duties will increase. Use of Pima CD4 will increase patients initiated on ART. Connectivity will be central to ensure quality management of results but overall impact will need to be addressed.

Keywords

Multiple-disciplinary; point-of-care testing; HIV; antiretroviral; implementation

Introduction

Laboratory systems and services are critical in global health and point-of-care testing (POCT) may have a place within this framework to address unmet diagnostic needs, especially in resource-limited environments [1-3]. Appropriate clinical management of ill patients presenting at primary health care clinics (PHC) remains a global health challenge and lack of accessibility to an appropriate laboratory diagnosis is a major reason why health services are failing. A recent report in the New England Journal of Medicine describing 20 years of health care in South Africa, stated that improving access to health care requires restructuring and strengthening of existing district-based PHC facilities, with nurses and community healthcare workers (HCWs) playing an increasingly important role in remote areas [4].

POCT is currently the fastest growing market in medical diagnostics with many innovative technology developments [1, 5]. The purpose of POCT is to provide a test that has immediate impact on patient outcome [6] and that can be used in outpatient clinics, emergency rooms, theatres, mobile clinics, PHC clinics, or even small laboratories [7]. The potential benefits for POCT identified in low to middle income countries are to avoid patient hospitalisation (or reduce length of stay), help manage chronic conditions [3, 7, 8], improve accessibility of services, reduce turnaround times, potentially improve patient retention and improve staff convenience and satisfaction [9-13].

A number of disadvantages also exist, such as the poor regulatory control [14], lack of connectivity, inadequate quality control and assurance [15, 16], a potential increase in cost and over-use (duplication) of existing laboratory and POC services, as well the need for appropriately trained POC operators [17]. Several guideline documents detailing the requirements for POCT exist [18-20] and all emphasise the need for quality in POCT. The complexities of managing quality of the entire process (pre-analytical, analytical and post-analytical) however, are well described for glucose testing [21], but less so elsewhere.

The massive expansion of anti-retroviral (ARV) therapy (ART) in lower and middle-income countries has relied entirely on the use of one or more rapid tests for diagnosing HIV, which are frequently performed by lay counsellors or lower-level HCWs. Although this has facilitated expansion of testing services in many countries [22, 23], the track record for HIV rapid testing at POC in South Africa, has been challenged with studies showing poor compliance to standard operating procedures and poor quality management [24].

In addition to rapid strip-based testing for diagnosis of HIV, ART initiation has relied on CD4 count testing for treatment initiation. The value of the CD4 assay is under scrutiny with treatment thresholds increasing to 500cells/µl and emphasis being placed on viral load testing for monitoring treatment success [25, 26]. ART treatment guidelines in South Africa [27] also include additional diagnostic assays prior to ART initiation that highlight the need for a multi-disciplinary array of testing requirements for both ART initiation and subsequent monitoring.

Prior work has alluded to the fact that the expanded repertoire of assays could possibly be performed by nurses or other HCWs at POC [28]. A limitation to this process however, in many countries including South Africa, has been the need for phlebotomy skills for which the scope of work is defined for a certain cadre of nursing staff and is mandated by the Health Professions Council of South Africa (HPCSA) [29]. The use of finger stick testing can eliminate the need for skilled phlebotomists, but for HIV treatment could mean patients may require up to four finger sticks for POCT at each visit [30], over and above the initial two finger sticks required for HIV rapid testing.

While numerous reviews are available on the use of POCT and the need in resource limited settings [2, 31-33] in the HIV testing arena, few have dealt with logistics around sample collection, connectivity, result reporting or whether improving logistics would be more cost-effective. In addition, most of the new POC technologies have limited field evaluation and few studies have evaluated clinical outcome, impact on overall health care, cost effectiveness and cost benefit of POC, especially in the developing world and specifically for

multi-disciplinary POCT. To address some of these issues, we implemented nurse operated multiple POCT in two busy ART clinics in South Africa, to assess the feasibility and accuracy of the process.

Methods

This project formed part of a Grand Challenges Canada study (grant # 0007-02-01-01-01). Human Ethics was obtained and approved through the University of the Witwatersrand, (M10333) and the University of Pretoria, South Africa (M090688).

Clinic sites

All laboratory validations, training and research and development were performed at the National Health Laboratory Service (NHLS) Department of Molecular Medicine and Haematology in Johannesburg, South Africa. The clinic phase validation to determine nurse operated POCT versus laboratory testing was performed in two well managed urban ART PHC sites: a) non-governmental organisation (NGO) supported Themba Lethu Clinic, part of the Clinical HIV Research Unit (CHRU) located within the infrastructure of the Helen Joseph Hospital, Right to Care in Johannesburg, which manages 21 000 HIV infected patients on ARV treatment [34]; b) Comprehensive Care Management and Treatment (CCMT) Clinic, Tshwane District Hospital in Pretoria. Both clinics enrol more than 350 patients per month, 5 days a week and both are within walking distance from high throughput routine laboratories managed by the NHLS. A POCT laboratory was established in each clinic in a dedicated room adjacent to the consultation rooms. The POCT instruments were installed by suppliers as per good clinical laboratory practice guidelines (GCLP) [35]. Reagent kits were procured and stored appropriately. Three dedicated research nurses (professional nurses experienced in phlebotomy and HIV/Tuberculosis (TB) treatment) were employed and trained on all POC instruments by the instrument suppliers and local laboratory staff. In all sites selected, provincial approval and support was obtained and dedicated staff and instrumentation were placed to support all the project activities.

Participant eligibility for POCT

Individuals (>18 years of age, with known HIV-positive status) were approached for enrolment in the study when they presented for routine phlebotomy related to their HIV ARV initiation and monitoring at the clinics. The nurses conducted informed consent, enrolled participants and performed the required phlebotomy. The selection of POCT was based on the SA HIV treatment guidelines at the time of the study [36], and included the following tests: CD4 for ART initiation, followed by Creatinine (Cr), Alanine aminotransferase (ALT) and Haemaglobin (Hb). Lactate was included but rarely requested (stavudine usage high at time of study). Each participant consented to providing an additional $EDTAk_3$ (for CD4, Hb, Cr and lactate) and/or a Heparin tube (for ALT), which was used for on-site POCT. The POC platforms were the PIMA (Alere, Inc., Waltham, MA, USA) for CD4; HemoCue DM201 (HemoCue AB, Ängelholm, Sweden) for Hb; Reflotron Plus (Roche Diagnostics, GmbH, Germany) for ALT and Cr; and COBAS Accutrend Plus (Roche Diagnostics, GmbH, Germany) for Lactate. The selection of these POCT platforms was based on the POC diagnostic pipeline document at the time[37], available literature [28, 38-42] and in-house validations.

Post-phlebotomy, the nurses took the additional blood tube to the POCT room in the clinic, opened the vacutainer tube and performed POCT. A fixed volume pipette supplied with the Reflotron (Roche Diagnostics) was used to dispense the required blood volume onto the rapid strips (ALT, Cr and lactate) or to dispense blood into the Hb microcuvette or PIMA cartridge. Results were manually recorded in a log book. At CHRU, the nurse also used a Vacudrop (Greiner Bio-One, Dublin, Ireland) device which allows the withdrawal of a single drop of blood from a closed blood tube and allows the capability of multiple analyte testing from a single venous blood draw, and the potential for repeat testing. This method was investigated to determine the performance of the POC tests without the use of a pipette. POC results were not used for clinical management. The routine bloods were sent as per standard-of-care to the NHLS laboratories (within the same complex as the clinic) for routine

laboratory testing. These reference result values were made available to the study through the NHLS laboratory information system and used for patient management.

POC instrument verification and quality management

After placing the POCT platforms in the clinic sites and prior to their use, each platform (Pima CD4, HemoCue and Reflotron) was verified using 25 specimens (ensuring they were "fit for purpose" as part of GCLP requirements)[43]. The verification specimens were randomly collected from routine, residual patient specimens in the adjoining NHLS reference laboratories. As lactate measurements need to be performed immediately upon blood collection, the first 25 patients recruited on the study requiring a lactate test, were used as verification material for the Accutrend Plus instrument.

For quality monitoring throughout the study, quality control (QC) material was tested on each of the instruments according to manufacturer's instructions by the POC nurses. A log sheet was used to record QC test results. In addition, one round of external quality assessment (EQA) was performed at the CHRU clinic on the PIMA CD4, HemoCue and Accutrend instruments using EQA material obtained from the NHLS EQA regional and national programs. Results were sent to the NHLS EQA Division for independent analysis and reporting (Z-scores of <2 were considered acceptable). No NHLS EQA material was available for the Reflotron instrument as this is a dry chemistry based system compared to the laboratory platforms which use wet chemistry.

Comparator laboratory testing platforms

NHLS derived results were considered the reference standards against which the POC results were compared, these included: CD4 single platform Pan*Leuco*gating method using flow cytometry (Beckman Coulter, Miami, FL); Advia 120 and 2120 Heamatology system for Hb (Siemens, Diagnostic Solutions, Tarrytown, NY); Advia 1800 Chemistry analyser (Siemens Healthcare Diagnostics, Inc, Germany) and Synchron DXC 800 (Beckman Coulter, Miami, FL) for ALT and Creatinine; Advia 1800 for Lactate.

Statistical analysis

The performance of multidisciplinary POCT performed by nurses directly in clinics was compared to laboratory generated reference results using the Bland-Altman [44] ,percentage similarity [45] and concordance correlation (*pc*) [46, 47] methods of agreement. Accuracy was measured using the bias (POCT – laboratory reference) and this was reported in the context of the data sets summarised by their median values. Confidence intervals (CI) at 95% were included. Overall agreement between the laboratory reference and POC results was measured using the percentage similarity coefficient of variation (CV), which includes accuracy and precision. Total misclassification (false positive and false negative compared to predicate) was reported for CD4 counts at the 350cells/µl and 500cells/µl level and included sensitivity and specificity (including 95% CI), as well as upward and downward misclassification as previously described [48].

POC instrument errors were recorded (as defined by any 'no result' due to an error code or invalid). Functions were performed using STATA 12 and MedCalc [49]. Scatter plots were used to represent outliers in the clinically relevant ranges for each analyte. Normal ranges for each analyte were determined by the NHLS reference technology as follows: Hb 12–18g/dl; ALT 10-40U/l; Cr 64-104umol/l, lactate <2.2mmol/L. Royal College of Pathologists of Australasia (RCPA) allowable differences [50] were also applied to determine outliers: Hb ±0.5 <10g/dl and ±5% >10g/dl, ALT ±5 ≤40 U/l and ±12% >40U/l, Cr±8 <100umol/l and ±8% ≥100umol/l, lactate ±0.5mmol/L ≤4mmol/L and ±12% >4mmol/L.

Qualitative data (measured prior to and during the study) of the multiple POC implementation process addressed workflow and feasibility issues, rather than simply comparative laboratory data. These variables included: training and additional consumable needs, length of time and number of added duties required to perform multiple POCT and number of transcription errors during manual result recording.

Results

Data summary

A total of 324 patients were approached to participate over a 6 month period at CHRU (December 2010 to June 2011) and 469 patients at CCMT over 1 month (January 2012 to February 2012). No patient declined participation. Clinical data was available for 305 CHRU study participants as follows: 65% (n=198) of the patients were female; mean age of females was 39.8 [21-61] years and males was 43.2 [26-61] years; mean number of days on ART at the time of POC testing was 833 days for men and 764 days for women. Patients on first line ART: n=175; the remainder were either not on therapy (being initiated on ART) or had missing demographics at time of blood draw.

The number of diagnostic tests requested by HCWs for patients at a particular visit attending the CCMT site is represented in the pie chart in Figure 1 and shows that 70% (325/464) of patients required 3 or more POCT to be performed per visit.

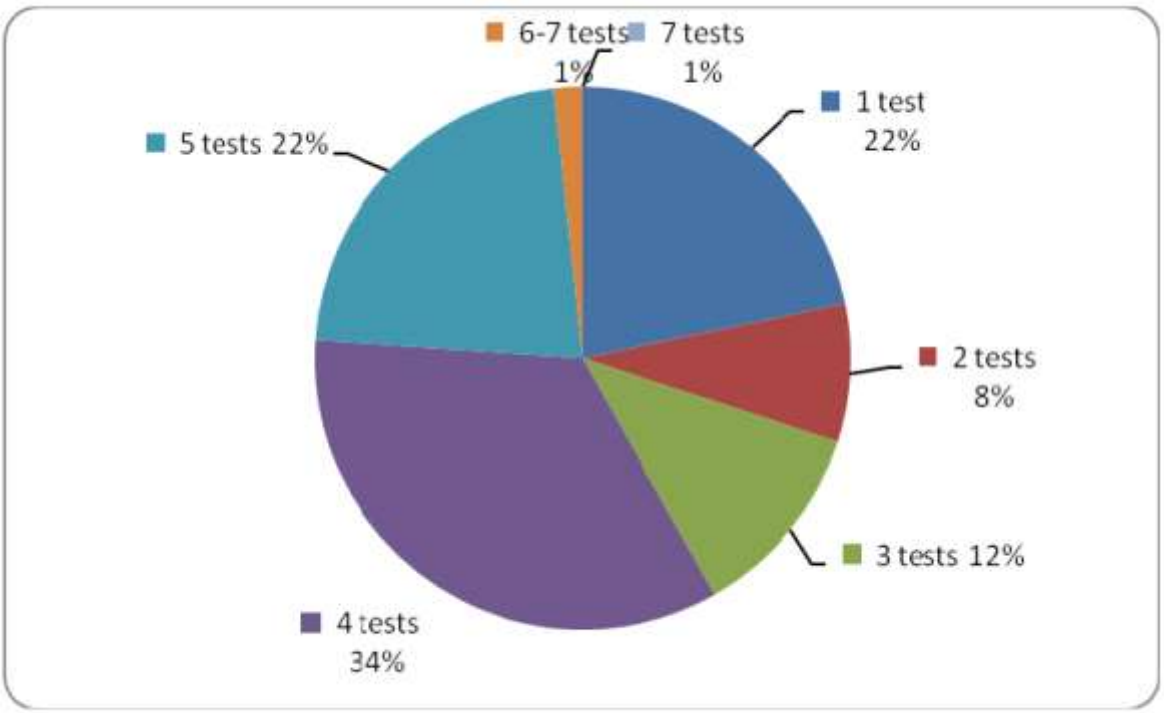


Figure 1: A pie chart representing the percentage of tests requested by HCW on their patients (n=469) attending the CCMT clinic. The pie chart reflects the number of POCT tests required per visit from 464 patients (n=5 not recorded).

Table 1: Internal quality control (QC) results for CD4, Hb, ALT, Creatinine and lactate analytes performed by nurses at two POCT sites and external quality assessment (EQA) performed at one POCT site.

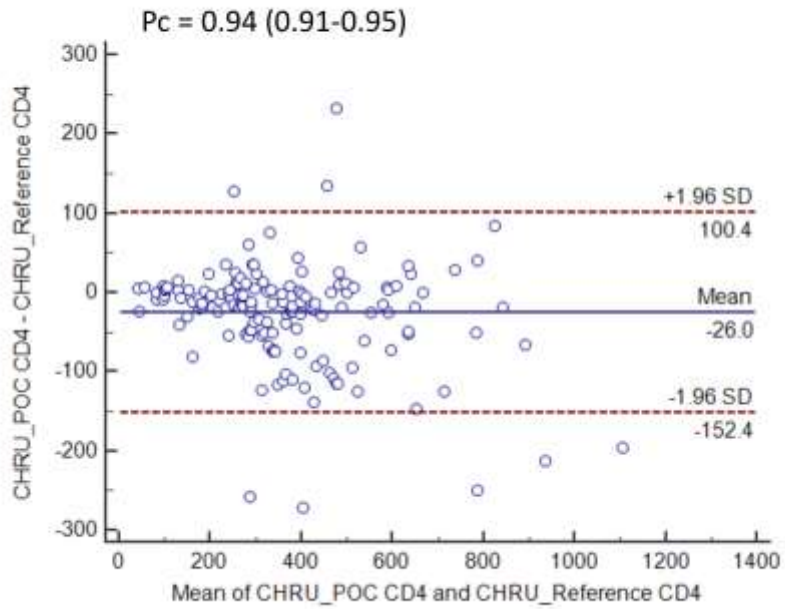
Analytes	CHRU		CCMT
	QC	EQA	QC
PIMA CD4	Daily low (n=26), high control (n=26), 0 failures, 100% compliancy	Survey 1 Trial 1 sample A: Error (internal cartridge error) Survey 1 Trial 1 sample B: 110c/ul (Z-score -0.68) Survey 2 Trial 2 sample A: 573c/ul (Z-score -2.05)*	Daily low (n=33), high control (n=33), 0 failures, 100% compliance
HemoCue Hb	Weekly High (n=5), normal (n=6), low (n=6)., 0 failures, 100% compliancy	0710W: 9.3g/dl (Z-score 1.94) 0710X: 8.0g/dl (Z-score 2.46) 0810W: 9.5g/dl (Z-score 0.12) 0810X: 11.2g/dl (Z-score 1.65)	Weekly High (n=7), normal (n=7), low (n=6). 0 failures, 100% compliance
Reflotron Cr	One monthly universal control (n=4) 0 failures, 100% compliancy	No POCT EQA material available from NHLS	One monthly universal control (n=7) on each instrument, 0 failures, 100% compliance
Reflotron ALT	One monthly universal control (n=4), 0 failures, 100% compliancy	No POCT EQA material available from NHLS	One monthly universal control (n=7) on each instrument¥, 0 failures, 100% compliance
Accutrend Lactate	Monthly low (n=3), high (n=3) controls, 0 failures, 100% compliancy	Sample 1: 3.8mmol/l (Z-score 1.7) Sample 2: 0.8mmol/l (Z-score 0.64) Sample 3: 4.5mmol/l (Z-score 2.5)	Monthly low (n=32), high (n=32) controls per instrument¥, 0 failures, 100% compliance

Values underlined are>z-score 2, however *not in the clinically relevant range; ¥ two instruments were used during the study time frame

Method comparison of POCT versus laboratory testing

All POCT platforms placed in both clinics passed verification using 25 laboratory specimens (and clinical specimens for lactate). No QC failures were observed on any of the instruments and 100% compliance was obtained by the POC nurses in performing instrument QC as reflected in Table 1. EQA material tested on the PIMA, HemoCue and Accutrend showed results to be within acceptable limits despite material not being specific for all POC

A.



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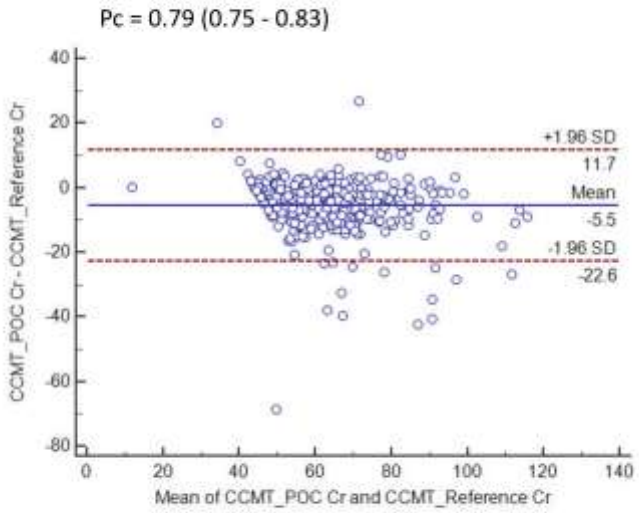

Figure 2: Scatter plots of method comparison of POC testing arms for the two sites compared to routine laboratory results. The vertical axis in each plot (A-J) is the difference between POC and predicate results and the horizontal axis is the absolute value of predicate tests. Mean and limits of agreement lines are indicated on all plots. A-J) Bland Altman difference scatter plots for POC versus predicate methodology for at CHRU and CCMT respectively for CD4 (A-B), Hb (C-D), ALT (E-F) and Cr (G-H) and lactate (I-J at CHRU and CCMT.

Table 2: Method comparison summary statistics of nurse operated POCT for CD4, Hb, ALT, Creatinine and lactate versus laboratory generated reference results. The sections highlight independent studies performed at two different clinic sites (CHRU and CCMT) using venepuncture derived specimens. A section is included for the use of the Vacudrop at one site.

Venipuncture POCT at CHRU	**CD4 (cells/μl)**	**Hb (g/dl)**	**ALT (U/l)**	**Cr (umol/l)**	**Lactate (mmol/l)**
n	152	157	146	156	93
Median routine lab	361	14	23	68	2.3
Bias* (95% CI)	-26 (16; 36)	0.3 (-0.36; -0.14)	-7.4 (5.6; 9.0)	-4.5 (2.09; 6.95)	0.01 (-0.13; 0.1)
Mean % similarity (CV)	97 (8.1%)	101 (3.1%)	90 (11.5%)	97 (10.9%)	104 (14.7%)*
Error rate (%)	6	0	0	0	0
CD4 misclassification 350cell/μl **Total misclassification** **Sensitivity ; specificity (95% CI)** **Up; downward misclassification**	 9.85% (false positive 9.2%) 98.63% (92.60 - 99.97); 82.28% (72.06 - 89.96) 1.4%; 17.7%				
CD4 misclassification 500cell/μl **Total misclassification** **Sensitivity ; specificity (95% CI)** **Up; downward misclassification**	 7.2% (false positive 4.6%) 96.61% (91.55 - 99.07); 79.41% (62.10 - 91.30) 3.4%; 20.6%				
VacuDrop POCT at CHRU	**CD4 (cells/μl)**	**Hb (g/dl)**	**ALT (U/l)**	**Cr (umol/l)**	**Lactate (mmol/l)**

n	82	71	22*	Not done	Not done
Median routine lab	432	13.5	18.5		
Bias* (95% CI)	7.2 (-15.8; 1.5)	0.3 (-0.43; -0.2)	-9.62 (1.79; 17.4)		
Mean % similarity (CV)	103 (11%)	101 (2.0%)	86 (13.3%)*		
CD4 misclassification 350cell/µl **Total misclassification** **Sensitivity ; specificity (95% CI)** **Up; downward misclassification**	7.3% (over = false positive 3.6%) 89.5 (71.77 - 97.73); 94.4 (84.61 - 98.84) 10.7%; 5.5%				
CD4 misclassification 500cell/µl **Total misclassification Sensitivity ; specificity (95% CI)** **Up; downward misclassification**	4.9% (false positive 1.2%)94.23% (84.05 - 98.79); 96.67% (82.78 - 99.92) 5.8%; 3.3%				

Venipuncture POCT at CCMT	**CD4 (cells/µl)**	**Hb (g/dl)**	**ALT (U/l)**	**Cr (umol/l)**	**Lactate (mmol/l)**
n	276	309	310	320	192
Median routine lab	379	12.8	23	65	1.2
Bias* (95% CI)	-54 (45; 63)	0.16 (-0.19;-0.13)	-3.1 (2.11; 4.14)	-5.5 (4.49; 6.42)	1.1 (-1.18;-1.04)
Mean % similarity (CV)	94 (10.3%)	101 (1.2%)	95 (9.5%)	96.5 (6.3%)	148 (19.4%)*
Error rate (%)	4.3	0	0	0	0

CD4 misclassification 350cell/μl	
Total misclassification	15.6% (false positive 14.1%)
Sensitivity ; specificity (95% CI)	96.75 (91.88 - 99.11); 26.42% (15.26 - 40.33)
Up; downward misclassification	3.3%; 73.6%
CD4 misclassification 500cell/μl	
Total misclassification	11.6% (false positive 10.1%)
Sensitivity ; specificity (95% CI)	98% (94.96 - 99.45); 63.16% (51.31 - 73.94)
Up; downward misclassification	2%; 36.8%

*smaller sample size

instruments. One sample for each instrument tested flagged outside the reference range according to the Z-score of >2, but the values were not in the clinically relevant range.

Table 2 and Figure 2 (A-J) detail the method comparison statistics and scatter plots of nurse operated POCT compared to laboratory reference results. Pima CD4 testing performed at CHRU had a bias of -26cells/µl which showed better accuracy than testing performed at CCMT (-54cells/µl), in spite of their similar CD4 results (similar CD4 median and range). CD4 testing performed at CCMT also yielded more misclassification at the 350cells/µl and the 500cell/µl thresholds than testing performed at CHRU. At both sites, however, misclassification of CD4 using Pima would have resulted in more patients identified for ART initiation. The Pima CD4 error rates at both sites were similar.

The performance of ALT and lactate POCT was variable and significantly different between the sites (CI did not overlap), but the majority of specimens were within the clinically relevant range, and would not have resulted in a change in clinical management.

The bias for Hb and creatinine testing was accurate and similar at both sites. POC testing of CD4, Hb and ALT using the VacuDrop at CHRU generated acceptable bias values similar to the main study at this site.

Qualitative analysis multi-disciplinary POCT

POCT ease of use: Practical training for the nurses on all the POCT instruments took approximately half a day per instrument and included sample testing, performing QC, instrument maintenance and troubleshooting. Additionally, the POC nurse had to be trained on general laboratory safety, handling of a pipette, waste disposal and laboratory spill clean-up. Apart from hard copy standard operating procedures provided to each POC testing laboratory, it was found that quick reference charts containing visual aids were preferred. Upon interview of the nurses after the study, no difficulties in performing the individual POCT were reported. Both the Reflotron pipettes and Vacudrop were easy to use. However, with the Vacudrop there was no guarantee or quality measure to ensure single use only.

***The need for additional consumables to perform multiple POCT*:** Several POCT consumables were required which were not typical to the clinic environment. These were: pipettes (10-100µl) (requiring calibration) and sterile pipette tips (universal: 10-100µl) for blood sample dispensing, parafilm/plastic for Hb microcuvette filling and specimen racks for transport of blood tubes to the POCT laboratory. To ensure safety, several additional components were required: laboratory coat, non-powdered gloves, suitable disinfectant, ethanol and bleach for instrument cleaning, measuring cylinder for preparing cleaning reagents, wash bottles for storing reagents and paper towel. Miscellaneous items required were: multi-plugs, network cables, fridge for EQA/QC material storage, paper for result printing.

***The number of added duties required to perform multiple POCT*:** Table 3 lists the general responsibilities (duties) required by nurses in HIV ART clinics (not specific to the two

Table 3: List of general clinic duties for nurses in HIV ART clinics and the added duties required for performing multiple POCT.

Current clinic duties	**POC DUTIES (pre-analytical, analytical, post-analytical)**
Patient registration	Additional finger stick/venepuncture
History taking	Specimen labeling
Physical examination	Multiple instrument QC testing (~ four instruments)
Counseling	Multiple instrument maintenance (~four instruments)
Rapid HIV testing (HCT)	Perform POCT (ALT, Creat, Hb: <2minutes; PIMA = 20 minutes; Xpert MTB/RIF =2 hours*)
Pregnancy testing	Result recording/printing/reporting
Phlebotomy	External quality assessment (EQA)
Treatment	Infection control
Return visit booking	Spill cleaning
	Waste disposal
	Additional skills required: Phlebotomy and pipetting skills
	Additional duties: Operator certification and on-going monitoring, managing test failures, instrument downtime, stock and waste control, specimen storage.

*GeneXpert test added since this could also be included for POCT in ART clinics.

clinic sites in our study) and then the additional list of duties that the nurse would perform if they were responsible for POCT, as seen in our study.

The length of time to perform the multiple POCT: This was measured at the CHRU site (n=160) and showed the earliest time a POCT was performed was 9:30am (median 11:00; which did include patient consent and enrolling). The latest time a POCT was performed was 16:26pm (median 12:25). The median time from starting the first POCT to starting the last POCT varied, depending on the number and type of tests requested; when CD4 was included, 4 tests took 1hr47minutes; when CD4 was not included, 3 tests took 6minutes. The median number of patients that could be consented, enrolled, bled and tested by one study nurse in one day was 7 (minimum 2, maximum 12). It should be noted that this was under circumstances where dedicated nursing staff were placed at sites to only perform this study.

POCT errors**:** At the CHRU site, the PIMA CD4 instrument reported 9 errors (6%). Channel filling error was reported once and device application errors were reported 8 times, all of which were repeated. CCMT reported an error rate for the PIMA CD4 up to 4.3% (13/302) of which only one specimen could not be resulted on repeat testing. No errors or invalids were reported for the HemoCue, Reflotron and Accutrend. A total of five (5/469) transcription errors (incorrect value) were discovered during the statistical analysis at the CCMT site and three (3/324) at the CHRU site, totalling 1%.

Discussion

A plethora of POC technologies are in the HIV and TB diagnostic pipeline which will require rigorous evaluation to assess performance in the field. This is the first study in South Africa to investigate nurse operated multi-disciplinary POCT for ART initiation and monitoring in a clinical site. In our setting, nurses were easily trained on multiple POCT platforms placed in a dedicated POC testing room, with minimal disruption to clinic workflow. The combination of training materials developed was effective in ensuring competency.

Although POCT has been shown to reduce errors in only a few steps of the entire testing process compared to laboratory testing, quality and risk management is still required [51]. To this end, our dedicated nurses showed 100% compliance on the test specific QC procedures from each of the POC manufacturers. In addition, NHLS EQA material was also trialled on the Pima, HemoCue and Accutrend and demonstrated suitability on POC instruments tested performed by non-laboratory trained staff. EQA in future will be an important component of ensuring quality management of the entire POCT process but may require development or modification before scale up of current services for POCT sites. In South Africa, the South African National Accreditation System (SANAS) has ISO guidelines for medical testing laboratories (ISO 15189) and more recently, specifically for the implementation of POCT (ISO 22870).

Overall, 70% of our study patients required 3 or more tests per visit in both clinic settings. This raises several issues if multiple POCT is to be implemented. Firstly, if a venepuncture specimen is used, which has been shown in some circumstances to be more accurate [40], this could be used for repeat testing and/or referral of residual blood to the laboratory in the case of test failures. Venepuncture will however, require skill in phlebotomy and qualification as HPCSA/SANAS/National Department of Health/NHLS regulated personnel (at least in South Africa where the study was conducted), as well as extra training on opening blood specimens in a “non-laboratory” environment (or use of the Vacudrop). A further challenge will be to minimise duplication in services. Capillary sampling is easier to perform by “non-regulated” operators and will allow task shifting and decentralisation [52], but would require multiple finger sticks per patient per clinic visit a process which has been shown to be accurate [40].

The accuracy of nurse operated multiple POCT was demonstrated. Hemocue Hb testing in particular, showed excellent agreement with predicate methodology as shown previously [53] and the same was true for CD4 and ALT. Cr and lactate at POC showed increased variability, the former is known to be challenging due to variations in haematocrit and

interference by bilirubin [54]. This may be due to variability between operators (two different nurses performed POCT at CCMT site) and some seasonal variability (some testing done in winter at CHRU site, possibly leading to colder hands, poorer blood flow) [30]. This seasonal variability may also have resulted in the differences in CD4 bias observed between the two clinic sites [30]. The CD4 misclassification using Pima was within reported limits of a recently published Pima CD4 meta-analysis [48]. In spite of quality systems in place at the POCT sites, error rates (4.3-6%) were evident from the PIMA CD4 instrument only, but were in line with other studies [39, 55]. The frequency of these errors could be minimized with intensive and ongoing training as was shown previously [40]. Although the study was performed on a venipuncture specimen and residual blood was available for repeat testing, this would have an impact on increasing overall POC testing costs. This together with characteristics of the CD4 technology platform (Pima CD4 over-misclassification) will need to be taken into consideration before implementation.

Another aspect which will impact on overall POCT costs and should be considered prior to implementation of POCT in the field, is the need for added 'consumables' to ensure the safety of POC operators and patients. At a bear minimum, the use of gloves and gown/ laboratory coat, hand-washing facilities and disinfectants for cleaning should be imperative to protect the POC operator from blood-borne pathogens. Most of these items are not commonly available within a clinic environment and thus for the purposes of this study, a clinic POC 'starter-kit' was developed which provided all needed items such as laboratory coat, wash bottles (for disinfectant), plastic measuring cylinder (for preparation of disinfectants), ethanol, bleach, hand-wash, standard operating procedures and quick reference testing charts. Going forward this would need to be the responsibility of the service provider.

The length of time taken to perform and result multiple POCT would require workflow considerations within the clinic. In this study, at least 22 extra duties were required by a

NIMART (nurse initiated management of antiretroviral treatment) trained nurse [56]. This will further increase with the addition of screening tests such as cryptococcal antigen and hepatitis B antigen [25]. An increase in workload leads to increased transcription errors and even in this study, where dedicated nurses performed POCT without any NIMART duties, transcription errors occurred. The need for centralized data monitoring and the ability to interface with information systems is required [10, 57] to ensure that data can be audited and managed.

For wide-scale implementation of POCT in South Africa, the first step will need to be identification of appropriate clinics where there are gaps in service delivery. This is already being done through Geographical Information System (GIS) mapping tools, not only to identify gaps but also decide on the most cost-effective implementation strategies. The role of connectivity, cost-effectiveness and overall impact of POCT remain to be addressed through a randomised controlled trial.

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