Head to head comparisons in performance of CD4 point-of-care assays: a Bayesian meta-analysis (2000–2013)

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ABSTRACT

Timely detection, staging, and treatment initiation are pertinent to controlling HIV infection. CD4+ cell-based point-of-care (POC) devices offer the potential to rapidly stage patients, and decide on initiating treatment, but a comparative evaluation of their performance has not yet been performed. With this in mind, we conducted a systematic review and meta-analyses. For the period January 2000 to April 2014, 19 databases were systematically searched, 6619 citations retrieved, and 25 articles selected. Diagnostic performance was compared across devices (i.e., PIMA, CyFlow, miniPOC, MBioCD4 System) and across specimens (i.e., capillary blood vs. venous blood). A Bayesian approach was used to meta-analyze the data. The primary outcome, the Bland–Altman (BA) mean bias (which represents agreement between cell counts from POC device and flow cytometry), was analyzed with a Bayesian hierarchical normal model. We performed a head-to-head comparison of two POC devices such as PIMA and PointCareNOW CD4. PIMA appears to perform better vs. PointCareNOW with venous samples (BA mean bias: –9.5 cells/μL; 95% CrI: –37.71 to 18.27, vs. 139.3 cells/μL; 95% CrI: –0.85 to 267.4, mean difference = 148.8, 95% CrI: 11.8, 285.8); however, PIMA's best performed when used with capillary samples (BA mean bias: 2.2 cells/μL; 95% CrI: –19.32 to 23.6). Sufficient data were available to allow pooling of sensitivity and specificity data only at the 350 cells/μL cut-off. For PIMA device sensitivity 91.6 (84.7–95.5) and specificity was 94.8 (90.1–97.3), respectively. There were not sufficient data to allow comparisons between any other devices. PIMA device was comparable to flow cytometry. The estimated differences between the CD4+ cell counts of the device and the reference was small and best estimated in capillary blood specimens. As the evidence stands, the PointCareNOW device will need to improve prior to widespread use and more data on MBio and MiniPOC are needed. Findings inform implementation of PIMA and improvements in other CD4 POC device prior to recommending widespread use.

INTRODUCTION

Universal access to antiretroviral therapy (ART) and increased levels of HIV testing have created hope that HIV infection can be controlled globally. Approximately 9.7 million people now receive ART in low- and middle-income countries, representing a 32-fold increase over the last decade [1].

Effective ART reduces viral load (VL) to undetectable levels and dramatically reduces associated mortality and morbidity [2–4]. As a public health intervention, ART is at the core of a treatment-as-prevention strategy, as reducing community viral load reduces HIV transmissions [4].

CD4+ cells counts and measures of VL are surrogate biomarkers of disease progression that help to stage, initiate and monitor treatment. CD4+ cell counts provide an immunological measure of HIV progression; these counts are utilized in the care of HIV+ patients for staging infections and in assessing patients for ART eligibility [5–8]. Specialized laboratories use highly trained personnel and sophisticated flow cytometry techniques to perform CD4+ cell counts, as this is the current gold standard technique [6, 9].

When ART is available, rapid staging, continual monitoring, and retention of individuals on ART become crucial to controlling HIV infection, but the availability of quality patient monitoring in all field settings remains a challenge [10].

In global settings, patients are often required to travel long distances to clinics with specialized central laboratories to be staged and initiated on ART [11, 12]. However, the nature of a centralized laboratory demands that patients attend on separate days for testing and treatment, which strains patients' time and resources [11, 12]. As a consequence, estimates from studies suggest that only about 60% (range 35–88%) of individuals who receive an HIV diagnosis in sub-Saharan Africa receive a CD4+ count, meaning many remain oblivious to the need for treatment initiation or switching [3]. Furthermore, 25% are initiated on ART at CD4+ counts below 100 cells/μL, by which point the virus has already inflicted considerable damage to the immune system [1, 14]. In addition, once initiated on ART about 30% are lost to follow up later on in the cascade of care, reflecting the inefficiencies in delivery mechanisms [9, 11, 13, 15–18]. Centralized laboratories must transport specimens to and from the laboratory and they cannot always deal with the demand for CD4+ cell counts [9, 16, 19]. Decentralized and linked point-of-care (POC) systems will help to plug some of the inefficiencies in the monitoring and delivery systems, preventing loss to follow up of patients.

CD4 and VL POC tests that are less reliant on infrastructure, and can operate in the absence of a continuous electricity supply and without laboratory equipment, specialist personnel or sample transport systems [9, 15, 16]. Some CD4 POCs aim to provide individual CD4+ cell counts in as little as 8 minutes at the POC contact with a finger stick specimen. These assays could expedite staging and allow for ART to be initiated at the same site and within the same clinic visit, saving time and money for providers and health systems with reduced burden on patients. This should translate into greater adherence to treatment, better compliance with prescribed regimens, and a reduction in loss to follow up [16]. Indeed, in a recent study, when a POC CD4 device was successfully introduced in the primary health sites in Mozambique, the total computed lost to follow up prior to ART initiation dropped substantially from 64% to 33% [15].

POC CD4 devices that are now being marketed or developed use different underlying technologies. The PIMA (Alere, USA) device uses dual fluorescence image analysis. In turn, the MiniPOC (Partec, GmbH), the PointCareNOW (PointCare, USA), and the HumaCount (Human Diagnostics, GmbH) use miniaturized flow cytometry, whereas the Daktari CD4 (Daktari Diagnostic, USA) device is based on microfluidics and the MBio CD4 analyzer (MBio Diagnostics, Inc., USA) uses optical technology. Two smaller devices are also in development: the Zyomyx's CD4 test (Zyomyx, Inc., USA) and the VISITECT CD4 (Omega Diagnostics group, UK) [10, 16, 20].

Although the performance of some of these devices has been evaluated against the gold standard (flow cytometry), a comparative evaluation of their performance in finger stick and venous blood specimens has not been done. In view of the likely increased use of POC CD4 assays across the sub-Saharan and Asian settings, there is a need for a meta-analysis that is independent-of-industry evaluations. This will help answer a number of questions: (1) which device performs best, (2) how do they compare with the gold standard, and (3) are capillary blood specimens better than venous specimens. We therefore performed a meta-analysis to present combined estimates of these parameters.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report this review [21]. Two reviewers (SW and TC) completed the search and reviewed the literature. The flow chart is presented in Figure 1. Search strategy was designed by a librarian (BN). Literature was searched for the period 1 January 2000 to 1 January 2013, with a Medline update to 24 April 2014; the databases included in the search are detailed in Appendix 2 and search in Appendix 1. Bibliographies and citing articles of our eligible studies (and selected reviews) were retrieved using Web of Science and Scopus. Authors were contacted for additional data where necessary, and one study team provided additional information for the meta-analysis [22]. Manufacturers of the devices were also contacted for data. In the first review for eligibility, we independently screened the titles and citations for inclusion (SW and TC). In the second review, we retrieved the full texts of selected articles to determine eligibility; discrepancies were resolved through discussion and in consultation with a third reviewer (NPP).

Working definitions of POC were based upon criteria established by our group in 2012 [23]. We included studies of devices that provided CD4 counts for HIV+ adult populations. CD4 counts were obtained, either for pre-ART staging of infection in those newly diagnosed with HIV or for regular follow-up monitoring of treatment response. We excluded studies where HIV– specimens were used, as well as studies including children as they constitute a separate group where there is a huge variability.

DATA ABSTRACTION

A standardized data form was created and used. Data were abstracted on study setting, participant characteristics, sample size, reference test, index tests, Bland–Altman (BA) mean bias, sensitivity, specificity, and raw data (true positives, etc.). Reviewer one (SW) abstracted all data from the eligible articles, reviewer 2 (TC) abstracted data from 50% of the articles to check for consistency.

STATISTICAL ANALYSIS

Bland–Altman mean bias

To investigate our questions, our primary outcome measure was the BA mean bias. The BA mean bias is an average of the difference between the result from the index test and the reference. It is a popular method for assessing the

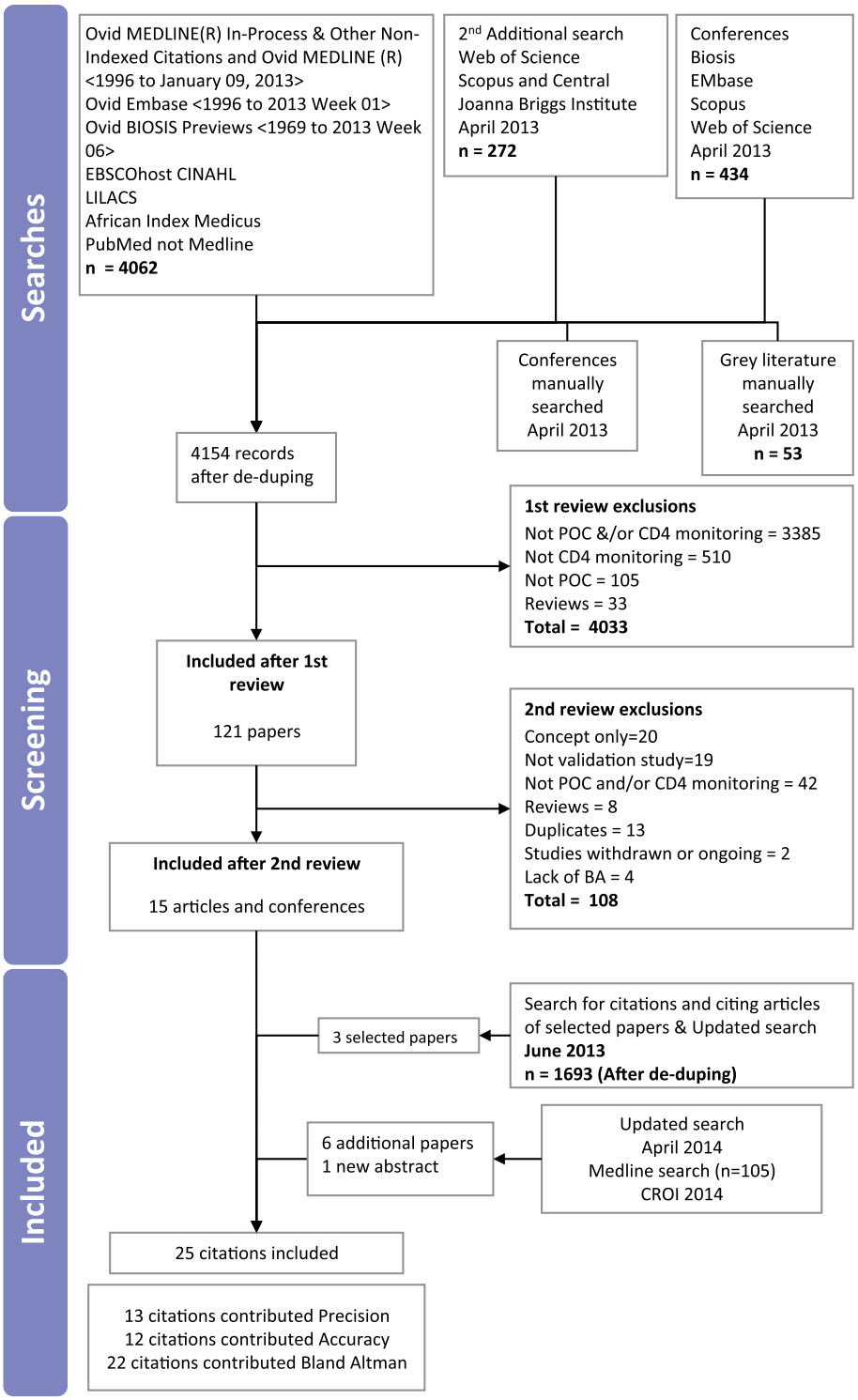

Figure 1. Flow diagram of study screening.

agreement between two continuous measures and more appropriate than correlation coefficients for comparing continuous diagnostic tests to a gold standard [24]. In the context of our review, the BA mean bias represented the average number of cells by which the result from the POC device differed from the reference test [24].

In order to understand whether performance differed between the types of specimen used, we performed a

subgroup analyses by specimen (capillary and venous). The PIMA device was heavily represented in the dataset (80%, 32/40) and we were only able to meta-analyze the data for the PIMA (venous and capillary) and the PointCareNOW (venous only). Data for the MBio CD4 System and CyFlow miniPOC were limited (two and one data points, respectively), therefore we were unable to meta-analyze Bland–Altman data for these devices. Instead, the performance of these devices was explored graphically, using forest plots created in R (R 3.0.2 GUI 1.62 Snow Leopard build). In pooling our data in meta-analysis both operators and settings were assumed to be equivalent as POC devices should be robust to these factors in order to perform well in the field. We used a Bayesian hierarchical normal model to combine the BA results across studies. At the first level of the hierarchical model, the BA mean bias from each study is assumed to follow a normal density, with study specific mean and study specific standard deviation. At the second level of the hierarchy, the means across studies are assumed to follow a normal density, with an overall mean and an overall variance across studies. We converted the standard deviations within each study from standard errors by multiplying by the square root of the sample size. We assumed that the logarithms of the study specific variances then followed a normal hierarchical density. We used diffuse priors across all parameters so that the data drive the final inferences.

Sensitivity and sensitivity

Due to lack of data, use of varying CD4+ cell count cutoffs, and sporadic use inclusion ranges, we were only able to complete a meta-analysis for a CD4 cutoff of 350 cells/mL. The remaining data were explored visually using forest plots.

We used a Bayesian hierarchical logistic regression model for meta-analysis of the sensitities and specificities, each modeled separately. All sensitivity and specificity values were first converted to a logit scale. On this scale, we assumed that sensitivities and specificities from different studies followed a normal density. We used a uniform prior for the SD with an upper limit of 3 on the logit scale, and wide normal priors for the mean parameters. Once meta-analyses were completed, all results were converted back to the probability scale by an inverse logit transform.

Repeatability

Although we did abstract data on repeatability, due to lack of data, we presented the available information in Appendix 3. Regarding quality, both reviewers independently assessed each study using the QUADAS-2 criteria [25]. Disagreements were resolved by consensus or by consulting a third reviewer (NPP).

RESULTS

For the period January 2000 to April 2014, about 19 databases were systematically searched, 6619 citations retrieved, and 25 articles were selected. Diagnostic performance was compared across devices (i.e., PIMA, CyFlow, miniPOC, MBioCD4 System) and across specimens (i.e., capillary blood vs. venous blood).

Figure 1 details the study selection process. In total, of the 6619 papers that we screened, 25 studies were included in our analysis, summarized in Appendix 2.

By assessing each study using the QUADAS-2 criteria [25] we found that included studies were of moderate quality, Figure 2.

Bland–Altman

For the PIMA meta-analysis by specimens, 13 studies contributed 15 data points to the venous meta-analysis and 13 studies contributed 17 data points to the capillary meta-analysis (32 data points in total).

With regard to our first objective, which device performs the best, we found that the PIMA device was superior. Our findings highlight a severe lack of evidence for all other devices.

We found that the PIMA device was comparable to flow cytometry. The results from the meta-analysis for the PIMA device

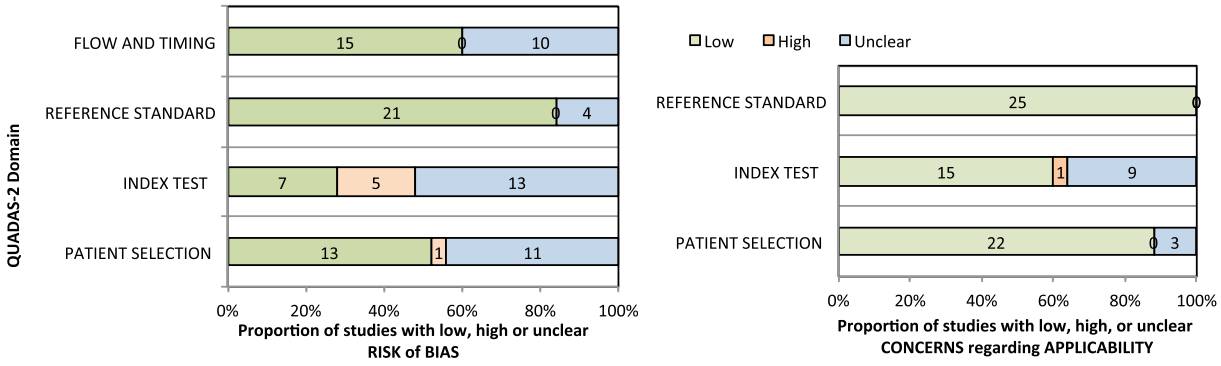

Figure 2. Results of QUADAS-2 analysis.

indicates that, when used with capillary specimens, the device will agree well with the reference flow cytometry method.

The PointCareNOW device did not appear to agree well with the reference standard, and the device appears to overestimate the CD4 cell count. The data for the PointCareNOW device were contributed by just two studies, and the results from these two studies appears to substantially differ: the more recent study indicated that the device performed better, perhaps indicating that the PointCareNOW device is still under development.

The other devices in our review, the MBio and MiniPOC appear to be promising; however data are severely lacking for these devices at this time.

We also found that capillary specimens yielded more accurate results than the venous specimens (Figure 3). The results of the meta-analysis for the PIMA data indicate that on average

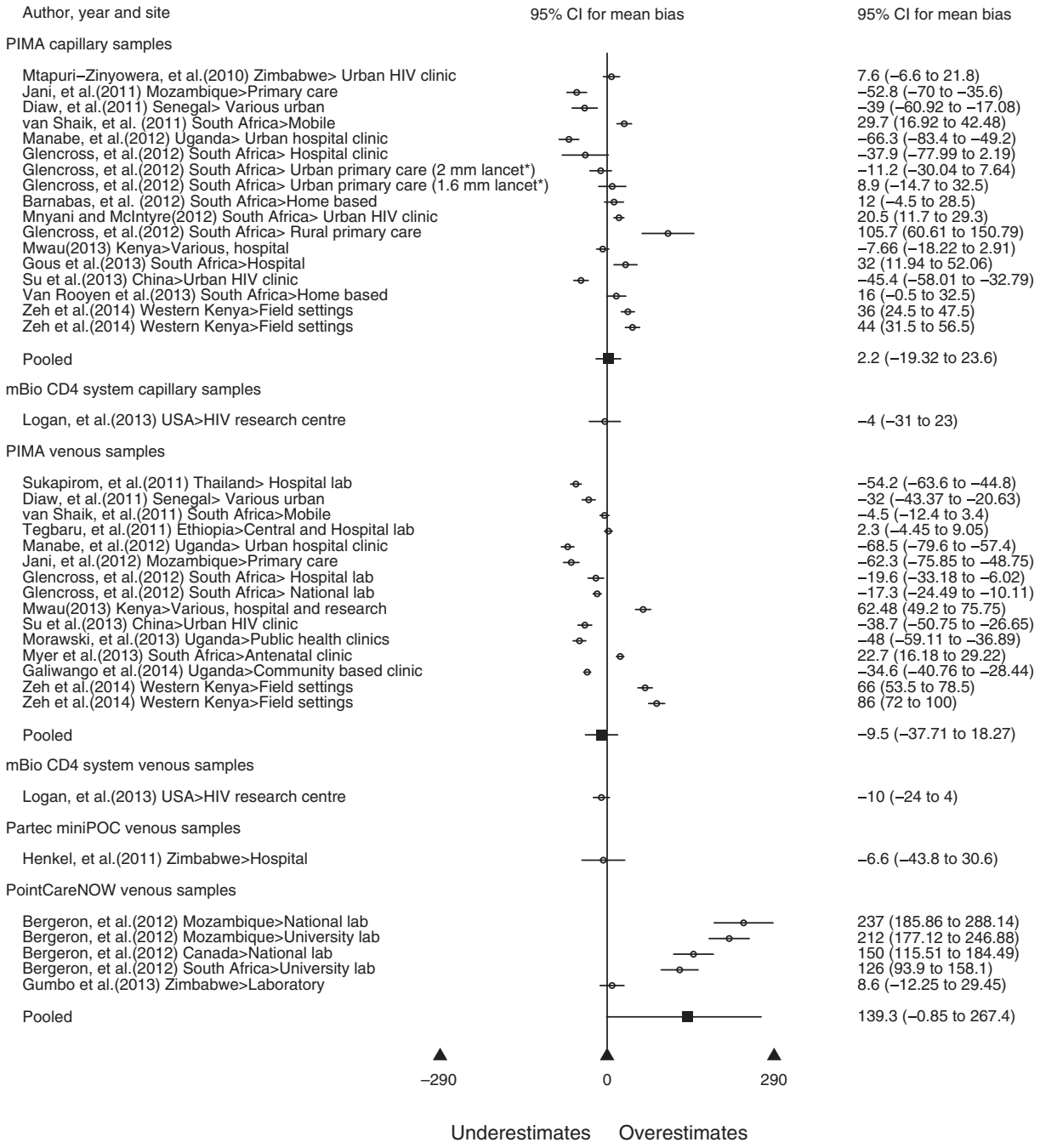

Figure 3. Bland–Altman results. Forest plot and pooled results, grouped by substrate used and POC device.

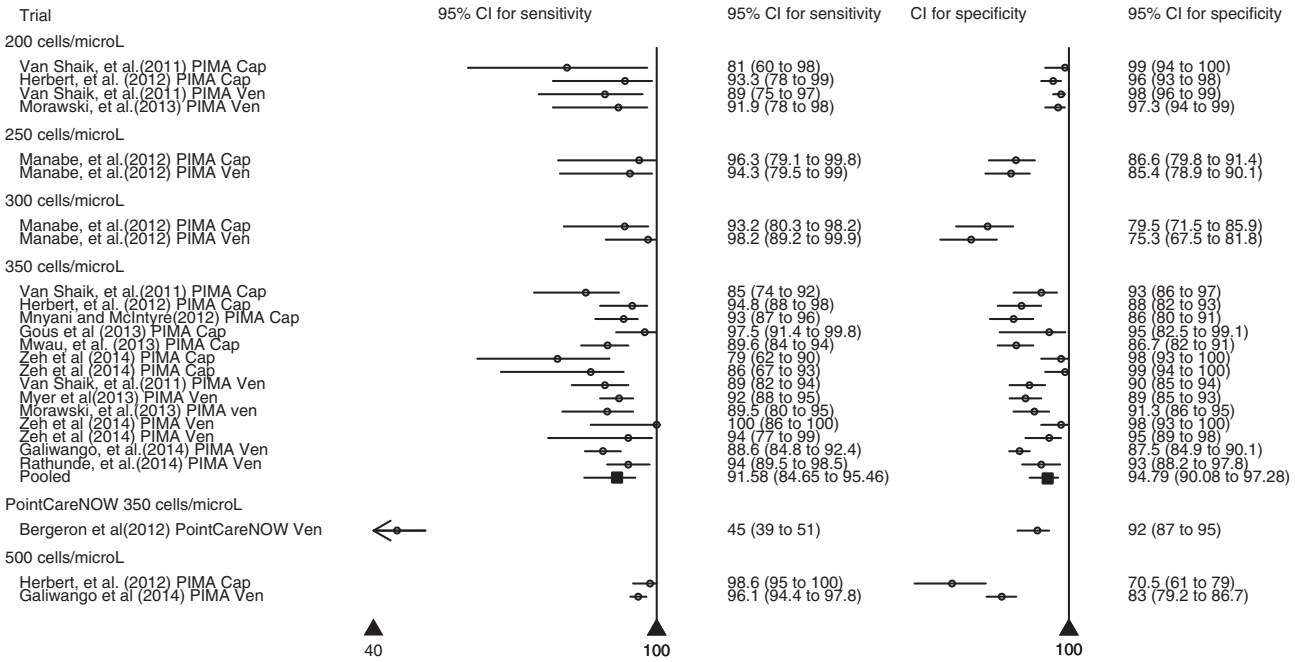

Figure 4. Accuracy results. Forest plot and pooled results, grouped by substrate used and POC device.

the PIMA device better estimates capillary specimens compared to venous specimens. The capillary specimens had a small BA mean bias point estimate of 2.2 cells/μL; 95% CrI: –19.32 to 23.6, vs. 9.5 cells/μL; 95% CrI: –37.71 to 18.27 for venous specimens.

Sensitivity and specificity

Our meta-analysis of the results of diagnostic accuracy (i.e. sensitivity and specificity) data may be a more easily understood analysis, in that it provides direct information about the ability of CD4 devices to correctly identify patients for treatment. We found that of the 26 included articles, only 12 reported accuracy information, refer Figure 4. Of these, a majority (10) reported at the 350 cell/μL cutoff; the cutoff used in other papers varied widely (three reported on the 200 cell/μL cutoff, one used 250 cell/μL, another one used 300 cell/μL, and two chose 500 cell/μL as the cutoff). Much of this variation is probably due to the World Health Organization's (WHO) steadily increasing CD4 cutoff guidelines for ART initiation over the last 5 years [7, 26] Again, the PIMA device dominated the data, only one study contributed data for the accuracy of the PointCareNOW device.

We found that at the 350 cells/μL cutoff the PIMA device identifies patients for treatment with a sensitivity of 91.58 (CrI: 84.65–95.46) and specificity of 94.79 (CrI: 90.08–97.28).

Repeatability

Data relating to the repeatability of CD4 POC devices were difficult to summarize due to a wide range of measures used, inter-rater, inter-assay, and quality control runs. The data appear to indicate good levels of repeatability (Appendix 3).

DISCUSSION

Summary of evidence

Our review suggests that, overall, the POC CD4 device, the PIMA was comparable in performance to conventional flow cytometry. In comparison, the PointCareNOW device does not appear to perform as well, and further development of the technology should be completed prior to widespread use of this device. For other devices, we found that the data are still limited; more POC CD4 devices evaluations are urgently needed to respond to the global demand for HIV patient monitoring.

In interpreting our findings for the PIMA, it is vital that the mean bias results are not considered in isolation; the credible intervals (CrIs, the Bayesian equivalent term for the frequentist 95% confidence intervals) are more informative and provide a complete picture of overall performance, the bias, and the range of variability. The CrIs estimate the likely range of the difference between the CD4+ cell counts of the device and that of the reference. Given this, the PIMA device performed well for capillary specimens as the range of expected agreement was –19.32 to 23.60 cells/μL, so we can be confident that the PIMA can be used interchangeably with flow cytometry. For venous specimens, the CrIs are wider, indicating more variability in the agreement –37.71 to 18.27 cells/μL. Thus, we concluded that despite a small number of data points, the PIMA device for now offers the potential to be scaled up and operationalized in decentralized settings for the monitoring and staging of HIV-infected individuals.

Our secondary findings suggest that current POC devices work better for capillary specimens (compared to venous); it was clear that most devices are best optimized for capillary specimens. This finding reflects that capillary blood could be safely used to monitor CD4 counts, which is important for all international settings. Oftentimes, phlebotomists are not easily available on site to procure venous specimens, but capillary specimens, can be obtained easily, by clinic staff with minimal training and certification in testing.

Implication of our findings for practice

In addition to provide a staging and treatment initiation solution at one clinic, portable CD4 POC devices will help solve a number of barriers to accessing care (i.e., number of clinic visits, long waiting time in clinics, physical distances and location of clinics). These barriers impact on timely access to services by rural poor communities. If portable CD4 devices can also be taken to the rural village clinic, then high-quality HIV care could be delivered at the very place it is most needed, in a convenient and patient friendly way. Additionally, current services available in clinics could be expanded to include both POC CD4 counts and VL counts, allowing for faster triage of the sickest individuals and patients could be tracked for follow-up.

Furthermore, these technologies are developing fast and many manufacturers are equipping their devices with data storage and global positioning system capabilities, which can allow data to be transferred to online storage; encouraging technology-assisted quality control systems. For example a service in Mozambique is using general packet radio service-enabled PIMA devices to make use of the already available cellular communication networks [27]. Such capabilities allow for regional- and national-level supervision of performance of laboratories, tracking test results, of skilled personnel, and with tracking a rapid resolution of problems. These modern, high-quality integrated care systems are sensitive to patient needs with data storage and quality capability.

For global use, the absolute CD4 count has been shown to be unreliable in pediatric populations, making many CD4 POC devices unsuitable for staging in this patient group; this issue does not apply to adult HIV-infected populations [28]. New generations of POC CD4 devices will need to incorporate the ability to provide CD4% for the less sensitive pediatric populations [7]. Currently, only two devices (PointCareNOW and the miniPOC) offer that option, so further improvements and evaluations of these devices would be welcomed.

Strengths of this review include a comprehensive search, a synthesis of current evidence relating to the precision of POC CD4 devices, and with advanced analytical techniques; in addition, this is the first Bayesian meta-analysis that compares POC tests using a Bland–Altman bias.

Limitations

As is always the case with the pooling of published data, our meta-analysis is vulnerable to bias. Because of the restricted data available, we were only able to fully pool data for the PIMA and the PointCareNOW devices. More evidence must exist for the full range of devices that are on the market, but these data have not yet been published. We were unable to find any published data relating to the performance of some high-profile POC devices (i.e., Zyomyx, VISITECT, Daktari). We also noted that a majority of the BA plots were funnel shaped, perhaps indicating some interference. The use of the absolute mean bias can make the BA plots appear to be funnel shaped, when in fact this is due to a large range of the CD4 count. Because the ranges in the CD4 counts are wide, the mean bias is relative to the CD4 count, and should be reported as such. However, in our sample only two studies [29, 30] reported the relative mean bias [27, 30]. Future evaluations should report the relative mean bias, and more useful for comparison in future meta-analyses.

Implications for future research

More evaluations of newer CD4 POC devices such as handheld devices will always be useful for evidence. Cost-effectiveness analysis will help understand the incremental benefit of use in dollar amounts, prior to their large-scale implementation. The reliability of the devices will need to be considered in the future; for this analysis insufficient and inconsistent data were available.

CONCLUSIONS

To conclude, our meta-analysis suggests that, for one, the PIMA device performed comparably to conventional flow cytometry and was superior in performance compared to the PointCareNOW device. Secondly, capillary specimens were more accurately counted than venous specimens. We recommend that PIMA CD4 POC devices could be operationalized in decentralized settings with capillary blood, and more field research, data, and improvements in technology are needed for other CD4 POC devices.

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CONTRIBUTORS

NPP, SW conceived the study, and LJ designed the study methods and analyses.

BN designed and completed the searches.

SW, NPP and TC reviewed the literature and generated the results.

LJ performed the meta-analysis, SW created forest plots.

NPP, SW, LJ wrote the first draft. NPP, LJ, SW, TC and BN critiqued the final draft of the report.

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COMPETING INTERESTS

We declare that we have no conflicts of interest with the industry.

PUBLISHING NOTES

Appendix 1. Search strategy for Medline, run on 14th January 2013.

Databases searched, between 2000 and 2013	Conferences manually searched	Grey literature manually searched
>Ovid Medline		
>Embase (Ovid)	>IAS 2011	Health technology assessment agencies (mainly Canadian) including:
>BIOSIS Previews (Ovid)	>AIDS 2012	
>Cinahl Plus with Full Text (EBSCOhost)	>IDSA 2011	>CADTH
>LILACS	>Idweek 2012	>Ontario Ministry of health and Long Term Care
>African Index Medicus	>ISSTDR 2011	>WHO
>PubMed (not Medline)	>CAHR 2011	>INAHTA,
>Web of Science	>CAHR 2012	>mRCT
>Scopus	>CROI 2013	>ClinicalTrials.gov
>Cochrane Library and CENTRAL	>CROI 2012	>Thomson Centerwatch
>Joanna Briggs Institute	>IAS 2013	
>Web of knowledge		

Appendix 2. Summary table of selection studies.

Author	Year	Population	Intervention, type of study	POC test name	Reference flow cytometer	Site	Country	*n*	POC Operator	Reference
Mtapuri-Zinyowera et al.	2010	Newly diagnosed HIV+ male and female participants	Paired blood samples	PIMA	FACSCalibur	Urban HIV clinic	Zimbabwe	165	Nurses and lab technicians	[31]
Mnyani and McIntyre	2012	Consecutive HIV+ pregnant women in a prevention of mother-to-child transmission of HIV service in Johannesburg	Parallel CD4+ cell count testing was done using capillary specimens for the PIMA and venous samples for flow cytometry.	PIMA	Beckman Coulter Flow Cytometer	Urban HIV clinic	South Africa	296	Clinic staff	[41]
Bergeron et al.	2012	Five sites independently conducted studies primarily using samples mostly from HIV+ patients	Samples were tested with both the PointCare NOW and reference flow cytometry	PointCareNOW	FACSCalibur	National lab	Mozambique	143	Clinic staff	[27]
						University lab	Mozambique	114		
						National lab	Canada	89		
					EPICS-XL	University lab	South Africa	71		
Sukapirom et al.	2011	HIV+ blood samples, at various stages of HIV-1 infection.	Simultaneous testing on PIMA and reference	PIMA	FACSCount	Hospital lab	Thailand	203	Lab technicians	[42]
Manabe et al.	2012	Adults attending an infectious disease clinic a Hospital, for a routine clinic visit.	Evaluation of the PIMA compared to the BD FACSCalibur	PIMA	FACSCalibur	Urban hospital clinic	Uganda	176	Clinic staff	[34]
Glencross et al.	2012	Coordinated through an Academic Hospital CD4 reference laboratory, located in Johannesburg	Baseline accuracy, followed by field testing in primary care sites	PIMA	SP PanLeucogated CD4	National lab	South Africa	100	Lab technicians	[29]
						Hospital lab		91	Lab technicians	
						Hospital clinic		77	Nurse	
						Rural 1° care		96	Nurse	
						Urban 1° care (1.6mm lancet)		87	Nurse	
						Urban 1° care (2mm lancet)		52	Nurse	
Diaw et al.	2011	Patients presenting for HIV follow-up or other laboratory examinations presented in 4 different clinical sites	CD4 counts were measured by PIMA and by FACSCount considered as the reference	PIMA	FACSCount	Various urban	Senegal	100	Lab and clinic staff	[35]
								95		

Appendix 2. (Continued)

Author	Year	Population	Intervention, type of study	POC test name	Reference flow cytometer	Site	Country	*n*	POC Operator	Reference
Barnabas et al.	2012	Home-based counseling and testing	POC CD4 testing and a venous blood draw by Facs Calibur	PIMA	FACSCalibur	Home based	South Africa	185	Nurse	[43]
Tegbaru et al.	2011	Evaluation of a point of care-CD4 testing in Ethiopia	Evaluation study	PIMA	FACSCalibur	Central and Hospital lab	Ethiopia	316	Lab technicians	[44]
Logan et al.	2013	HIV+ individuals were recruited for this study from a research centre in the US	Venous and capillary and tested using the MBio system and conventional flow cytometry.	MBio CD4, SnapCount™	FACSCalibur	HIV research centre	USA	52	Lab technicians	[36]
					FACSCalibur	HIV research centre	USA	94	Lab technicians	
Henkel et al.	2011	Blood samples were collected from an infectious disease Hospital	Each sample was processed twofold for the miniPOC and the reference instrument	miniPOC	CyFlow SL-3	Hospital	Zimbabwe	125	Lab technicians	[45]
Jani et al.	2011	Adult HIV+ patients enrolled consecutively at primary healthcare clinics in Mozambique	Paired samples of finger prick and venous blood tested on the POCT CD4 device and with laboratory instruments	PIMA	FACSCalibur	Primary care	Mozambique	135	Nurses	[33]
				PIMA	FACSCalibur	Primary care	Mozambique	140	Nurses	
Thakar et al.	2012	Participants at 21 ART centers from different parts of the country	Evaluation study against the reference methods (FACSCalibur, FACSCount and CyFlow SL3).	PIMA	FACSCount	HIV research centre	India	175	Clinic staff	[32]
					Multiple	ART centre	India	1790	Clinic staff	
van Shaik et al.	2011	Consecutive HIV+ individuals (both on ART and not on ART) had a capillary and/or venous sample in a mobile clinic	Cross-sectional, convenience based sampling. Both PIMA™ and laboratory CD4 counts done	PIMA	XL-MCL	Mobile	South Africa	325	Nurses	[30]
Morawski et al.	2013	Testing in a multisite real-world setting at 7 Kampala city health facilities under general clinic conditions.	Venous samples were run on the PIMA, excess portions were sent to the University laboratory for reference testing.	PIMA	FACSCalibur	Public health clinics	Uganda	225	Clinic staff	[46]
Mwau et al.	2013	Nine health facilities offering CD4+ T cell enumeration. All patients attending the facilities for HIV treatment.	Comparison study, venous and capillary blood specimens were collected consecutively patients presenting	PIMA	FACSCount	Various, hospital and research	Kenya	822	Lab technicians	[47] [22]
							Kenya	521	Lab technicians	

Appendix 3. Summary table of accuracy data.

Author	Year	POC test name	Substrate Ven: Venous Cap: Capillary	Cut off point cells/μL	Sensitivity (%)	Specificity (%)	Total misclassified (%)	Misclassified above (%)	Misclassified below (%)	Notes	Reference
Diaw et al.	2011	PIMA	Ven	200	90	98	–	–	–	10% bilateral inclusion range used	[35]
Diaw et al.	2011	PIMA	Cap	200	91	96	–	–	–	10% bilateral inclusion range used	[35]
Diaw et al.	2011	PIMA	Ven	350	98	79	–	–	–	10% bilateral inclusion range used	[35]
Diaw et al.	2011	PIMA	Cap	350	91	80	–	–	–	10% bilateral inclusion range used	[35]
Herbert et al.	2012	PIMA	Cap	200	93.3	96	–	–	–	–	[41]
Herbert et al.	2012	PIMA	Cap	350	94.8	88	–	–	–	–	[41]
Herbert et al.	2012	PIMA	Cap	500	98.6	70.5	–	–	–	–	[41]
Jani et al.	2011	PIMA	Cap	350	–	–	17	2.2	14.8	–	[33]
Jani et al.	2011	PIMA	Cap	200	–	–	5.2	0	5.2	–	[33]
Thakar et al.	2012	PIMA	Cap	350	96	91	–	–	–	–	[32]
Mtapuri-Zinyowera et al.	2010	PIMA	Cap	200	–	–	6.6	2.4	4.2	–	[31]
Mtapuri-Zinyowera et al.	2010	PIMA	Cap	350	–	–	6.6	4.2	2.4	–	[31]
Tegbaru et al.	2011	PIMA	Cap	200	–	–	9.2	–	–	–	[42]
Logan et al.	2013	MBio CD4, SnapCount™	Cap	350	–	–	3.8	3.8	0	–	[36]
Logan et al.	2013	MBio CD4, SnapCount™	Ven	350	–	–	5.3	2.1	3.2	–	[36]
Manabe et al.	2012	PIMA	Cap	250	96.3	86.6	–	–	–	–	[34]
Manabe et al.	2012	PIMA	Cap	300	93.2	79.5	–	–	–	–	[34]
Manabe et al.	2012	PIMA	Ven	250	94.3	85.4	–	–	–	–	[34]
Manabe et al.	2012	PIMA	Ven	300	98.2	75.3	–	–	–	–	[34]
Mnyani and McIntyre	2012	PIMA	Cap	350	93	86	–	–	–	–	[43]
Mnyani and McIntyre	2012	PIMA	Cap	350	82	94	–	–	–	–	[43]
Bergeron et al.	2012	PointCareNOW	Ven	350	53	94	–	–	–	10% bilateral inclusion range used	[27]
Bergeron et al.	2012	PointCareNOW	Ven	200	39	94	–	–	–	10% bilateral inclusion range used	[27]
Van Shaik et al.	2011	PIMA	Ven	200	89	98	–	–	–	–	[30]
Van Shaik et al.	2011	PIMA	Ven	350	89	90	–	–	–	–	[30]
Van Shaik et al.	2011	PIMA	Cap	200	81	99	–	–	–	–	[30]
Van Shaik et al.	2011	PIMA	Cap	350	85	93	–	–	–	–	[30]
Mwau et al.	2013	PIMA	Cap	350	89.6	86.7	–	–	–	–	[44]
Morawski et al.	2013	PIMA	Ven	200	100	>99	–	–	–	–	[45]
Barnabas et al.	2012	PIMA	Not reported								[46]
Henkel et al.	2011	miniPOC	Not reported								[47]
Sukapirom et al.	2011	PIMA	Not reported								[48]
Glencross et al.	2012	PIMA	Not reported								[29]