

HIV Point Of Care Diagnostics: Meeting The Special Needs Of Sub-Saharan Africa

Godwin A. Aleku^{1,2}; Moses P. Adoga^{3,4}; Simon M. Agwale^{5,6}

1. Manchester Institute of Biotechnology, University of Manchester, Manchester, United Kingdom.
2. National Agency for Food and Drug Administration and Control (NAFDAC), Lagos, Nigeria.
3. Microbiology Unit, Department of Biological Sciences, Nasarawa State University, Keffi, Nigeria.
4. Computational and Evolutionary Biology / Bioinformatics, Faculty of Life Sciences, University of Manchester, Manchester, United Kingdom.
5. Innovative Biotech, Keffi/Abuja, Nigeria.
6. Innovative Biotech USA Inc, Frederick Innovative Technology Center, 4539 Metropolitan Ct, Frederick MD 21704, US.

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
EIA	Enzyme Linked Immunosorbent Assay
HIV	Human Immunodeficiency Virus
POC	Point of Care
UNAIDS	Joint United Nations Programme on HIV and AIDS
WHO	World Health Organisation
RDT	Rapid diagnostic test
RLS	Resource Limited Settings
EID	Early Infant Diagnosis
PCR	Polymerase Chain Reaction
TB	Tuberculosis
DBS	Dried Blood Spot

Abstract

Sub-Saharan Africa, accounting for 70% of the 35 million people living with HIV worldwide, obviously carries the heaviest burden of HIV epidemic. Moreover, the region's poor health system occasioned by limited resources and inadequate skilled clinical personnel usually makes decentralization of HIV care difficult. Therefore, quality diagnostics that are easy to use, inexpensive and amenable for use at point of care (POC) are a dire necessity. Clearly, such diagnostics will significantly lessen the pressure on the existing over-stretched centralized HIV laboratory services. Thankfully, some POC diagnostics are already being validated while others are in the pipeline. As POC test kits emerge, implementation hurdles should be envisaged and planned for. This review examines emerging HIV diagnostic platforms, HIV POC product pipelines, gaps, perceived POC implementation challenges and general recommendations for quality care.

Key words: Point of care, diagnostics, resource limited settings, sub-Saharan Africa

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1.0 Introduction

The statistic for HIV epidemic is disproportionately alarming. Sub-Saharan Africa carries the heaviest burden of the global epidemic. The UNAIDS 2013 report reveals that over 35million people are infected with HIV worldwide, with sub-Saharan Africa accounting for 70% of the epidemic [1]. Sadly, the region also faces other equally serious challenges such as poverty, famine, infrastructural decay, political instability and other debilitating diseases [2] which directly or indirectly drive the epidemic.

Paradoxically, the health systems in sub-Saharan Africa are ill-equipped to contend emerging threats [3,4]. This is further worsened by inadequate healthcare professionals. Only 1.3% of the world's healthcare workforce caters for this region that experiences 25% of global disease burden [5]. Consequently, delivery of quality healthcare in sub-Saharan Africa is still far from ideal. This is particularly worrisome in chronic disease management like HIV/AIDS treatment.

However, global response to the epidemic by all stakeholders has been impressive and commendable. For example, in 2003, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the “3 by 5” programme to scale up antiretroviral (ARV) coverage in sub-Saharan African countries [6]. The results have been encouraging. Today over 9.7 million infected persons are estimated to be receiving these life-saving medications in low and middle income countries representing 61% ARV coverage [1]; a huge difference from the 2% coverage in 2003 [6].

Despite this historic achievement gained in scale-up of ART services, infected people requiring ARVs exceed those currently on ART judging from the WHO 2013 revised guideline [1,7] . Accordingly, emphasis now centers not only on numbers of care enrollees but more importantly on quality of care for enrolled persons [8,9]. This brings to mind the enormous

task that lies ahead. On one hand, there is the need to continue the scale up of ART enrolment to guarantee universal access. The other concerns a critical need to monitor effectively and retain ART and would-be ART patients.

The birth of HIV rapid diagnostic tests (RDTs) and its successful incorporation into HIV testing at the point of care (POC) in resource limited settings (RLS) saw to the massive enrolment into HIV care [1,10]. However, clinical diagnostic monitoring tools, such as those for CD4 cells enumeration, viral load measurement and early infant diagnosis are largely laboratory-based, distant from the point of care, costly and requiring skilled personnel [8-10]. This presents a special challenge on how scale-up and decentralization of ART services can be suitably accompanied with laboratory services in RLS to guarantee quality in HIV care.

To resolve this and also provide a robust HIV care, quality HIV diagnostics and monitoring tools that are affordable, sensitive, accurate, easy-to-use, rapid, portable and deliverable at the point of HIV care are being developed [9, 11, 12]. These advances in rapid diagnosis and clinical monitoring technologies offer promise of increasing access to treatment and improving clinical outcomes for people living with HIV/AIDS.

However, it is pertinent to note that translating technological successes to improved clinical care in resource-limited, geographically remote, and harsh climate regions may not always be smooth. A viable implementation model adaptable to this region worst hit by the epidemic must accompany the future deployment of these technologies to ensure that the real values of such innovations are captured.

Here, the leveraging of portable device technologies to bring HIV laboratory services to the patient through innovative point of care diagnostic technologies is reviewed. The perceived implementation hurdles are appraised. Also, the need to develop a viable and adaptable model that allows the incorporation of evolving POC devices into existing healthcare structures and systems in sub-Saharan Africa for improved care is discussed.

2.0 HIV Diagnostics: Current Landscape and Pipeline

HIV care involves coordinated and linked spectrum of services encompassing diagnosis, treatment, monitoring and support in such structure that guarantees and optimizes access and adherence to treatment- continuum of HIV care (figure 1). As a gateway and monitoring tool in HIV continuum of care programme [11], HIV diagnosis spectrum encompasses testing, early infant diagnosis, disease staging, treatment monitoring and drug resistance assay all contributing towards goals engendered in the holistic care package.

2.1 Technologies for HIV Testing

HIV testing programmes often accompanied by prevention campaigns are largely decentralized and HIV+ persons are appropriately triaged to facilities with capacity to provide comprehensive ART programme.

Technologies for HIV testing in adult and children above 18 months of age include devices that detect specific viral antigen (e.g. p24 antigen) [13], HIV antibody-based tests kits (e.g. western blots) and nucleic acid amplification tests (e.g. reverse transcription polymerase chain reaction amplification)[14, 15]. HIV quantitative antibody based testing methods (e.g. western blood and Enzyme Linked Immunosorbent Assays-EIAs) are now for reserved use, usually to validate the more cost-effective, stable and potable HIV rapid test kits in RLS. While nucleic acid amplification and p24 antigen test methods detect early HIV infection, they are complex, expensive and require skilled technicians and laboratory settings, hence are not routinely deployed in HIV testing in RLS.

As progress in HIV testing technologies was made, enzyme immunoassay-based methods were formulated into POC RDT kits. Most HIV RDTs are immunochromatographic-lateral flow devices and offer advantages of quicker turn-around time, cost-effectiveness, user-

friendliness and are heat-stable [16], hence the incentives for their successful scale up and wide application in HIV testing and surveillance in RLS.

Although there has been consensus on RDT high accuracy [16], flaws in their performance have been highlighted even where the recommended use of two sequential RDT test kits is practiced. Some of these flaws have been attributed to individual or regional variation of circulating HIV subtypes and immune cross-reactivity [17]. For example, a study in Democratic Republic of Congo reports 10.5% false-positive despite using two sequential RDT in HIV testing [17]. This suggests the need to incorporate quality assurance system and where significant performance flaws are observed and verified, alternative testing strategies should be employed in such affected regions.

RDT technologies have evolved to the use of non-blood fluid samples like saliva and urine. Oral mucosal fluid-based RDTs show comparable accuracy to blood tests [18] and demonstrated positive impact in reducing mother-to-child transmission in a rural hospital in India [19]. However, in a recent evaluation of Oraquick RDT, clinical sensitivity of 86% on oral fluid samples was reported [20] and a cohort study in Nigeria with oraSure shows low accuracy especially in diagnosing HIV acute infection [21].

Notwithstanding the downsides, oral fluid RDTs holds potential for application in home based HIV self-testing programmes as highlighted in a study in Africa [18]. There is however reluctance on adopting HIV self-testing surveillance because the linkage to HIV care for self-testers is poorly defined. The legal, ethical, gender, human rights, and public health implications relating to HIV self-testing have been weighed and countries are now encouraged to scale up HIV self-testing as complimentary strategy to increase access to HIV testing [22]. In parallel, ongoing effort to provide practical logistic systems in RLS and the growing relevance of telemedicine [23] may provide platforms for wide acceptance and scale

up of self-testing programmes in the foreseeable future. Ultimately, more evidences on performance of rapid oral test and other non-blood based tests will be needed in countries considering their implementation, even as more FDA-approved oral fluid RDT kits are launched.

POC fourth generation multiplex HIV RDTs are being developed and are uniquely capable of simultaneously detecting HIV p24 antigen and antibodies to HIV-1 and HIV-2 (e.g. ARCHITECT HIV Ag/Ab Combo Assay), as well as detecting other viral co-infections like hepatitis B and C (e.g. Multiplo®) [15]. A recent performance evaluation by Pilcher and colleagues (2013) demonstrated that a new 4th-generation POC antigen-antibody combo rapid immunoassay (ARCHITECT) has comparable effectiveness in detecting HIV acute infection as the HIV RNA test method [20], hence, may be employed as primary screening assay in high-risk HIV testing. Evidence on their test performance in clinics is limited, but the advantage of simultaneous detection of two or more acute infections is attractive and offers convenience to patients and care providers.

2.2 Technologies for Disease Staging and Treatment monitoring

2.2.1 CD4 Counts technologies

The debate on “when to start” antiretroviral drugs (ARVs) followed the introduction of the first ARV in 1987 and expert opinions on the subject are still very much aligned divergently. In a recent debate, Franco and Saag (2013) articulated the urgency in starting ART early regardless of CD4 cells level adducing reasons such as: a better understanding of HIV biology has been gained, newer and safer drugs options have been launched, evidences from cohort studies are supportive and the public health implications of delayed therapy are critical [24]. Conversely, Lundgren and colleagues (2013) have cautioned the initiation of ART in the early phase of HIV infection on the premise that favourable evidence from risk: benefit

ratio analysis drawn from large randomized trials are lacking, as such they uphold the use of ART only in moderate HIV-induced immunodeficiency or severe HIV complications [25].

Amidst vigorous debate and increasing research evidence on when to initiate ART, the WHO recently raised eligibility requirement from the initial CD4 counts cut-off mark of 350cells/ μ l to 500cells/ μ l [7], hence establishing a new global consensus on when patients should initiate therapy. Judging from continuous upward revision of the CD4 cells eligibility criterion and the improvements in HIV therapeutics and monitoring, it may be predicted that ART eligibility status may be granted to all HIV+ patients irrespective of CD4 count in the next few years. Needless to say, for this to be the case there must be convincing research evidence to support it.

Notwithstanding the direction of swing of the ART eligibility pendulum, CD4+ T cells enumeration will continue to remain an important biological indicator in the staging of HIV disease progression, decision on ART eligibility and selection, monitoring the effectiveness of treatment and also as a guide to the diagnosis of opportunistic infections. Prompt availability of CD4 test results has been demonstrated to increase ART initiation and retention of patients in care [26,27].

Traditional, expensive and cumbersome laboratory-based flow cytometric technologies for CD4 T cells count have been very reliable as clinical monitoring tools but they are largely centralized, requiring laboratory infrastructure, skilled personnel and frequent equipment maintenance. As such, their use in resource constrained and remote regions of sub-Saharan Africa goes with challenges [4]. The need to decentralize ART laboratory monitoring for better care, the success recorded in the scale up of malaria and HIV RDTs testing kits [28] in RLS all together make clearer the inherent benefit of developing cost-effective, user friendly, accurate and rapid POC CD4 T-cell testing options. While some are already in the market (Partec CyFlow miniPOC, PointCare Now/HumaCount CD4 Now and Alere Pima Analyser)

[12, 29], a handful is in the pipeline (e.g. Visitect CD4, Daktari CD4 counter, Mbio Diagnostics' POC CD4 device, Zyomyx CD4 kit and BD FACSPresto) [15].

POC technologies for CD4 count include miniaturized flow cytometric devices, cartridges with microfluidic adaptations to flow cytometry (e.g. microfluidic image cytometers) or immunochromatographic strips [29-31]. Newer POCs options incorporate automatic biochips hence eliminating the manual sample preparation step, as this was a limitation with earlier versions of CD4 POC devices [32].

Evidence of the impact of POC CD4 testing kits on therapeutic outcomes is limited but positive. A study in Mozambique reported a reduction in total loss- to-follow-up before initiation of antiretroviral treatment from 64% to 33% [27]. In another study in South Africa, the introduction of POC CD4 enumeration devices increased the proportion of ART-eligible patients [33].

However, reports on sensitivity and performance of the available POC test kits are divergent. A peer reviewed assessment of the Poincare NOW™ reveals low sensitivity; misclassifying 53% and 61% of adult patients at the 350 and 200 cells/ μ L thresholds respectively [34, 46]. While CD4 POC PIMA analyzer (Alere, Inc.) evaluated in South Africa and in Zimbabwe performs well compared to standard protocol [33, 35].

As more POC technologies for CD4 count emerge from a robust pipeline [15], improvements in first generation CD4 POC diagnostics are anticipated. Unbiased performance evidences in different countries will help sieve the good from the not-so-good and guide scale-up decision.

2.2.2 Technologies for Early Infant Diagnosis (EID)

Early infant diagnosis (EID) of HIV infection confers substantial benefits to HIV-infected and HIV-exposed infants, to their families, and to programmes providing prevention of mother-to-child transmission (PMTCT) services [36].

Marston et al. analysed pooled data from 12 studies in sub-Saharan Africa and estimated that without ARV treatment, annual net survival would be 52% among infants infected perinatally [37]. While early ART initiation in children dramatically decreases morbidity and mortality, ARV coverage of HIV-infected children remain low [38].

The persistence of maternal antibodies in the child's system makes antibody-based tests unsuitable for exclusion or confirmation of HIV infection in children less than 18 months [39]. Therefore, technologies for EID are based on detection of viral components in infant's blood including cell-free RNA, viral DNA incorporated into host cells, or the viral capsid p24 antigen [39 -41]. Polymerase chain reaction (PCR)-based methods typically demonstrate higher sensitivities across HIV-1 than p24-based tests as such are preferred. Qualitative DNA PCR assays have traditionally been preferred for EID over quantitative RNA PCR assays [41] with the latter often used for viral load monitoring after established diagnosis. Multiplexed RNA and DNA PCR assays are now being used for EID in resource-limited settings. Ultrasensitive (immune complex-dissociated) p24 antigen assays may represent an accurate, low-cost method for EID [39] and recombinase polymerase amplification-based POC test devices has shown preliminary promising results [40].

Despite significant improvement in EID diagnostics, many infants enrolled into care are lost from care at each step in the EID cascade and many more do not have access to care[37, 41]. The EID point-of-care testing offers promise of improving access to treatment and optimizing retention in remote clinics. For example, EID in Nigerian EID study reported a median EID result of 47 days, with only 25% of infected infants in the study centre enrolled into ART

care [41]. Quick and cost-effective POC test options (e.g. rapid ultrasensitive assay P24 antigen assay) are being evaluated for EID in RLS [38-40] while some may become available in the next few years [15].

2.2.3 Technologies for HIV Viral Load (VL) Measurement

It is consensually held that viral load measurement remains the most informative and reliable biological indicator for timely detection of treatment failure. Hence, it has been adopted as a gold standard for monitoring clinical prognosis in patients receiving ART in the developed world [42,43]. Also, it is routinely deployed as a tool for monitoring treatment adherence, diagnosing HIV infection during early infancy and conducting HIV sentinel surveillance [42]. Studies in South Africa highlight the positive impact of viral load monitoring in conjunction with targeted adherence monitoring for conserving first-line drug regimens [44] and in early detection of treatment failure [45]. In addition, the limitation of CD4 cell count in diagnosing treatment failure [46] calls for adoption of viral load measurement as standard of care in resource limited settings. At present, routine HIV viral quantification remains unaffordable, unsustainable, centralized and only done periodically in the great majority of RLS [12, 47].

Technologies for viral load measurement include: Nucleic acid-based tests (e.g Roche Amplicor HIV-1 Monitor test), in-house nucleic acid tests [47]; non-nucleic acid-based tests (e.g. Cavidir ExaVir Load: HIV-specific reverse-transcriptase activity assay, shows good correlation with viral load measurement) [48]; and ultrasensitive p24 antigen detection assay [47].

Typically, viral load testing protocols require continuous power supply, air conditioning, centrifugation facilities, cold chain system and other infrastructures which are not available in remote regions in sub-Saharan Africa. As such, nucleic acid-based HIV load measurement in this region is performed at reference laboratory; making loss-to-follow-up inevitable due to

long turn-around time [45,49]. Non-nucleic acid-based assays have also been developed, but their clinical validity has been questioned [48], while in-house real-time PCR for HIV quantification are being validated in RLS [47] and with appropriate logistic may become an affordable option for viral load measurement and EID. Generally, in-house testing methods will need continuous validation and quality management if they are to be scaled up in clinical laboratory monitoring of infected patients. A robust and efficient system is needed to incorporate in-house testing system into mainstream diagnostic services.

Computational models capable of predicting virological response to ART are being developed and evaluated [50], and the operationalization may include an accessible online treatment support link [50]. Computer model prediction requires thorough calibration and validation at community level. This model may prove useful in the future, however, baseline and periodic follow-up viral load investigations will need to be carried on the traditional laboratory services.

Although no POC devices for viral load assay is commercially available, a number of assays are progressing rapidly towards platform for evaluation in RLS [15] and if they are successfully validated, viral load measurement may become a gold-standard in treatment monitoring in RLS in the nearest future.

POC diagnostics product pipeline for viral load include amplification-based assay being developed by the University of Cambridge which is now be, a nucleic acid based test kits, the LiatAnalyser, NAT system and the EOSCAPE-HIV HIV Rapid RNA Assay System and others [15].

2.2.4 Technologies for HIV Resistance Testing and HIV Companion Diagnostics

The high genetic diversity of HIV and its variability in selecting drug resistant strains when subjected to ARV is well documented [51-54]. Unfortunately, one of the aftermath of ART scale-up is an increasing incidence of treatment failure and increasing spread of drug-resistant viral strains. A review published by Stadel and Richman (2012) reveals that acquired resistance to ARVs was detected in 20.7% of patients on ART at ≥ 36 months in sub-Saharan Africa [51]. A similar review by Gupta et al. (2012) shows that East Africa and southern Africa have annual increase in drug resistant HIV prevalence of 29% and 14% respectively [52].

Predictive genotypic resistance profile as demonstrated in adult patients cared-for in the private sector of Cameroon or in the public sector in Bangui, Central African Republic [53] can potentially guide regional and individualized treatment selection to 2nd line ARVs and in conserving effectiveness of first line ARVs [44]. Pre-treatment resistance testing seems to be the cherished solution to decreasing incidences of treatment failure; however this solution is not handy in RLS. Drug resistance testing is not yet recommended for individual ART monitoring in resource-limited settings; and only available in regional or national reference laboratories as they are prohibitively expensive [54]. POC technologies for HIV resistance testing is still a far-cry, and investment into POC technology should be intensified.

Similarly, the gradual roll-out of pharmacogenomics technologies (companion diagnostics) is enabling prior identification of patients at risk of atypical adverse drug reactions [55] and determination of individual response to drugs before drug exposure [56]. This facilitates tailoring drug administration to suit individuals' genetic dispositions to such drugs (personalized medicine). For example, companion diagnostics for abacavir (abacavir/HLA B*5701) have been demonstrated to eliminate the risk of life-threatening hypersensitivity associated with the use of abacavir, a first line ARV [57]. HLA B*5701 is already being

extensively used in some countries (e.g. Australia, United Kingdom, and Ireland). Also, cell-based tropism diagnostic test is used to determine the tropism status of patients to be placed on maraviroc (HIV CCR5 co-receptor antagonist) [58]. The promotion of the concept of co-development of companion diagnostics alongside their drug candidates [56] may make inroads to improving access to this technology, as they are unavailable in RLS. As this new class of diagnostic evolves, research into companion diagnostic POC options should be encouraged to meet the special circumstances in RLS.

2.2.5 Diagnostics for HIV/AIDS related opportunistic infections

Immunological suppression with progressing HIV infections increase vulnerability of HIV+ persons to certain infections when compared to the background population. These infections can cause varying degrees of morbidity which may eventually lead to death if undiagnosed and untreated. Life threatening opportunistic infections are common in patients with significantly compromised immunity (CD4 T cells below 200cells/ul), and threatens the success of ART programme [59,60]. Among the several opportunistic infections that invade these immuno-compromised persons, cryptococcosis and tuberculosis (TB) are leading causes of death in HIV co-infections [59]. This is particularly severe in sub-Saharan Africa where these diseases are endemic [61,62].

TB diagnostic platform in RLS is weak. In addition to the 4-point clinical symptom score (of the presence of cough, fever, night sweats, and/or weight loss), the readily available method for diagnosing TB in RLS is smear microscopy. Unfortunately, both clinical symptom score and smear microscopy may give misleading results in severely immuno-compromised individuals. Low sensitivity of 20% for smear microscopy and 50% specificity for the 4-point symptom score have been reported [60]. Also, smear microscopy protocol for TB diagnosis

requires three samples collection, presenting logistic challenge to both patients and service provider [12].

Evolving TB diagnostic platform includes nucleic acid amplification-based test devices. An example is Xpert MTB/RIF which possesses attractive features of accuracy, user-friendliness and dual functionality of detecting *Mycobacterium tuberculosis* and rifampicin resistance, however it is unaffordable in many settings and requires sophisticated equipment [12,63,64]. Other technologies include antibody based serological testing devices which are also relatively expensive [65] and have been demonstrated to perform poorly in immuno-compromised HIV+ individuals and as such not recommended for routine TB testing [12]. Antigen based test devices (e.g. Determine® TB-LAM) demonstrated low sensitivity but proved valuable when used in combination with sputum smear microscopy in screening for TB among severely immuno-compromised HIV-infected patients [64], but this evidence is limited and requires further investigations.

While an ideal conceived TB POC has not been hatched, the progress in TB molecular testing technologies promises the birth of such desired POC for TB in the foreseeable future.

Similar to TB, POC diagnostic option in RLS for diagnosing cryptococcal infection is not available. The most commonly used serum-based screening tests for cryptococcosis, the latex agglutination test and the enzyme immunoassay, require complex laboratory infrastructure including a spectrophotometer and skilled personnel, as such they are not implementable in RLS [66]. Monoclonal antibodies-based device recently developed has >95% sensitivity when evaluated against cryptococcal latex agglutination and culture and has been licensed for use using serum and cerebrospinal fluid samples [67]. Lateral flow immunoassay device is an attractive POC kit in RLS as it can also be used in urine or whole blood hence eliminating the need of centrifugation and it is relatively cost-effective [66]. However, evidence of performance in urine and serum specimens in asymptomatic HIV and cryptococcosis co-infected individual is limited.

The positive impact of service integration of HIV care and other health services in reducing total cost of care and improving overall health outcomes has been advanced by Sweeney and co-workers (2012) in a systematic review [68]. The potential gains from integrating ART services with those of TB and cryptococcal infections have further been stressed [69].

The availability of POC devices for HIV, TB and cryptococcosis may facilitate the integration of these services and maximize the potential values from such integration. Conceivably, POC diagnostic tool box containing POC devices for spectrum of HIV testing (including CD4 cell count and viral load measurement) and for the diagnosis of TB and cryptococcosis may dramatically improve care retention and overall clinical outcomes for co-infected persons and should be envisioned. A multiplex device capable of testing HIV, TB/cryptococcosis simultaneously is a “big ask” but an attractive incentive for scale-up and integration of HIV, TB and cryptococcosis care services.

2.2.6 Sample collection and transportation

In RLS, laboratory services for viral load testing, p24 antigen quantitation and HIV drug resistance studies (when necessary) are delivered at sub-regional, regional and national reference laboratories [70]. Hence, collection, storage and transportation of samples from point of care to these reference service centres in an uncompromising manner constitute a huge challenge due to infrastructural, logistical, economic and personnel limitations. The use of dried fluid spot cards has been suggested to bridge this gap. Already, dried blood sampling method has been successfully implemented and widely used in many RLS providing EID services. In addition, these cards have been used in the spectrum of diagnosis in HIV care including serologic testing, p24 antigen quantitation, and more recently, viral-load determination and resistance genotyping [71]. Snijdewind and colleagues (2012) have reviewed the application of dried blood spot (DBS) testing in other viral diseases [72].

The limitations of DBS sampling technique have been appraised by Hamers et al. [73] and Snijdewind et al. [72]. These limitations include low sample volume (50 microlitres), likelihood of contamination, and possible degradation of HIV RNA in events of prolonged storage at room temperature under high humidity, and the inefficiency of extraction procedures to retrieve samples from the dried spot [71,73]. However, both authors argued that the caveats of DBS notwithstanding, its role in improving clinical outcomes of HIV care programmes in RLS should necessitate its wide adoption. Moreover, some of the limitations can easily be overcome: automated RNA extraction in reference laboratory may eliminate human error and inconsistencies [73], prompt dispatch of collected DBS to eliminate the need for long storage, high sensitivity of newer diagnostics should address the concern of small sample size in DBS [71]. DBS sampling techniques and implementation framework may be optimized to address the aforementioned limitations. This may widen its application in the scale-up of laboratory services in resource limited settings.

Overall, improvements in sampling techniques have aided in addressing logistic challenges in RLS. DBS being an immediate example- DBS specimens are heat stable, non-infectious, and can be shipped via mail or courier as such reducing the cost of specimen transport to reference laboratories from remote clinics [71,72] figure 2. The reference laboratory on its part relays test results to point of care delivery almost immediately after test are completed with the use of smart phones (Figure 2). In this way, turn-around time is minimized.

As ART and PMTCT services are being scaled up and decentralized to include primary healthcare facilities in sub-Saharan Africa, accompanying laboratory services have largely remained centralized. Transportation of samples and relays of test results to-and-fro remote treatment centres and reference laboratories is challenging and costly. Recently, Kiyaga and his group (2013) reported how Uganda's new coordinated sample transport model increased access to EID services from 36% to 51%. The system significantly reduced transportation costs by 62%, reduced turn-around-time by 46.9%, and by a further 46.2% through introduction of SMS printers [74]. Improvising near-efficient transport systems and the scale up of DBS may significantly improve access to laboratory services and HIV care in sub-Saharan countries.

3.0 HIV Diagnostics Platforms: Gaps and Needs

Unmet needs in HIV diagnosis could be seen firstly in the lack of simple, affordable, quick, accurate, equipment-free and reliable POC options for early infant diagnosis and for viral load measurement [4,12,43]; but equally important is the gap created by poorly defined implementation logistic system in RLS [75].

Also, POC options for resistance assays has potential of bringing personalized medicine to RLS and guide decision on HIV programmatic projects but resistance testing remains extremely expensive, centralized and runs only as part of clinical studies[12]. In a similar

vein, advances in pharmacogenomic technologies should be leveraged in developing companion diagnostic POC options as newer ARVs are being developed. These are capable of predicting patient's response to drug prior administration therefore reducing incidences of life-threatening toxicities, therapeutic failure and bringing personalized medicine to the reach of HIV+ people in RLS.

In addition, POC technologies for population incidence studies and HIV surveillance have potential of dramatically improving effectiveness and ease of HIV epidemiological studies. Such assays are being developed albeit current challenges faced in their development [76].

Increasing TB drug resistance and the high number of patients co-infected with TB and HIV buttresses the urgent need for POC diagnostic devices for TB and other life-threatening opportunistic infections (e.g. cryptococcosis). Portable and sturdy devices for hematology and physio-chemistries testing (e.g. full blood count, serum creatinine and others) will be immensely beneficial to ART programmes.

Furthermore, parallel advances and growth in mHealth and mobile telemedicine can be leveraged into HIV care programme to improve communication and linkages [23].

Arguably, diagnostic portfolio for HIV testing is impressive; however uptake of tests and scale-up remain unsatisfactory in RLS. 49% of infected persons are still unaware of their status in Sub-Saharan Africa [1]. Current logistic structures for implementation of innovative technologies is complex and ineffective [8] and will urgently need to be addressed to allow successful incorporation of POC testing portfolio into existing diagnostic systems in sub-Saharan Africa.

As attention gradually shifts towards implementation and subsequent scale up of POC devices in RLS, understanding and preparing for the implementation challenges is imperative to increasing access to the right populations in the right way.

4.0 Incorporating POC into HIV care in sub-Saharan Africa

Advances into rapid diagnosis and portable device technologies are being leveraged into POC diagnostics to bring laboratory services to patients' bedsides; hence by-passing the requirement for sophisticated laboratory systems. Existing HIV laboratory monitoring services in RLS are largely centralized, often distant from ART care delivery points or inaccessible to remote community dwellers. Geographical, socio-economic and skilled personnel limitations constitute barriers to accessing quality HIV care. An estimated 40% of persons diagnosed with HIV infection in sub-Saharan Africa either do not provide a blood sample for CD4 cells evaluation or do not return to obtain their CD4 count results as access routes are complex [8,77]. With existing diagnostic platform in sub-Saharan Africa, it becomes difficult to recruit more into care while effectively monitoring patients already in care. Obviously, access to POC technologies in RLS is pivotal to improving ART programme outcomes in geographically remote and resource constrained regions.

Importantly, the clinical impact of POC CD4 technologies is being evaluated and their potentials to reduce loss-to-follow-up and improve retention in care are being carefully examined. For example, the Pima™ Analyzer (Alere rapid POC CD4 device) has been validated in various settings [33]. However, the mere availability of high-performing POC devices does not automatically translate to successful implementation in the field. An experience from the use of HIV RDT testing is not far-fetched. Despite the decentralization of HIV testing protocols and the availability of HIV RDT test kits in RLS, 49% of persons living with HIV in sub-Saharan Africa do not know their status [1], and many present to care

late. The implication is an increased cost to health systems, higher risk of transmissions of the infection and a possible slack in reducing mortality rate with ART [80].

A range of perceived barriers to successful implementation of evolving POC technologies may include economic, regulatory and policy-related factors [75,78,79], hence implementation plans should devise strategies to overcome these perceived hurdles. Regulatory affairs agencies in sub-Saharan Africa countries need to ensure that performance evaluation of emerging POC kits are carried out locally prior to registration of such products. Quality assurance system should be efficient to ensure continuous quality control of registered products. One key area which perhaps is as important as the technology is documentation. Systems that ensure immediate reporting of test results to care providers and a mechanism to link test results to appropriate counseling and treatment must accompany implementation of the of technology.

Also, POC implementation programmes require viable business models to ensure sustainability and affordability in low income countries [75]. These strategies may include designing economic structures to strengthen private-public sector partnership. National governments in sub-Saharan Africa, donor agencies and partners may consider subsidizing cost for POC devices and should invent harmonized pricing strategies to address the huge disparities on cost of receiving HIV care between the public and private health facilities. The biopharmaceutical and diagnostic industries may adopt a differential pricing method for HIV POC diagnostics to encourage high patronage in RLS. This may be in a form of corporate social responsibility gestures to guarantee affordability of newly launched HIV POC kits.

In addition, the leveraging of mobile smart phones and development of telemedicine can help address challenges of POC implementation in regions where access to computing system is

limited [23,77]. For example, telephonic counseling has been shown to improve outcomes in HIV in-home testing [23].

If the real value behind the innovation of POC technologies is to be captured, it is pertinent to understand current diagnostic practices and the peculiar health system structures of regions in which POC technologies implementation is planned [78]. Logistic management systems will need to be robust and efficient. Supply chain of diagnostic commodities should be strengthened and inventory control systems should be well managed to avoid stock-out of such commodities. Referral and transfer systems should be as simple as possible and well defined; and personnel should be well acquainted with such procedures. Implementation strategies may include building health facilities internal and external linkages to ensure effective service referral and transfer systems, strengthening capacity for forecasting, inventory management, reporting and documentation, enabling reliable quality assurance and management system. Training and retraining of implementers should be regular.

Ultimately, the goal of HIV diagnosis is to provide accurate, efficient, cost-effective and accessible diagnostic services for the spectrum of testing required to diagnose, stage and monitor ART effectively. As POC testing options for different diagnostic stages emerge in batches, the dried fluid sampling method can fill the gap and augment diagnostic services that are likely to remain centralized in RLS (e.g. resistance assay).

Eventually, a design of framework that allows the use of both centralized and POC testing systems to run complementarily or supplemental would be necessary. HIV national coordinating centres will need to devise policies and implementation strategies that allow the incorporation of POCs devices into the existing laboratory systems in sub-Saharan countries. Such strategies will need to address community level implementation hurdles on case by case

basis; ensuring that the peculiarities of these communities (e.g. perceptions and beliefs, conflict-prone) are addressed.

5.0 Conclusion

The goal of “test and treat” and the campaign for universal access to HIV diagnosis and treatment are realizable with the advent of POC technologies and laboratory services decentralization in sub-Saharan Africa. However, the success or otherwise will depend on how the implementation strategies are adaptable and implementable in RLS.

Key gaps remain in the performance validation of emerging CD4 POC technologies, lack of POC devices for viral load measurement and EID. Others include non-availability of POC testing options for HIV drug resistance assay, multiplex HIV/TB/cryptococcosis diagnostic and population incidence surveillance tools. Also, POC devices for other opportunistic infections that can potentially improve the quality of HIV care and the management of co-infections are lacking. It is also not too early to ask for POC options for pharmacogenomic testing (companion diagnostics) as HIV+ patients in sub-Saharan Africa will benefit greatly from personalized medicine delivered at community level.

Finally, collaborative efforts built around combining technical expertise, regulatory capacity as well as implementation strategies might speed up the development of product pipeline, performance evaluation and implementation at the country and community level. In the end, it is about creating that environment where HIV infected persons can live near-normal lives and the society can be freed of the risk of contracting the disease.

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Figures

Figure 1. Linked Services in HIV Continuum of Care programme. POC devices will reduce turn-around time between initial testing and treatment and ensures effective clinical monitoring of treatment at community level. Incorporation of POC devices in the cascade will reduce loss-to-follow-up, facilitate the integration of care services for HIV and other co-infections and improve engagement/retention in HIV care. ART: Antiretroviral therapy.

Figure 2. Implementation of Dried blood sample (DBS) in HIV care in resource limited settings. DBS reduces the difficulty with sample preparation and storage. DBS is stable at room temperature, can be sent through the post, results may be relayed to clinics via SMS or scanned copy with smartphones to reduce turn-around time. While POC devices are rolled out, DBS can augment laboratory services that are centralized and are likely to remain centralized over the coming years.