Tropical Medicine and International Health doi:10.1111/j.1365-3156.2010.02669.x

VOLUME 16 NO 1 PP 37–41 JANUARY 2011

Viewpoint

Why do we need a point-of-care CD4 test for low-income countries?

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Summary In this paper, we discuss the reasons why we urgently need a point-of-care (POC) CD4 test, elaborate the problems we have experienced with the current technology which hampers CD4-count coverage and highlight the ideal characteristics of a universal CD4 POC test. It is high-time that CD4 technology is simplified and adapted for wider use in low-income countries to change the current paradigm of restricted access once and for all.

Keywords CD4 count, point-of-care, low-income countries

Introduction

Korpo is an ill HIV-positive mother who has walked for over five hours on a hot and humid day to get to a comprehensive health centre in a remote corner of north-western Liberia. The terrain has been difficult as there are no paved roads, and public transport is almost non-inexistent and anyway unaffordable. The clinician tells her that she will need a blood test - the enumeration of the absolute numbers of T helper cells (commonly referred to as the CD4 count) - to make a decision on whether or not she can start antiretroviral treatment (ART). A blood specimen is collected and sent away on a motorcycle to a distant off-site laboratory. Korpo is told to return 2 weeks later to get the result.

In low-income countries, most health care workers in health centres and even in district hospitals who wish to order a CD4 test are faced with the challenge of not only transporting the blood specimen to an off-site laboratory but also getting the CD4 result back to the patient. There are the many additional problems, of blood specimens being damaged or unsuitable for testing as a result of delays in samples reaching the CD4-count laboratory, of machine malfunctions as a result of poor maintenance or breakdown and of lack of reagents owing to stock-outs or financial constraints. For the patient, getting a CD4 test result often means repeated visits to the health facility, leading to delays in accessing ART. By the time, the result is finally available, the patient is often too sick to return to the clinic. Such individuals are frequently impossible to find again and end up being declared lost to follow-up (Losina *et al.* 2010; Tayler-Smith *et al.* 2010). This scenario is typical of low-income countries where 90% of the world's HIV/AIDS population reside (WHO 2009). The core of the problem is that current CD4 technology is too sophisticated and inappropriate for the context in which it is being used.

In this paper, we discuss the reasons why we urgently need a point-of-care (POC) CD4 test, elaborate on the problems we have experienced with the current technology which hampers CD4-count coverage, and we highlight the ideal characteristics of a universal CD4 POC test.

Why do we need a POC CD4 test for low-income countries?

There are a number of reasons why a POC CD4 count is urgently needed in low-income countries (Table 1). First,

Table 1 Reasons why a point-of-care (POC) CD4 test is required in low-income countries

Reasons	Potential benefits
1. To assess eligibility for ART	CD4 testing will help identify PLHIV in WHO clinical stage 1 and 2 who are eligible for ART
2. To start ART earlier	Earlier access to ART reduces mortality, incidence of tuberculosis and mother-to-child transmission of HIV
3. To improve PMTCT uptake	PMTCT sites will be able to implement early initiation (at 14 weeks) with the appro priate WHO PMTCT regimen.
4. To simplify ART at the primary care level	A POC CD4 test will reduce dependence on clinical acumen and the need for WHO staging. This will increase the decision-making power and numbers initiated on ART by nurses and other health workers
5. To enhance task-shifting	ART eligibility assessments could be carried out at peripheral health facilities and at the community level. Early referral and earlier ART initiations could be promoted.
6. To reduce early attrition from programmes	Reduced visits and waiting time for patients would foster patient retention in care Possibility of offering an HIV test+ POC CD4 test as a ''one-stop serial package'' to promote immediate decision-making

PLHIV, Person living with HIV; ART, Antiretroviral treatment; WHO, World Health Organization; PMTCT, Prevention of mother-to-child transmission of HIV.

although recent WHO (2010) guidelines state that a CD4 count is no longer required for individuals in WHO clinical stage 3 or 4, individuals in stages 1 and 2 need to have a CD4 count <350 cells/mm^3 to be eligible for ART (WHO 2010). Thus CD4 testing is the gateway for identifying individuals in WHO stage 1 and 2 who need ART.

Second, access to a CD4 count is important to start ART early, i.e. before the patient is too sick. Earlier or so-called ''upstream'' ART access may reduce individual mortality, mother-to-child transmission of HIV and the incidence of HIV-associated tuberculosis (TB). A recent study from Haiti (Severe *et al.* 2010) showed a 75% reduction in mortality and a 50% reduction in TB incidence associated with starting ART earlier. On the ground, there are huge gaps in access to CD4 testing countrywide. CD4 counting facilities remain laboratory-based with either standard flow cytometers from Beckton Dickinson or Beckman Coulter or newer, simpler machines from Partec and others. Many existing laboratory instruments end up offline or without reagents to carry out the diagnostic testing (Malkin & Keane 2010). In Malawi in mid-2010, of 396 ART delivery sites of which 52(13%) had a CD4 cytometer, only 42(11%) had a functional CD4 machine (MOHP 2010). Thus, only 1 in 10 sites had a functioning CD4 cytometer. Over the period 2009–2010, there was progressive stagnation in CD4 capacity associated with machine breakdowns (Table 2).

Third, a CD4 count is the pivotal test to decide how to implement prevention of mother-to-child HIV transmission (PMTCT) for HIV-infected women. The recent 2010 PMTCT guidelines recommend two key approaches: lifelong ART for HIV-infected women in need of treatment for their own health (if the CD4 count is below 350 cells/mm^3) and ARV prophylaxis to prevent MTCT during pregnancy, delivery, and breast feeding for HIV-infected women not in need of treatment (if the CD4 count is above 350 cells/mm^3) (WHO 2010). However, in Malawi, where 454 facilities countrywide provide PMTCT to 151 750 enrolled pregnant women, only 5338 (57%) of the 9286 HIV-positive women were assessed for ART eligibility (MOHP 2010). This lack of coverage is not unique to Malawi, since in 2008 only one-third of the 1.4 million HIV-positive pregnant mothers in low- and middle-income countries (90% of the world's burden) were assessed for ART eligibility (WHO 2009).

Fourth, WHO clinical staging is a clinical skill. It requires clinical acumen and time, both of which are lacking in low-income countries because of the limited numbers of clinicians (Philips *et al.* 2008). Recent evidence

Table 2 Evolution of CD4 testing capacity at antiretroviral delivery sites in Malawi (2009–2010)

Yearly quarter	Sites with a CD4 machine	Functioning CD4 machine	CD4 results
Quarter 2, 2009	52	47	41 171
Quarter 3, 2009	52	47	43 882
Quarter 4, 2009	52	44	53 017
Quarter 1, 2010	53	42	43 343
Quarter 2, 2010	52	41	44 841

Source: Adapted from reference ''MOHP 2010''.

from MTCT-Plus Initiative has demonstrated the utility of CD4 counting over WHO staging for ART initiation in pregnant women (Carter *et al.* 2010). A POC CD4 test would simplify ART delivery at the primary level by reducing dependence on clinical acumen and thereby increase the numbers of patients initiated on ART by nurses and other health workers (Philips *et al.* 2008; Zachariah *et al.* 2009).

Fifth, with ART scale-up, there is a need to enhance decentralisation and task-shifting. A POC CD4 test will favour ART eligibility assessments at remote peripheral facilities and at community level (Zachariah *et al.* 2009). This is likely to have a positive influence on early referrals and early initiation of ART.

Finally, current CD4 testing is associated with the need for repeated patient visits and long waiting times which constitute a heavy burden for patients. This is an important reason for programme attrition and providing a POC CD4 test would help to limit this problem (Bassett *et al.* 2010; Losina *et al.* 2010; Tayler-Smith *et al.* 2010). The ideal scenario would be to offer an HIV test and a POC CD4 test in a one-stop package as this would rationalize the visit schedule as well as promote immediate decision-making on management.

Although CD4 counts have been recommended for ART monitoring (WHO 2010), a study in South Africa showed a low positive predictive value (37%) compared to a viral load test (Mee *et al.* 2008). Similarly, in a programme setting in Mozambique(Maldonado *et al.* 2009), only 33% of patients with detectable viral loads had clinical and immunological signs of failure implying that 7 in 10 such patients would be missed without a viral load test. The DART study in Uganda and Zimbabwe on routine versus clinically driven laboratory monitoring of ART in Africa showed that CD4 cell count monitoring might be useful from the second year on ART to guide the switch to second-line treatment (Mugyenyi *et al.* 2010). However, mistakes are made with this approach and evidence is now strong to support the use of a cheap point-of-care viral load test to identify early viral failure and limit the emergence of resistance (Gupta *et al.* 2009).

Problems with traditional non-POC CD4 technology hampering CD4 coverage

In our experience, the main problems hampering CD4 coverage in low-income countries are linked to available technology, health facility logistics and patient factors.

Table 3 Characteristics of a universal point-of-care CD4 test for low-income countries

Characteristic	Rationale
Simple to use (dip stick/lateral flow i.e. HIV test like preferable, no electronic instrumentation)	Important for scaling-up access to CD4 testing Will permit task-shifting and use by unspecialized staff Complex electronic instrumentation will require maintenance and increase capital outlay. Maintenance of electronic instruments is difficult to implement in low-income settings
Use non-venous blood	Phlebotomy may not be available for venous blood collection Finger-prick or other capillary blood source will allow task-shifting and decentralization.
Easy to read	Will permit task-shifting and use by unspecialized staff
Robust/reliable	Avoid the need for repeat testing Reduce per person test costs.
Not cold chain dependent/ withstands hot climates of up to 40 °C	Reduce the burden of cold-chain logistics Reduces waste
Long shelf life (at least 15 months)	Delays between procurement and supply need to be taken into account Cold chain storage not always possible.
Short test processing time (about 10 min)	Minimize patients waiting time Avoids the need for batch testing
Relatively cheap ($1–2 US Dollars/test)	Ensure affordability for scaling-up at country level.
Material waste can be disposed easily and safely	Avoid exposure to infectious waste material
Quality assurance. The test must be adaptable to a quality assurance programme	Quality assurance ensures tests are functioning normally and results are trustworthy.

On the technological side, non-POC CD4 machines require regular maintenance, supervision and stocks of reagents. The instruments themselves are very costly. Importantly, these machines have to be placed in central locations (district or tertiary hospitals) making them practically inaccessible to distant rural communities. They require skilled staff who are already overworked or unavailable. Health staff shortages and especially shortages in medically trained staff (nurses, medical assistants) often result in tasks being shifted to trained non-medical staff. There are a number of so-called POC CD4 count devices, bench-top machines of little help in increasing access to CD4 count tests. At country level, quality assurance issues and ensuring adherence to maintenance contracts in the medium- to longer term are also often unresolved. In summary, what we have is inappropriate CD4 technology that is inaccessible for rural communities in low-income countries.

From a health facility perspective, because of the scale-up efforts, there are often too many CD4 tests to be carried out in the face of limited capacity for CD4 testing, particularly in high-prevalence contexts. Blood is transported from peripheral health facilities to an off-site laboratory which proves cumbersome, expensive and impractical. Unavoidably, blood samples are picked up too late or are improperly transported and the results deemed unreliable. Blood collection in tubes for transport requires dedicated staff time, and there is a risk of wrong labelling or mixing-up of results. In summary, health facility logistics are complex and often unsustainable.

Finally, from the patient perspective, non-POC CD4 technology often means repeated visits to the health facility which in turn means repeated travel, time and costs. This burden often results in patients being lost to attrition (Losina *et al.* 2010; Tayler-Smith *et al.* 2010).

Characteristics of a universal POC-CD4 test

The ideal characteristics of a universal POC CD4 test are summarized in Table 3. It should be: (i) a dip-stick test or a test similar to the HIV rapid which can be performed on finger-prick whole blood; (ii) simple to perform and easy to read; (iii) reliable, not cold chain dependent, with a long shelf life and relatively cheap (<$5). The new PIMA Alere^{TM} PIMA POC CD4 test has produced promising results (Mtapuri-Zinyowera *et al.* 2010), but instrument costs are significant (>$6000) and throughput is relatively low at 10–15 CD4 tests per day. (iv) Finally, a test that avoids the need for electronic instrumentation, whether a/c power or battery operated, would be highly advantageous. Electronic instruments are often offline, insufficiently maintained and lacking spare parts or batteries.

Conclusion

Over recent years, there have been a number of interesting and laudable developments in the field of simplifying CD4 technology, for example the Alere^{TM} PIMA CD4 test (Mtapuri-Zinyowera *et al.* 2010). Further, very promising POC tests are emerging from the CD4 Initiative (CD4 Initiative 2010), particularly the instrument-free POC CD4 test from Zyomyx, Inc. Independent evaluations in London with samples from an HIV outpatient clinic have shown high correlation with flow cytometry (data not shown). Field trials are scheduled for the end of 2010 for this rapid CD4 test which produces results in <10 min.

Although these initiatives considerably improve the potential for decentralized CD4 access, a quantum shift is still needed to achieve greater simplicity and meet the requirement of an ideal universal CD4 - POC test for low-income countries. POC CD4 remains a vital entry door to accessing ART, improving immediate decision-making, patient management and referral, improving patient retention in care and alleviating the testing burden at centralized laboratories. A simplified CD4 counting technology adapted for wider use in low-income countries will change the current paradigm of restricted access once and for all.

Acknowledgements

We are grateful to donors who support the development of POC CD4 count technology in low-income countries.

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