The evolving role of CD4 cell counts in HIV care

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Purpose of review
The role of the CD4 cell count in the management of people living with HIV is once again changing, most notably with a shift away from using CD4 assays to decide when to start antiretroviral therapy (ART). This article reflects on the past, current and future role of CD4 cell count testing in HIV programmes, and the implications for clinicians, programme managers and diagnostics manufacturers.

Recent findings
Following the results of recent randomized trials demonstrating the clinical and public health benefits of starting ART as soon as possible after HIV diagnosis is confirmed, CD4 cell count is no longer recommended as a way to decide when to initiate ART. For patients stable on ART, CD4 cell counts are no longer needed to monitor the response to treatment where HIV viral load testing is available. Nevertheless CD4 remains the best measurement of a patient’s immune and clinical status, the risk of opportunistic infections, and supports diagnostic decision-making, particularly for patients with advanced HIV disease.

Summary
As countries revise guidelines to provide ART to all people living with HIV and continue to scale up access to viral load, strategic choices will need to be made regarding future investments in CD4 cell count and the appropriate use for clinical disease management.

Keywords
advanced HIV disease, antiretroviral therapy, CD4 cell count, treatment monitoring, viral load

INTRODUCTION
The CD4 cell count has been an essential component of HIV treatment and care programmes since HIV was identified as a disease compromising the immune system. For healthcare providers, the CD4 cell count has guided key clinical decisions ranging from when to start antiretroviral therapy (ART) [1**] to whether or not to screen for or provide prophylaxis against opportunistic infections [2,3]. CD4 testing has also provided valuable insight into programme performance over time [4,5] and predicted patient prognoses, with epidemiologists having identified associations between CD4 cell counts and a risk of death [6], life expectancy [7] and treatment adherence [8*]. As a critical test for ART programmes, deployment of point-of-care (POC) CD4 test devices has been used as a way to improve linkage to care and accelerate treatment initiation [9]. Most importantly though, CD4 cell count provides the best direct measurement of a patient’s immune status and risk for opportunistic infections, and it remains an important test with regard to diagnostic decision-making, particularly for patients with advanced HIV disease.

The role of the CD4 cell count in the care of persons with HIV/AIDS has evolved over the last 30 years. It began as and remains the best way to quantify the degree of immunosuppression and associated risk of AIDS illnesses. However, it is likely best known for its role in guiding the initiation of ART in national treatment programs. The roots of using CD4 thresholds for ART initiation lie in the early days of the ART era when drug toxicity, affordability, and accessibility of paramount concern. CD4 subsequently developed into a measure for...
When it was worth the risks and expense to initiate ART and was also used to prioritize treatment to those with more advanced disease in settings where resources were scarce. The role is again changing [10], most notably with a shift away from using CD4 to decide when to start ART. Recent randomized trials have shown that ART should be started in all HIV-infected patients, irrespective of CD4 cell count [11**,12**]. Responding to this evidence, WHO guidelines have been revised to recommend starting ART as soon as possible following a confirmed diagnosis of HIV infection [13], and many countries are in the process of revising their national guidelines to reflect this shift in policy [14]. WHO has also recommended a shift to HIV viral load instead of CD4 cell count for monitoring ART [13], though WHO continues to emphasize CD4 cell count’s important role in evaluating disease status at baseline and prioritizing appropriate care for patients found to have progressed to advanced stages of HIV [10**].

This article reflects on the past, current and future role of CD4 cell count testing in HIV programmes, and what this could mean for clinicians, programme managers and the diagnostics industry.

THE EVOLVING ROLE OF CD4 CELL COUNT TESTING

When to start treatment
Over the last 30 years, clinicians, researchers and policy makers have debated the ideal CD4 threshold for starting ART. During the late 1990s, treatment was expensive and associated with significant drug toxicity. Most drug combinations were less robust, carrying a higher risk of causing drug resistance, there were fewer treatment options and the decision about when to start treatment needed to balance benefits against the significant risks. The prevailing view during this period was that rates of disease progression and death were low at a CD4 cell count greater than 200 cells/mm$^3$ [6], and any drug exposure above this threshold could result in severe and unnecessary side-effects or development of drug resistance at a time when alternative treatment options were limited [1**].

As treatment became more affordable and less toxic, evidence supporting the overall benefits of starting treatment at higher CD4 thresholds accumulated, and the threshold for starting treatment was progressively raised in guidelines. This evolution is reflected in the WHO guidelines over this period, during which the recommended CD4 cell count threshold for when to start ART rose from 200 cells/mm$^3$ in 2002 to 350 cells/mm$^3$ in 2010 and again to 500 cells/mm$^3$ in 2013 [15]. In 2015, just prior to the WHO Guideline Development Group meeting for revision of global guidelines, two large randomized trials were completed and results from both studies showed that, in terms of reduced morbidity and mortality as a combined endpoint, the benefit of starting ART at CD4 cell counts above 500 outweighed the risks [11**,12**]. In light of these trials, together with evidence that early ART with virologic suppression reduces the risk of HIV transmission [16], WHO subsequently updated their guidelines in September of the same year to strongly recommend that all HIV-positive individuals should start ART irrespective of CD4 cell count [17].

Although the implementation of this recommendation remains challenging in many resource-limited settings, the evidence supporting starting ART at any CD4 cell count is strong, and countries are moving to revise their national guidelines in line with the evidence and WHO recommendation [14]. In settings where access to ART may be limited, WHO continues to recommend prioritizing those patients with a CD4 cell count less than 350 cells/mm$^3$, highlighting that CD4 cell count continues to be the best predictor of those at highest risk of disease and death and that these priority patients stand to gain the most from treatment in the short term.

How to monitor treatment
In the early days of the HIV epidemic, the development of specific CD4$^+$ T-cell antibodies paired with the increasing availability of flow cytometry technology in a variety of formats and platforms made CD4 cell counting and thus monitoring of a patient’s condition during treatment possible for the first time. However, there has been considerable debate around the role of such laboratory monitoring in HIV treatment programmes over the past decade. Initially, there was concern that, without
the capacity to undertake laboratory monitoring, low-income countries with a high burden of HIV may be reluctant to offer ART. In response, the first WHO guidelines for ART provision issued in 2002 stated that lack of laboratory testing should not be a barrier to ART [15]. From 2003 onward, WHO guidelines stated that CD4 cell count testing was advisable, but noted that access remained a barrier and that initiation of ART remained the priority.

Viral load monitoring of ART was first described in 1991 [18] and has been recommended by WHO since 2006 as a more direct measure of response to treatment, although initially the use was limited to tertiary centers because of cost and technical constraints [15,19]. The cost–effectiveness of viral load monitoring has been debated. Some studies conducted in Cameroon [20] and Uganda [21] found that viral load monitoring was not cost-effective when compared with alternative strategies of clinical and immunological monitoring. However, other studies that assessed viral load to confirm failure in Côte d’Ivoire [22], or to use viral load instead of CD4 cell count in Southern Africa [23], found viral load to be cost effective. WHO and national guidelines have evolved toward recommending viral load as the preferred way to monitor treatment efficacy because of the poor accuracy of CD4 monitoring in predicting viral suppression [24], and concern that delays in switching ART among people failing treatment could lead to an accumulation of drug resistance and increased risk of mortality and morbidity [25]. The latest WHO guidelines recommend that, where viral load monitoring is available and patients are stable on ART, CD4 monitoring can be stopped. This is in recognition of the fact that CD4 cell count offers little added information in patients who are clinically well and virologically suppressed on ART [26**, and that the cost of scaling up viral load can be partially offset by limiting CD4 testing to a single baseline or several early tests, where it is still necessary to assess the patient’s clinical status before safely initiating ART [23].

**Informing treatment choices**

Until 2013, nevirapine was among the most widely used antiretroviral drugs, and was recommended by WHO as part of first-line ART. However, nevirapine use has been associated with a heightened risk of hepatic and cutaneous adverse drug reactions particularly in women at higher CD4 cell counts, leading to recommendations against using nevirapine in women with CD4 cell counts more than 250 cells/mm$^3$ and in men with CD4 cell counts more than 400 cells/mm$^3$; this concern further complicated clinical management [27]. In 2013, WHO gave preference to efavirenz over nevirapine in first-line ART [13], and there has been a rapid shift away from nevirapine use by countries [14]. New drug options such as dolutegravir are even better tolerated, removing any prospect that CD4 cell count determination will be needed in the future to guide antiretroviral drug choice.

**Availability of tests**

Recent survey findings indicate that global capacity of available CD4 instruments is sufficient to meet the needs of all people living with HIV/AIDS, irrespective of treatment status [28]. However, CD4 instruments are considerably underutilized, with only 13.7% of existing CD4 capacity utilized in 2013 across 50 countries reporting data. Key reasons for nonutilization included noninstallation, breakdown for CD4 conventional instruments with limited or no maintenance contracts and lack of reagents for POC CD4 instruments [28].

In contrast, viral load instrument capacity is not adequate to meet the needs of all people living with HIV/AIDS. In 2013, 28% of reporting countries did not have adequate viral load (VL) capacity to perform at least one VL test per patient/year on ART. In addition, only 37% of theoretical instrument test capacity was actually being used, mainly because of noninstallation and lack of reagents [28]. Many countries continue to rely substantially on donor funding to deliver viral load, which raises concerns about long-term sustainability.

As viral load continues to be scaled up, countries will need to make strategic decisions regarding relative investments in scale-up and placement of CD4 and viral load technologies.

**FUTURE ROLE OF CD4 CELL COUNT TESTING**

WHO guidelines no longer recommend CD4 for ART initiation or disease monitoring, though baseline CD4 is still recommended and plays a vital role in guiding clinical management of patients with advanced disease, a group that still makes up nearly half of all people living with HIV starting/restoring treatment [7]. WHO guidelines recommend that ART can be started irrespective of CD4 cell count and that CD4 cell count monitoring can be stopped in patients who are stable on ART and that ART efficacy can thereafter be monitored with viral load. These two recommendations in particular are likely to result in fewer CD4 cell counts needed and thus fewer resources necessary to commit to CD4 testing in HIV programmes. For example, in Namibia,
changing from CD4 to viral load monitoring and using CD4 only as a baseline test have resulted in nearly a 90% decrease in CD4 cell counts being performed, which has helped to offset the increase in costs for more viral load monitoring. Nevertheless, CD4 cell count testing still has an important role to play as a way to assess clinical status of a patient at first initiation of treatment, most notably in the management of advanced HIV disease (Table 1). CD4 cell count will also be important in evaluating patients who are failing ART and who come in after being off treatment for some time.

Management of advanced disease

CD4 cell count testing is one of the most important tools for assisting clinical management decisions in patients with advanced disease. In particular, a CD4 cell count less than 200 cells/mm$^3$ is considered a critical threshold for heightened risk of death [6,29] and is used as the current WHO definition of advanced HIV disease [30]. Screening for cryptococcal antigen (CrAg) is recommended for all patients with a CD4 cell count less than 100 cells/mm$^3$[13], and several randomized trials have found a positive benefit associated with a package of interventions aimed at reducing mortality among patients presenting below this CD4 cell count threshold [31,32]. WHO also recommends the use of the urine lateral flow-LAM assay to assist in the diagnosis of TB in a specific category of HIV-positive individuals presenting with CD4 less than 100 cells/mm$^3$; this threshold was chosen because of reduced diagnostic accuracy (in particular poor sensitivity) at higher CD4 cell counts [13,33]. Cotrimoxazole is a fixed-dose combination of two antimicrobial drugs (sulfamethoxazole and trimethoprim) that prevents morbidity and mortality from a variety of bacterial, fungal and protozoan infections. Provision of cotrimoxazole prophylaxis has been recommended by WHO since 2006. The latest guidelines, issued in 2014, recommend giving cotrimoxazole prophylaxis to all HIV-infected adults with a CD4 cell count less than 350 cells/mm$^3$, and discontinuing once patients are stable on ART [2]. In settings where malaria and/or severe bacterial infections are highly prevalent, cotrimoxazole prophylaxis should be initiated and continued regardless of CD4 cell count; cotrimoxazole prophylaxis should also be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.

Although the notion that advanced disease will cease to pose a problem as ART programmes expand, trends in CD4 cell counts over the past decade indicate the advanced disease is and will for the foreseeable future remain an issue for HIV programmes. The average CD4 cell count at start of ART has somewhat risen globally over the last decade, reflecting the evolution in treatment guidelines toward recommending starting treatment at higher CD4 cell counts [4,34]. However, the proportion of patients presenting with advanced HIV disease has remained relatively constant, with a 2015 meta-analysis of CD4 trends estimating that over half of patients have progressed to advanced disease by the time of ART initiation [4,35,36]. Tuberculosis, bacterial infections, fungal infections and other AIDS-related infections continue to be leading causes of hospitalization and mortality among people living with HIV globally [37]. Although this persistence of advanced HIV disease partly reflects the fact that people continue to be diagnosed late in their HIV infection – almost one-third of HIV-positive patients admitted to hospital are diagnosed at the time of admission [37] – an important proportion of patients presenting with advanced disease is also represented by HIV-positive individuals who have already started ART but subsequently interrupted their treatment [38,39]. Persons with HIV/AIDS who are defaulting on therapy represent an ever increasing number of patients seen in clinics and admitted to hospital [38], with defaulters constituting over half of late presenting patients (CD4 < 350 cells/μl) in some settings [40]. These challenges will be critical to address moving forward in the test and treat era.

For these reasons, WHO recommends that HIV programmes should retain the capacity to perform CD4 cell count at baseline and during the case of treatment failure, as this remains one of the best predictors of general patient wellness, disease progression and mortality risk, and can guide further diagnostic tests to address the causes of these mortality concerns [13].

Future research in CD4 testing

Much has been learned about CD4 testing over the past three decades and a couple of the major
concerns remain to be addressed in the near future. One major concern is the potential for delay in treatment initiation that could result from CD4 turnaround times and another is the cost of continuing to support a CD4 infrastructure based on flow cytometry, especially as the bulk of testing moves to viral load. More affordable and user-friendly POC testing platforms have offered a viable alternative, although issues remain with quality assurance, testing volumes maintenance and supply chain management. Considerable progress has been made in the development of even more robust, simpler, faster and more affordable testing platforms, such as highly accurate microchip assays and semiquantitative lateral flow assays (LFAs) that would indicate whether or not a patient was above or below a certain CD4 cell count. Although much of this work has fallen to the wayside in the wake of WHO guidance to treat regardless of CD4 cell count, this technology remains relevant in identifying patients with advanced disease and continued effort and investment remains important. Ideally, a simple semiquantitative CD4 LFA would provide a cheap and sustainable alternative to current CD4 testing in the future. Such a test could be performed during a patient’s initial visit without the need to collect and send off specimens, and would allow clinicians to determine if a patient has advanced disease (CD4 < 200 cells/mm³) and needs additional screening and treatment/prophylaxis of opportunistic infections necessary to safely initiate ART. Microchip technology, while slightly more costly, has the added benefit of multiplexing, allowing the consolidation of CD4 with other tests, such as CrAg and syphilis. A recent collaboration between UNICEF and South Africa’s Rhodes University is working on offering another alternative for rapid CD4 testing, using a colorimetric aptamer-based test strip and a reader that attaches to a cell phone camera to produce an accurate quantitative CD4 result in less than 20 min. Such innovation will be crucial to CD4 testing in the future. The development of better POC testing platforms should be strongly encouraged and not abandoned because of the elimination of CD4 thresholds for treatment initiation.

Another area of future research will be to explore the role of CD4 cell count monitoring as a tool to assist clinical decisions in current and future treatment strategies beyond the management of advanced HIV disease. Several new experimental HIV cure strategies and structured treatment interruption protocols are using high CD4 thresholds as a criterion to start/stop therapy [41,42]. There are several safety and ethical concerns about this approach that remain to be clarified [43]. A recent study suggested that CD4/CD8 ratio and its variation over time can be independent predictors of cardiovascular disease (CVD) events in HIV-infected individuals [44]. Further studies to examine its role as clinical biomarker of CVD outcomes and immune senescence are needed in prospective studies and larger cohorts. Finally, the use of CD4 cell count reference curves to identify immune nonresponse among virally suppressed patients can be an additional tool for clinicians when evaluating response to ART [45].

Specifications for an ideal CD4 test
As we move into the era of test and treat, CD4 count testing will be a critical component of clinical assessment at baseline initiation of ART and to evaluate immune status after ART interruptions and noncompliance. An ideal test would only need to be semiquantitative with cutoffs at either 100 or 200 cells mm⁻³, or possibly both, and in a rapid diagnostic test or POC format. This would ensure that testing could be done easily and quickly during initiation of ART at baseline and in treatment failure situations, where clinical status of the patient is a key to assess.

CONCLUSION
CD4 cell count testing has made a critical contribution to the management of people living with HIV over the past three decades. Increased access to ART and viral load, and recent policy changes recommending ART start in all HIV-positive individuals irrespective of immune status have brought into question the future role of CD4 cell count testing in the global HIV response. In light of this, the role of CD4 testing is likely to become more restricted to baseline testing, returning to its original purpose as an essential tool in the assessment of disease progression in patients and, most importantly, in the proper management of patients with advanced HIV disease. As viral load continues to be scaled up, countries will need to make strategic decisions regarding relative investments in further scale up of CD4 and viral load technologies. We encourage test manufacturers to pursue CD4 technologies that will allow this important test to continue to be accessible in resource-limited settings as this shift occurs.

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HIV and diagnostics

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Conflicts of interest
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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest


This review article summarizes the evolution in evidence and policy relating to when to start ART.


This systematic review assesses the relationship between CD4 cell count and adherence to ART.


This systematic review provided the evidence to inform the WHO recommendation to stop routine CD4 cell count testing in stable patients who were monitored clinically.


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