The future role of CD4 cell count for monitoring antiretroviral therapy

Nathan Ford, Graeme Meintjes, Anton Pozniak, Helen Bygrave, Andrew Hill, Trevor Peter, Mary-Ann Davies, Beatriz Grinsztejn, Alexandra Calmy, N Kumarasamy, Praphan Phanuphak, Pierre deBeaudrap, Marco Vitoria, Meg Doherty, Wendy Stevens, George K Siberry

For more than two decades, CD4 cell count measurements have been central to understanding HIV disease progression, making important clinical decisions, and monitoring the response to antiretroviral therapy (ART). In well resourced settings, the monitoring of patients on ART has been supported by routine virological monitoring. Viral load monitoring was recommended by WHO in 2013 guidelines as the preferred way to monitor people on ART, and efforts are underway to scale up access in resource-limited settings. Recent studies suggest that in situations where viral load is available and patients are virologically suppressed, long-term CD4 monitoring adds little value and stopping CD4 monitoring will have major cost savings. CD4 cell counts will continue to play an important part in initial decisions around ART initiation and clinical management, particularly for patients presenting late to care, and for treatment monitoring where viral load monitoring is restricted. However, in settings where both CD4 cell counts and viral load testing are routinely available, countries should consider reducing the frequency of CD4 cell counts or not doing routine CD4 monitoring for patients who are stable on ART.

Introduction

For more than two decades CD4 cell count measurements have been central to understanding HIV disease progression and making important clinical management decisions. Measurements of CD4 cell count are an important predictor of disease progression[1–5] and death[6–8] in people living with HIV and have been the main means to assess eligibility for initiation of antiretroviral therapy (ART), use of prophylaxis for opportunistic infections, and monitoring the response to treatment.[8–10]

In well resourced settings, monitoring of patients on ART has been supported by routine virological monitoring.[11] Viral load (plasma HIV RNA) monitoring also predicts HIV-related mortality, accurately detects virological failure usually before immunological or clinical deterioration, and signals the need for more intensive adherence support and resistance genotyping.[12,13] Recognising these benefits, WHO recommends measurement of HIV viral load as the preferred approach to treatment monitoring,[14] and concerted efforts are supporting scale-up of viral load capability in resource-limited settings.[15]

As access to viral load becomes increasingly available, the role of CD4 monitoring in virologically suppressed patients is increasingly being questioned. Several studies have recently suggested that CD4 cell count monitoring has little added value in situations where viral load is available and patients are virologically suppressed.[16–18]

In September, 2013, WHO held an expert consultation on the future role of CD4 testing for ART monitoring. We summarise the evidence and experience shared and the conclusions reached at this consultation.

Current policies for ART monitoring

During the past decade, WHO guidelines for ART in countries with low and middle incomes have evolved towards recommending that countries phase in viral load for monitoring of treatment. The value of viral load was recognised by WHO guidelines in 2003, although access at the time was restricted by the complexity and cost of available assays.[19] Since then, improvements in technology and access have led to increased use of viral load monitoring. WHO guidelines released in June, 2013, recommend that countries use HIV viral load as the preferred approach to ART monitoring.[20,21]

Guidelines for ART monitoring vary between countries. Several resource-limited settings, including Mozambique, Swaziland, and Zimbabwe rely on routine CD4 monitoring, with viral load used only in a targeted way to confirm virological failure in patients with immunological or clinical failure. Other countries, including Cameroon and Côte d'Ivoire, provide both CD4 cell counts and viral load measurement routinely, albeit with different frequencies. Malawi and South Africa rely on viral load for long-term monitoring. In South Africa, discontinuation of routine CD4 cell count is now recommended after 1 year for patients stable on ART, although CD4 cell counts are done when needed for decisions regarding the stopping of prophylaxis for some AIDS-associated opportunistic infections.[22] Monitoring strategies can also differ between public and private sectors: in India for example, targeted use of viral load is provided in the public sector, whereas routine viral load monitoring is offered in the private sector. The frequency of CD4 cell counts and viral load tests for ART monitoring also varies substantially between countries (table).

Prospects to increase access to viral load monitoring

Although viral load measurement is recommended by WHO as the preferred approach to treatment monitoring and is included in guidelines of most countries with high HIV burden, access is restricted. Several middle-income countries—notably Botswana, Brazil, South Africa, and Thailand—were early adopters of HIV viral load

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Department of HIV/AIDS, World Health Organization, Geneva, Switzerland (N Ford PhD, M Vitoria MD, M Doherty PhD); **Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa** (G Meintjes PhD); **Chelsea and Westminster Hospital, London, UK** (A Pozniak MD); **Southern Africa Medical Unit, Médecins Sans Frontières, Cape Town, South Africa** (H Bygrave MBChB); **Department of Pharmacology and Therapeutics, Liverpool University, UK** (A Hill PhD); **Clinton Health Access Initiative, Boston, MA, USA** (T Peter PhD); **Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa** (M-A Davies MD, N Ford); **Fundação Oswaldo Cruz, Ministry of Health, Brazil** (B Grinsztejn MD); **HIV/AIDS Unit, Infectious Disease Service, Geneva University Hospital, Geneva, Switzerland** (Prof A Calmy PhD); **YRG Centre for AIDS Research and Education, Chennai, India** (N Kumarasamy MD); **Thai Red Cross AIDS Research Centre, Bangkok, Thailand** (Prof P Phanuphak MD); **Institut de Recherche pour le Développement (IRD), Montpellier, France** (P deBeaudrap PhD); **Department of Molecular Medicine and Haematology, University of the Witwatersrand and National health Laboratory Services, Johannesburg, South Africa** (Prof W Stevens PhD); **and Maternal and Pediatric Infectious Disease Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, Rockville, USA** (G Siberry MD)

Correspondence to:
Nathan Ford, Department of HIV/AIDS, World Health Organization, Geneva, Switzerland
fordn@who.int

monitoring, integrating it into their ART scale-up plans from the outset. Viral load monitoring has been integrated into public health programmes more broadly since 2010, when WHO guidelines first recommended that countries should phase in viral load for routine treatment monitoring (figure).[23]

One of the most important barriers to the scaling up of viral load testing remains cost: for low and middle income countries test costs vary from around US$10 to more than US$50. The African Society for Laboratory Medicine recommends several approaches to reduce the cost of viral load testing, including negotiating volume-based regional or country-wide pricing for test supplies, leasing equipment if possible, encouraging competition between suppliers, and leveraging existing laboratory capacity and systems established for early infant diagnosis of HIV to support the scale-up of viral load monitoring.[15]

A key consideration to increase resource availability for phasing in viral load testing is to decrease the overall cost of laboratory monitoring. Recent modelling studies from South Africa[24] and the USA[25] have suggested that reducing the frequency of CD4 cell count monitoring can substantially reduce the overall cost of ART monitoring and thereby avoid unnecessary use of resources. In resource-limited settings, these resources could be directed towards increasing access to viral load.

The anticipated arrival of point-of-care technologies in the near future is expected to overcome some of the technological limitations to improving access to viral load, particularly in remote rural areas. As of March, 2014, nine point-of-care technologies were in the pipeline with six anticipated to receive market authorisation by 2016.[26] Other approaches that have been taken to increase capacity and access include the use of dried blood spot sample collection and sample pooling.[27,28]

	CD4 cell count monitoring	Viral load monitoring	Future perspective
India			
Public sector	6 monthly	Targeted	Routine: annually
Private sector	3–6 monthly	Routine: 6 months, then annually	Routine
Mozambique	6 monthly	Targeted	Evolution towards routine viral load
Botswana	3 months, 6 months, then 6 monthly	Adults: 3 months, 6 months, then 6 monthly; children: 3 monthly	Annual CD4
Cameroon	Every 6 months	Viral load should be tested at 6 months, 12 months, then every 2 years if viral load undetectable (ie, <5000 cell parts/mL)	CD4 tested every 6 months until 2 measures >350 cells.uL then stopped viral load tested at 6 months, 12 months, then annually
South Africa	At 12 months, then stop	Routine: 6 months, 12 months, then annually	Routine
Brazil	4 monthly	4 monthly	6 monthly
Thailand	6 monthly	Routine: 6 months, 12 months, then annually	Annual CD4 once virologically suppressed
Côte d'Ivoire	6 monthly	Adults: annually; children: 6 monthly	Routine
Malawi*	None	Routine: 6 months, then every 2 years	Routine
DR Congo*	6 monthly	Targeted	Unclear
Guinea*	6 monthly	Targeted	Unclear
Kenya*	6 monthly	Routine: annually	Consideration to drop CD4 monitoring in stable patients
Lesotho*	6 monthly	Routine: annually	Routine
Swaziland*	6 monthly	Targeted; routine: annually	Consideration to drop CD4 monitoring in stable patients
Zimbabwe*	6 monthly	Targeted	Evolution towards routine viral load
Myanmar*	6 monthly	Targeted	Routine
Ukraine*	3 monthly	Routine: 6 monthly	Routine
Switzerland†	6 monthly (at least)	At least 6 monthly (minimum, once virologically suppressed)	Routine
UK	Every 3–4 months Every 4–6 months (if stable)‡	3–6 monthly	CD4 and viral load 6 monthly§
USA	Adults: Every 3–6 months¶ Children: Every 3–4 months¶	At initiation, 2–8 weeks post initiation, then every 4–8 weeks until viral suppression achieved, then every 3–4 months||	Routine

*Data provided by Médecins Sans Frontières. †More frequent monitoring as considered necessary. ‡Defined as CD4 count >200 copies/mL and viral load <50 copies/mL for 1 year. §Already practiced in some hospitals. ¶Adults and children: in clinically stable patients with suppressed viral load and whose CD4 cell count has increased well above the threshold for opportunistic infection risk, CD4 count can be monitored every 6–12 months. ||Adults: for clinically and immunologically stable, adherent patients on ART for more than 2–3 years, 6 monthly monitoring of viral load can considered.

Table: **Current guidelines for CD4 cell count and viral load monitoring of patients receiving antiretroviral therapy by country**

The future of CD4 cell count for treatment initiation

The WHO 2013 Consolidated ART guidelines recommend that ART be initiated for all patients with CD4 count 500 cells per µL or less, and immediate initiation of ART regardless of CD4 count for children age up to 5 years, people with active tuberculosis or with hepatitis B co-infection and chronic liver disease, and HIV-infected people in serodiscordant partnerships; these guidelines further recommend that ART be immediately offered to all HIV-infected pregnant and breastfeeding women.[29]

Most high-burden countries are in the process of adopting and adapting these WHO recommendations according to their epidemic setting and resource availability. As of June, 2013, 19 countries had allowed for immediate ART in HIV serodiscordant couples, five countries had adopted an ART initiation threshold of CD4 count 500 cells per µL, and 12 countries had moved to immediate ART for all pregnant and breastfeeding women.[30] A few countries already offer ART to all patients irrespective of CD4 cell count,[31] or are considering to do so.

Thus, although there is a trend towards an increasing number of CD4-independent ART initiation scenarios, ART for all irrespective of CD4 cell count remains the exception rather than the rule, and for most countries CD4 measures will continue to play an important part to determine ART eligibility for some time to come.

The future of CD4 for treatment monitoring

Baseline measurements

Consistent with the trend towards earlier initiation of ART, the median baseline CD4 cell count at which patients start ART has risen in the past decade in all regions; however, the proportion of people initiating ART with very low CD4 counts remains high, with more than one in four patients starting ART at CD4 count 100 cells per µL or less across all regions.[32] Patients presenting with a low CD4 cell count are at increased risk of death in both low and high-income settings,[33,34] and determination of CD4 count has an important role in decisions for screening and prophylaxis for major opportunistic infections. A low CD4 count is predictive of several diseases associated with increased mortality, including cryptococcal meningitis, pneumocystis pneumonia, toxoplasmosis, *Mycobacterium avium* complex, and disseminated cytomegalovirus disease. CD4 cell counts can help to stratify clinical care requirements for patients presenting late to care and support diagnostic decision making at baseline and in patients with failing ART or those returning to care after a period of treatment interruption. Cryptococcal meningitis is a leading cause of mortality in people with HIV/AIDS, contributing up to 20% of AIDS-related deaths in low-income and middle-income settings.[35] WHO recommends systematic antigen screening for cryptococcal meningitis for all patients with CD4 counts of 100 cells per µL or lower and pre-emptive treatment for those who test antigen-positive.[36]

CD4 count also plays an important part in supporting decisions to start and stop co-trimoxazole prophylaxis. Co-trimoxazole improves survival by reducing the risk of death from a range of infections, including malaria, severe bacterial infections, *Pneumocystis jiroveci* pneumonia, and toxoplasmosis.[37] To reduce morbidity and mortality, WHO recommends co-trimoxazole prophylaxis to all HIV-infected people presenting to care who have advanced or severe HIV disease (WHO clinical stage 3 or 4) or those with a CD4 count of 350 cells per µL or less, to be discontinued once CD4 counts rise above this level.[38] In settings with a high prevalence of malaria or severe bacterial infections, WHO recommends starting lifelong co-trimoxazole prophylaxis irrespective of CD4 cell count.

Finally, a baseline CD4 measurement might have a role in decisions around use of nevirapine, in view of the potential increased risk of nevirapine-associated hypersensitivity reaction at increased CD4 cell counts.[39]

ART monitoring

Recent evidence from randomised trials and observational cohorts suggest that once people with HIV infection on ART are virologically suppressed, CD4 cell counts remain stable over time in most patients.

An analysis of data from the multisite ARTEMIS trial[17] showed that of 449 patients with sustained HIV-1 RNA suppression (<400 copies per mL) and CD4 count of 200 cells per µL or more who were followed for 192 weeks, only five (1%) had reductions in CD4 count below 200 cells per µL; these reductions were transient with follow-up results equal to or greater than 200 cells per µL.[17] A cohort study from the USA noted that of 832 patients followed for a median of 7·7 years, patients with an initial CD4 count of 300 cells per µL or more who were virologically suppressed (<200 copies/mL) had a probability of a durable CD4 count of 200 cells per µL or more at year 5 of 99·2% (95% CI 97·4–99·7), after exclusion of non-HIV causes of lymphopenia.[16]

Two studies from the UK support these findings. In the first study, 166 patients who were stable (CD4 >500 cells per µL and virologically suppressed [<50 copies/mL]) were followed for a median of 47 weeks; only five (3%) patients had a reduction in CD4 count less than 350 cells per µL and these reductions were again transient, with all CD4 measures greater than 350 cells per µL at subsequent visit.[40] The second study followed 141 stable patients with viral loads less than 50 copies/mL on ART and CD4 count 350 cells per µL or greater for a median of 2·5 years: only 13 patients (9%) had a drop in CD4 count during this period, of which eight (61%) were transient; for three patients (23%) the drop was explained by other treatments that lower the CD4 count such as interferon or chemotherapy. Results of CD4 monitoring did not change clinical management of any patients.[41]

Recent data from high HIV burden settings in sub-Saharan Africa support these findings. A cohort study from South Africa followed 5697 adult patients for up to 10 years on ART. Most patients with ongoing virological suppression maintained CD4 counts continuously greater than 200 cells per µL, at 2 years, (99·3%), at 5 years (95·8%), and at 10 years (92·9%). For those who were evaluable, reductions in CD4 count were transient in more than 90%.[42] Another cohort study from Uganda reported that less that 43 (3%) of 1482 who achieved a viral load of less than 400 copies per mL and CD4 count of 200 cells per µL had a subsequent reduction in CD4 cell count to less than

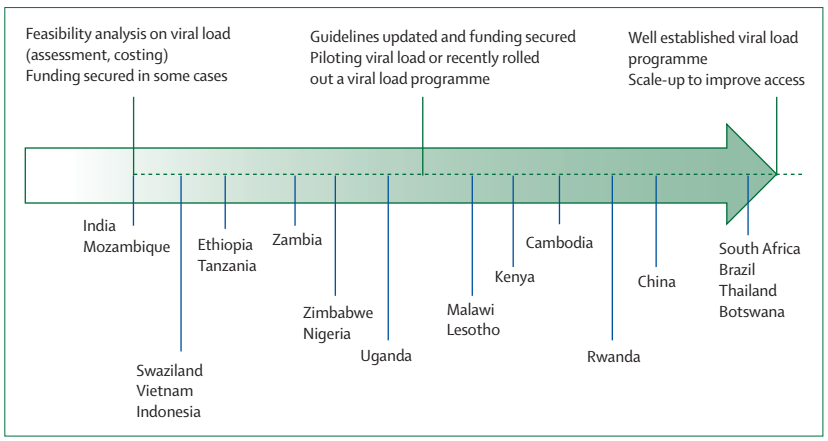

Figure: **Progress in viral load phase in in countries with low and middle income with time**

Panel 1: **Implementation considerations for reducing CD4 cell counts for antiretroviral therapy (ART) monitoring**

- Retain capacity for CD4 cell counts as a diagnostic instrument to support ART initiation and risk stratification for provision of a late presenter package of care, including prophylaxis for opportunistic infections, and cryptococcal antigen screening
- Ensure reliable access to routine viral load monitoring as a prerequisite for reducing or stopping CD4 monitoring
- Ensure access to CD4 for individuals who develop clinical problems or evidence of virological failure while on ART
- Develop guidance to define a stable patient on ART in whom CD4 monitoring can be stopped
- Train health workers and patients in viral load literacy as a way to understand health status and response to treatment
- Redirect resources saved from reduced CD4 monitoring to support viral load monitoring

Panel 2: **Research agenda for CD4 monitoring**

- CD4 dynamics in virologically suppressed patients in resource-limited settings
- Minimum period and criteria before CD4 cell count monitoring can be stopped (stable patients)
- Frequency of viral load monitoring required if CD4 monitoring is dropped
- Validation of change in CD4 count at increased virological thresholds used to determine failure in resource-limited settings (ie, 1000 copies per mL)
- Criteria to reduce CD4 monitoring in infants and children
- Criteria to reintroduce CD4 measures (eg, viral rebound, or clinical event, or toxic treatment (eg, interferon for hepatitis C, chemotherapy)
- Management of patients with persistent discordant immunological virological response
- Cost and cost effectiveness of different models of CD4 cell count versus viral load monitoring
- Define whether viral load criteria could replace CD4 cell count criteria in decisions regarding stopping primary and secondary opportunistic infections prophylaxis, mainly in resource-limited settings

200 cells per µL; this reduction was transient in 20 (83%) of 24 whose CD4 cell count was subsequently assessed.[18]

Data for children are insufficient, but in line with adult studies. A cohort study from South Africa followed almost 6000 virologically suppressed HIV positive children on ART for up to 3 years and identified that sustained reductions in CD4 counts were very rare, especially in children older than 2 years.[43] A recent model-based algorithm suggest that the frequency of CD4 cell count measures could also be reduced in children, with last CD4 count, last viral load, and patient age to predict risk of clinical disease progression.[44]

None of these studies reported adverse clinical events occurring in virologically suppressed patients with an unexplained reduction in CD4 count.

Criteria to stop routine CD4 cell counts for treatment monitoring

CD4 cell counts at baseline continue to be important for initial clinical management decisions, but once ART is initiated and patients have achieved virological suppression and stabilised on treatment, the additional value of CD4 testing in the presence of routine viral load monitoring is questionable. Nadir CD4 predicts the maximum CD4 cell count that can be expected,[45,46] but CD4 cell counts rarely reduce with time once virological suppression is achieved even for patients presenting late for care. Most patients achieve a CD4 count greater than 500 cells per µL after several years of ART, provided that the viral load remains suppressed.[47–49] However, recovery of CD4 count is variable and a few patients might fail to increase despite virological suppression.[50,51] These variabilities in CD4 recovery would not change treatment decisions because there is no evidence for changing ART in those patients with discordance between immunological and virological responses (ie, persistently low CD4 counts despite virological suppression), although there would be a benefit to continue prophylaxis in such patients.[52]

A growing consensus is that monitoring of CD4 count adds little additional value to viral load monitoring once patients are stable on ART with viral suppression. Guidelines issued by the Southern African HIV Clinicians Society recommend that for patients being monitored with viral loads, once the CD4 count is greater than 200 cells per µL and viral load is suppressed (ie, two consecutive undetectable viral loads), there is no need to continue CD4 testing, although CD4 testing is recommended if virological or clinical failure occurs. [22]

For these reasons, the WHO consultation endorsed the move to reduce routine CD4 monitoring for adults when access to viral load testing is assured. For children, the decision to stop CD4 is more complex, both because of differences in risk of disease progression, particularly for younger children, and determination of immunological recovery. A working definition of stability on ART for children might need to be age-dependent, and this is an important area for further research (panel 1).

Community considerations

CD4 cell counts are central to approaches to treatment literacy, and substantial emphasis has been placed on the use of CD4 counts as a way to explain to patients why ART is needed, to reinforce the importance of maintaining good adherence, and to show a positive response to treatment. At the same time, both clinicians and patients recognise that CD4 cell counts can fluctuate substantially for biological reasons, the inherent variability of CD4 cell counts, and inconsistency of

results obtained by certain CD4 tests; this can be a source of unnecessary anxiety for patients.[53,54]

If viral load is to be used as the main means to monitor ART, treatment literacy efforts will be needed so that it can take the place of CD4 counts as the main way that patients understand they are responding to ART. Successful pilot programmes have already shown that with appropriate communication materials the relation between viral load and treatment success is easy to convey and readily understood,[55] and patients' groups have expressed a willingness to support a reduction in or stopping of routine CD4 count monitoring for stable patients provided this is accompanied by clear messaging that patients can understand.

Directions for future research

Various research questions remain (panel 2). ART monitoring with or without CD4 count (as an addition to viral load) will unlikely be assessed in randomised trials because the required sample sizes to detect possible differences when none are anticipated would be very large; attempts to do such a trial have failed for this reason. In the absence of evidence from randomised trials, the collection and reporting of observational data will continue to be important, in particular from resource-limited settings and for children on ART.

Another important area for research is to determine whether certain clinical decisions that are dependent on CD4 count, notably decisions to stop cotrimoxazole prophylaxis, could be made on the basis of virological thresholds or duration of virological suppression. Cohort data from Europe suggests that risk of pneumocystis pneumonia is low in people who are virologically suppressed, even at low CD4 cell counts.[56]

Research is also needed to identify if and when CD4 measurement should be reinstituted (eg, viral rebound, clinical event, or concomitant therapy with immunosuppresive potential [interferon for hepatitis C or chemotherapy]) and to determine CD4 dynamics in virologically suppressed patients in resource-limited settings. Finally, because CD4 recovery is variable and might not increase despite virological suppression in some patients,[50,51] there is a need to better understand the reason for discordance between immunological and virological measures and the value of ongoing CD4 monitoring for these patients,[57] as well as with virological rebound.

Conclusions

CD4 cell counts have been the main instrument to make decisions about ART initiation and to monitor the response to treatment, and have had great value for both clinicians and patients. However, the use of ongoing CD4 monitoring in people who are stable on ART whose viral load is also being monitored and is undetectable is increasingly questioned, in settings with high and low income.

Almost 13 million people were on ART and more than 2 million people were newly initiated on ART in 2013 alone. Life-expectancy studies from both high-income[58] and low-income[59–61] settings have concluded that with timely ART initiation, people living with HIV can expect to enjoy near normal life expectancy. Therefore, a pressing need exists to identify the most rational and cost effective way to provide laboratory monitoring of HIV treatment over the long term.

CD4 counts will continue to play an important part in initial decisions around ART initiation and clinical management, particularly for those patients presenting late to care, and will remain an important instrument to monitor treatment in settings where viral load monitoring is still restricted. However, in settings where both CD4 and viral load testing are routinely available, countries should consider reducing the frequency of CD4 cell counts or not using them routinely to monitor treatment response once patients are stable on ART. Countries in the process of phasing in viral load monitoring capacity should consider reducing the indications for and frequency of CD4 cell measurements and redirecting those resources towards expanding access to viral load monitoring.

Contributors

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Declaration of interests

We declare no competing interests.

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