Time to reduce CD4$^+$ monitoring for the management of antiretroviral therapy in HIV-infected individuals

The relative importance of laboratory monitoring in HIV/AIDS programmes in low- and middle-income countries has been the subject of considerable debate over the past decade. The recent changes in South Africa (SA)'s HIV treatment guidelines focus primarily on maintaining a low viral load (VL) (preferably undetectable VL: <40 copies/ml) to reduce the risk of transmission and drug resistance.[1] Monitoring of HIV/AIDS and associated opportunistic infections represents a significant challenge to resource-limited countries, where the potential total cost of disease monitoring may exceed the annual health budget. Many obstacles are noted in the provision of affordable and accessible laboratory monitoring for HIV/AIDS, including limited laboratory infrastructure, absence of technical skills, high reagent costs and large capital outlay costs for sophisticated equipment.[2]

CD4$^+$ cell count testing has been central to monitoring disease progression, determining the need for antiretroviral therapy (ART), and assessing response to treatment. Efforts continue to expand access to CD4$^+$ measurement capacity, and a rich research and development pipeline promises a range of point-of-care CD4$^+$ tests that can potentially improve linkage to care and reduce time to treatment initiation.[3]

National and international guidelines generally recommend a CD4$^+$ test at baseline and then 6-monthly thereafter.[4,5] The threshold for initiation of ART based on a public health approach and World Health Organization (WHO) recommendations has increased from ≤200 cells/μl in the original 2002 WHO guidelines to ≤350 cells/μl in 2010 and ≤500 cells/μl in 2013, with the proviso that individuals with CD4$^+$ counts <350 cells/μl remain the priority treatment group.[6] In addition, it is recommended to start certain high-risk populations on treatment irrespective of CD4$^+$ cell count, such as HIV-infected pregnant or breastfeeding women, patients with active tuberculosis and/or hepatitis B with severe chronic liver disease, children <5 years of age, and the HIV-infected partner in serodiscordant couples.[6]

While there remains a clear role for the CD4$^+$ count in establishing baseline health status and focusing treatment provision on patients at higher risk of death, the role of CD4$^+$ in the monitoring of ART efficiency once patients have started ART is under scrutiny. In SA, a bold step was made to recommend against routine CD4$^+$ monitoring after

the first year on ART.[7] Treatment targets using the 2010 monitoring guidelines[7] would have meant that an estimated 7 million CD4+ tests would have been conducted in the 2013/2014 fiscal year, requiring a doubling of laboratory CD4+ capacity. For these reasons, and the fact that ART is altered on the basis of VL monitoring rather than the CD4+ count, stopping routine CD4+ for monitoring ART beyond the first year was recommended, unless the individual was ill. This single change has reduced the CD4+ cost estimates in SA by 51% (data modelled between 2013 and 2017), resulting in potential savings of over R740 million over the 5-year period (K Schnippel, personal communication).

Studies have questioned the reliability of CD4+ monitoring as opposed to VL monitoring in determining the need for a change in treatment to second- or third-line regimens. A recent meta-analysis of seven studies that assessed the accuracy of clinical or immunological criteria to define virological failure found very poor sensitivity (26.6%) and positive predictive values (49.4%).[8] The consensus reached from several studies is that VL testing is the most reliable method of determining treatment failure.[9]

Questioning the value of the CD4+ test has also gained momentum globally, and a recent analysis of data from the USA found that patients with CD4+ counts >300 cells/μl and virological suppression (defined as a VL <200 copies/ml) were unlikely to experience a dip in CD4+ count below 200 cells/μl; rather, 97% of individuals maintained CD4+ counts above 200 cells/μl for a period of 4 years.[10] Similar studies among adults in Uganda[11] and children in SA[12] have confirmed that the CD4+ cell count does not decline significantly in the vast majority of patients who respond to treatment and are virologically suppressed. Reflecting this growing evidence base, the WHO released a technical document in March 2014 summarising the considerations in support of a move towards stopping routine CD4+ monitoring where VL monitoring is available.[13]

In the most recent WHO guidelines,[14] access to VL monitoring is recommended as the preferred approach to support adherence, detect treatment failure early, assess transmission risk and avoid keeping individuals on failing regimens, especially as rates of drug resistance begin to rise in developing countries. Resources and research and development should therefore be channelled to both VL and HIV drug resistance testing.

So what could be the future role of the CD4+ cell count in settings where VL monitoring is available? Many countries with a high HIV burden will probably continue to use the CD4+ cell count to determine ART eligibility. The count at presentation also provides valuable information about disease risk and the need for prophylaxis, diagnosis and treatment of certain opportunistic infections. CD4+ cell counts will therefore continue to be of value for pre-ART patients, but more efforts are required to make them more meaningful and reduce the currently high attrition rates (only 57% of SA patients initially determined as being not yet eligible for treatment return for repeat CD4+ testing and eventually ART,[15] and similar challenges are reported from the USA[16]). Point-of-care CD4+ testing has been promoted as one way to improve linkage to care, and while there is evidence of reduced pre-ART attrition associated with the use of point-of-care CD4+ devices,[17] other efforts are also needed to ensure maintenance of linkage to care.

The historical approach of monitoring both CD4+ and VL in patients on ART, developed in high-income settings, is a misuse of scarce laboratory resources. HIV programmes should prepare for a shift away from CD4+ for routine monitoring of stable ART patients. This will require moving away from CD4+ for routine ART monitoring where VL testing is routinely available, as in SA, and therefore utilisation of VL as the benchmark of treatment success.

Disclaimer. This article represents the views of the authors and does not necessarily represent the views of their organisations.

Wendy S Stevens
Department of Molecular Medicine and Haematology, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa

Nathan Ford
Department of HIV/AIDS, World Health Organization, Geneva, Switzerland
Corresponding author: *W S Stevens (wendy.stevens@nhls.ac.za)*

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