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Title: The continuing value of CD4 cell count monitoring to differential HIV care and surveillance

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Authors: Brian Rice PhD, MSc; Andrew Boulle MBchB, PhD, MSc; Sandra Schwarcz MD, MPH; Amir Shroufi MB, ChB, MPhil; George Rutherford MD, AM; James Hargreaves PhD, MSc

1 Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom
2 Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
3 Global Health Sciences, University of California San Francisco, San Francisco, CA, United States of America
4 Médecins Sans Frontières, Cape Town, South Africa

Corresponding author: Brian Rice, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London, WC1H 9SH, UK; 0044 (0) 720 7927 2567; brian.rice@lshtm.ac.uk

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Abbreviations: ART: antiretroviral therapy; WHO: World Health Organization; UNAIDS: Joint United Nations Programme on HIV/AIDS
Abstract (78 words):
The move towards the universal provision of antiretroviral therapy, and the expansion of HIV viral load monitoring, calls into question the ongoing value of CD4 cell count testing and monitoring. We highlight the role CD4 monitoring continues to have in guiding clinical decisions and in measuring and evaluating the epidemiology of HIV. To end the HIV/AIDS epidemic we require strategic information, which includes CD4 cell counts, to make informed clinical decisions and to effectively monitor key surveillance indicators.

**Key words:** CD4; HIV; differential care; antiretroviral therapy; surveillance; monitoring
The CD4 cell count has been the principal basis for assessing an HIV-infected person’s level of immunosuppression and for timing initiation of antiretroviral therapy (ART) (1). In 2015, the World Health Organization (WHO) recommended starting ART at any CD4 count, regardless of clinical symptoms or conditions (2). These guidelines and subsequent studies argue that, for clinical purposes, the frequency of CD4 monitoring post-ART initiation can be reduced or ceased when viral load testing is available and patients are suppressed (2-6).

The move towards universal ART and the expansion of viral load monitoring (7-9), and recommendations to reduce or cease CD4 testing post-ART initiation, calls into question the value of CD4 testing. Decreased support for CD4 testing could potentially not only result in reduced CD4 monitoring among people who have initiated ART, but also unintentionally lead to reduced testing among persons diagnosed with HIV who are yet to commence treatment. In this communication, we highlight the continuing role of CD4 monitoring in guiding clinical decisions and in measuring and evaluating the epidemiology of HIV.

The routine collection of CD4 data at diagnosis from laboratories and facilities continues to provide an assessment of treatment and testing priorities. Importantly, this information remains critical in identifying late diagnosis (as often indicated by a count of <350 cells/µL) (10-12). A late diagnosis is associated with a significantly elevated risk of HIV-related opportunistic infections and mortality and has been identified as a primary cause of HIV-related deaths in settings where ART is widely and freely available (10, 12-13).

Low CD4 counts are triggers for more intensive follow-up and care in differentiated care models. For example, WHO guidelines on advanced disease recommend people with a CD4 count <100 cells/µL be screened for cryptococcal disease and managed with Fluconazole if asymptomatic, those with a CD4 <200 cells/µL receive tailored counselling, and those with a CD4 <350 cells/µL receive cotrimoxazole prophylaxis (14). In Uganda, ART-naïve adults with CD4 counts ≤250 cells/µL are currently
screened for tuberculosis, with those with CD4 ≤100 cells/µL also screened for cryptococcal antigen (15), as is also the case in South Africa (16). In a recent three-country trial, presumptive antimicrobial treatment in patients initiating ART with <100 CD4 cells/µL resulted in a 30% reduction in six-month mortality (17). As loss to follow-up is a common outcome along the HIV care continuum (18), it is important differentiated care models, as informed by CD4 cell counts, also consider persons re-engaging in care.

Clinically mediated CD4 monitoring has also been an important feature of HIV surveillance. At the population-level, the prevalence of CD4-defined late diagnoses helps monitor the success of HIV testing programmes and evaluate strategies to promote earlier testing (11, 19). The linkage of CD4 data at diagnosis with longitudinal CD4 cell counts up to the commencement of ART has provided important information on trajectories of CD4 depletion between diagnosis and treatment. This information has been used, at international, national, and sub-national levels, to back calculate from time of diagnosis to probable time of infection to estimate HIV incidence (20-24), estimate the prevalence of undiagnosed HIV (22-26), and assign probable place of infection (27-28).

In a number of settings the application of CD4-based models and analyses are either being expanded or newly adopted. In 2016, a new model incorporating CD4 test results at or after diagnosis, but before ART, was introduced in the United States of America to estimate HIV incidence, prevalence, and undiagnosed infections (22). Among European Union member states a CD4 back calculation model, which assigns probable place of HIV infection among migrant populations by estimating time of infection and comparing this with time of arrival in host country, is currently being promoted to inform prevention programming (27-28). In addition to informing pre-ART care and policy decisions concerning the use of ART for prevention (29), routine CD4 monitoring in South Africa has recently been utilised to assess the risk of subsequent loss to follow-up from care (30) and to estimate care cascade measures (31). Although
most of the CD4-based activities cited are focused in middle and high income settings, the promotion of HIV case surveillance (32), and the collection of CD4 within these systems, will hopefully further expand the application of these methods to low- and middle-income settings, including high prevalence settings in sub-Saharan Africa.

Clinical and surveillance activities reliant on CD4 testing will be impaired if testing is reduced or discontinued between diagnosis and treatment initiation or in setting where viral load testing remains suboptimal. Although it has been suggested that access to viral load monitoring in low-income, high HIV burden settings may be limited (4), the Joint United Nations Programme on HIV/AIDS (UNAIDS) recently reported a number of resource-limited countries as having drastically reduced CD4 monitoring in favour of increased viral load testing (33). Signatories of a 2017 advanced HIV position statement, which included Médecins Sans Frontières, claim that donor support for CD4 testing at the primary care level has decreased in recent years (34). The signatories argue that CD4 monitoring at and post-ART initiation remains essential for the detection and management of HIV-related opportunistic infections such as Cryptococcus (34). The reduction of CD4 monitoring both at, and subsequent to, diagnosis was brought to the attention of a research team carrying out HIV system assessments in resource-limited settings in 2015 and 2016 (35-36).

It is inevitable that the role of CD4 monitoring in guiding clinical decisions will become more selective and nuanced. However, vigilance and oversight are required to ensure that, while we reduce reliance on CD4 monitoring in virologically suppressed patients, we retain our capacity to conduct CD4 testing pre-ART and when people re-engage in care, and to inform differentiated care models. Pre-ART CD4 monitoring in particular remains vital to diagnosing and treating co-morbidities, while secondarily ensuring the continuity of critical data for HIV surveillance. To end the HIV/AIDS epidemic we must have essential data to make informed clinical decisions and to effectively monitor key surveillance indicators.
References:


