CD4 Cell Count: A Critical Tool in the Human Immunodeficiency Virus Response

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Reducing illness and death from human immunodeficiency virus (HIV) globally has relied on simplification of care delivery so that treatment can be started safely in as many people as possible. Using a public health approach, care provision has been shifted from physicians to nurses, and care delivery has been decentralized from hospitals to primary care clinics and within the community. Treatment has been simplified from combinations of different pills adjusted for age, pregnancy status, and coinfection to a single 3-in-1 pill that is safe and effective for almost everyone. The decision of when to start treatment has evolved from treating the sickest to treating everyone as soon as possible after diagnosis [1].

This public health approach has supported an impressive increase in the number of people receiving antiretroviral therapy, with 27.4 million people living with HIV on treatment in 2020, up from just 7.8 million in 2010. AIDS-related deaths have fallen by 43% since 2010, to 690,000 in 2020 [2].

A study from South Africa in this issue of Clinical Infectious Diseases [3] reports an increase in health status of people living with HIV, as measured by CD4 cell count at start of treatment, after the adoption of a universal test and treat policy in 2016. This study used an interrupted time series analysis—a quasi-experimental design used to assess the impact of an intervention or exposure when randomization is not possible or appropriate; interrupted time series analysis is a particularly useful approach for assessing the “real-world” effect of a health policy change [4–6].

The study found that while CD4 cell count at the start of antiretroviral therapy (ART) increased immediately after implementation of the universal test and treat policy in South Africa, the long-term effects were modest. Importantly, an increasing proportion of ART initiators did not have a baseline CD4 cell count and, among those who did, a large proportion had advanced HIV disease (defined as a CD4 cell count <200/μL). These 2 findings—a decrease in CD4 count being obtained at baseline, and a persistence of advanced HIV disease despite ART scale-up—have been reported by other studies [7, 8].

Laboratory testing is one aspect of the public health approach to HIV care delivery that has been questioned since it was first put forward 15 years ago [9]. In high-income settings, diagnostic tests are used to measure immunological and clinical status (CD4 cell count), virological response (viral load), drug resistance (genotyping), and toxicity monitoring. In low- and middle-income settings the relative importance of various laboratory tests has been seen as a trade-off against resources that could be directed instead at scaling up ART. For genotyping and toxicity monitoring, the consensus has been that these tests are not needed as part of routine care, provided that safe and effective treatment can be ensured [1, 9], viral load was initially considered too technologically complex for low- and middle-income settings, but major investment has been made to improve access to viral load, with viral suppression now recognized as major indicator of program success [10].

Measuring CD4 cell count was the first laboratory test used for HIV patient care and has been essential to monitoring the clinical risk of opportunistic disease and death. More recently, however, it has been one of the most contentious laboratory tests in the HIV response. This is due to that fact that CD4 cell counts have been used to support a range of clinical decisions—when to start ART [11], which medication to use [12], and how to predict viral suppression [13]—and much less often to decide when opportunistic infection diagnostics and prophylactics [14–16] should be administered. The more recent monitoring uses have fallen
away as practice has changed with new evidence, better drugs, and the availability of better tools to monitor treatment. This has contributed to a view that CD4 cell count testing is no longer needed.

As highlighted by the study from South Africa [3] and other studies in recent years [17–21], HIV programs are still challenged to provide care for people with advanced HIV disease—either because the disease is diagnosed late in its progression or because people disengage from care and present again to care after a period without treatment and with a low CD4 cell count.

The advanced HIV disease package of care recommended by the World Health Organization [22] includes diagnostic and prophylactic interventions to respond to the leading causes of disease and death among people living with HIV: tuberculosis, cryptococcal meningitis, and severe bacterial infections [23]. This approach is based on the results of 2 randomized trials [24, 25], each of which found a near-30% reduction in mortality rate associated with the provision of a simple package of interventions for people presenting with advanced HIV disease. Both of these trials relied on CD4 cell count to identify patients who would benefit from receiving the intervention package.

Provision of the advanced HIV disease package of care is part of the public health response to HIV to reduce mortality rates associated with advanced HIV disease. A CD4 cell count is needed to identify people who should receive the package of care, and for this purpose alone it remains a critical tool in the HIV response.

**Note**

**Potential conflicts of interest.** The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**

1. Ford N, Ball A, Baggaley R, et al. The WHO public health approach to HIV treatment and care: looking back and looking ahead. Lancet Infect Dis 2018; 18:e76–86.
2. UNAIDS. Global commitments, local action: after 40 years of AIDS, charting a course to end the pandemic. Geneva, Switzerland: UNAIDS, 2021.
3. Manisha Yapa H, Kim H-Y, Petoumenos K, et al. CD4+ T-cell count at antiretroviral therapy initiation in the “treat all” era in rural South Africa: an interrupted time series analysis. Clin Infect Dis.
4. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. BMJ 2015; 356:h2750.
5. Biglan A, Ary D, Wagenaar AC. The value of interrupted time-series experiments for community intervention research. Prev Sci 2000; 1:31–49.
6. Campbell D. Reforms as experiments. Am Psychol 1969; 24:409–29.
7. IDea and COHERE Cohort Collaborations. Global trends in CD4 cell count at the start of antiretroviral therapy: collaborative study of treatment programs. Clin Infect Dis 2018; 66:893–903.
8. Zaniewski E, Dao Ostinelli CH, Chammartin F, et al. Trends in CD4 and viral load testing 2005 to 2018: multi-cohort study of people living with HIV in Southern Africa. J Int AIDS Soc 2020; 23:e25546.
9. Gilks CF, Crowley S, Ekpiu R, et al. The WHO public health approach to antiretroviral treatment in HIV: resource-limited settings. Lancet 2006; 368:505–10.
10. Calmy A, Ford N, Hirschel B, et al. HIV viral load monitoring in resource-limited regions: optional or necessary? Clin Infect Dis 2007; 44:128–34.
11. Eholié SP, Badje A, Kouame GM, et al. Antiretroviral treatment regardless of CD4 count: the universal answer to a contextual question. AIDS Res Ther 2016; 13:27.
12. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva, Switzerland: World Health Organization, 2013.
13. Gilks CF, Walker AS, Munderi P, et al; DART Virology Group and Trial Team. A single CD4 test with 250 cells/mm3 threshold predicts viral suppression in HIV-infected adults failing first-line therapy by clinical criteria. PLoS One 2013; 8:e57580.
14. Suthar AR, Vitoria MA, Nagata JM, et al. Co-trimoxazole prophyaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. Lancet HIV 2015; 2:e137–50.
15. Ford N, Shubber Z, Jarvis JN, et al. CD4 cell count threshold for cryptococcal antigen screening of HIV-infected individuals: a systematic review and meta-analysis. Clin Infect Dis 2018; 66:152–9.
16. Broger T, Nicol MF, Szédy K, et al. Diagnostic accuracy of a novel tuberculosis point-of-care urine liposarabinomannan assay for people living with HIV: a meta-analysis of individual in- and patient data. PLoS Med 2020; 17:e1003113.
17. Oser M, Hildebrand K, Goemaere E, et al. The continuing burden of advanced HIV disease over 10 years of increasing antiretroviral therapy coverage in South Africa. Clin Infect Dis 2018; 66:118–25.
18. Lebelonyane R, Mills LA, Mogorosi C, et al. Advanced HIV disease in the Botswana combination prevention project: prevalence, risk factors, and outcomes. AIDS 2020; 34:2223–30.
19. Kaplan SR, Oosthuizen C, Stimson K, et al. Contemporary disengagement from antiretroviral therapy in Khayelitsha, South Africa: a cohort study. PLoS Med 2017; 14:e1002407.
20. Chihana ML, Huerga H, Van Cutsem G, et al. Distribution of advanced HIV disease from three high HIV prevalence settings in Sub-Saharan Africa: a secondary analysis data from three population-based cross-sectional surveys in Eshowe (South Africa), Ndhiwa (Kenya) and Chiradzulu (Malawi). Glob Health Action 2019; 12:1679472.
21. Carmona S, Bor J, Nattey C, et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa’s National HIV Program: data from a nationwide laboratory cohort. Clin Infect Dis 2018; 66:111–7.
22. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva, Switzerland: World Health Organization, 2017.
23. Ford N, Shubber Z, Meintjes G, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. Lancet HIV 2015; 2:e438–44.
24. Hakim I, Massme V, Szubert AJ, et al; REALITY Trial Team. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N Engl J Med 2017; 377:233–45.
25. Mfinanga S, Chanda D, Kivuyo SL, et al; REMSTART trial team. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet 2015; 385:2173–82.