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The declining value of CD4 counts for antiretroviral therapy eligibility

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Antiretroviral therapy (ART) has improved the lives of millions of people living with HIV by increasing life expectancy and reducing HIV transmission. The World Health Organization's (WHO) most recent guideline for the treatment of HIV reflects the immense benefit of ART by recommending ART for all individuals living with HIV. Although this new recommendation is gaining traction among wealthier countries, such as South Africa which will adopt this strategy in September 2016, many countries have not yet adopted this guideline. Instead, those countries follow a strategy of providing ART only to people with low CD4+ T-cell counts (Table 1) (1), which was necessary early in the HIV epidemic, but it is unclear whether the use of CD4 counts was based on sound science and logic.

In the early 2000's, the WHO and the United States Department of Health and Human Services (DHHS) proposed guidelines for ART provision. Both organizations based their recommendations on the same dataset, but came to vastly different conclusions. The WHO noted that "beginning therapy before the CD4 cell count falls below 200/mm3 clearly provides clinical benefits," but that treatment should be limited to those with CD4 count ≤200 cells/μL, because "the actual point above 200/mm3 at which to start therapy has not been definitively determined." Thus, they recommended limited ART provision, restricting it to individuals with CD4 counts ≤200 cells/μL (2). On the other extreme, the US DHHS recommended ART to all persons with a CD4 count ≤500 cells/μL or with a viral load >10,000 copies/mL. They stated that their "aggressive approach is heavily based on…the principle that one should begin treatment before the development of significant immunosuppression" (3). The disparate interpretations of how to use CD4 counts to guide ART, the ensuing 15 years of debate around when to start, and the recent WHO guidelines bring into question the reliability of CD4 counts as a surrogate marker for ART initiation.

For CD4 cell count to be used as a surrogate marker for ART initiation, it must have clinical and public health benefits. First, it must reliably predict disease progression and the risk of transmitting HIV. Second, it must be easily and reliably measured within individuals and among populations. Finally, it must be feasible to implement and facilitate the ultimate goal of ART expansion.

CD4 counts provide little clinical benefit

To provide clinical benefit, a surrogate marker for ART eligibility should indicate to a clinician a patient's disease state and prognosis. Although low CD4 counts have been demonstrated to be highly predictive of morbidity and mortality, the current debate is around whether or not high CD4 counts can be prognostic. A recent quantitative review suggests that CD4 counts exhibit substantial variability early in HIV infection and therefore, at high levels, have no prognostic value for predicting course of disease (4). Other studies have also found little to no relationship between CD4 counts and disease progression in people living with HIV (5).

From a public health perspective, a surrogate marker should also predict one's probability of transmitting HIV. Although numerous studies have demonstrated the correlation between HIV viral load and the probability of HIV transmission in both plasma samples and genital mucosa, CD4 counts poorly correlate with HIV viral load or HIV transmission (6, 7). In fact, multiple studies have found vastly different numbers of individuals at risk of transmitting HIV when using accepted criteria by CD4 count or viral load. In a South African township, 13% of the population had CD4 count ≤200 cells/μL, but 44% had a viral load >10,000 copies/mL (8). With the poor correlation between the two measures, a policy of prioritizing low CD4 counts would produce a different population of individuals considered at risk of transmitting HIV than a policy of prioritizing high viral loads.

CD4 measurements are unreliable

Critical to a surrogate marker is the ability to produce consistent measurements for a single individual. When tests are repeated for an individual, CD4 counts are rarely consistent. Numerous studies demonstrate the variability of CD4 counts by body mass index, environment, and smoking status (9), all of which may change from one visit to the next. Even by time of day, CD4 counts can vary by nearly 60 cells/μL. Furthermore, different laboratories produce different results. Studies suggest that a large proportion of CD4 variability could be attributed to laboratory factors, particularly among those with high CD4 counts, who can have variations of over 100 cells/μL as a result of the CD4 testing platform (10). The variable results can have clinical

consequences as well. In a recent study of community-based HIV testing, of the patients eligible for ART but not initiating, 65% were refused ART at the clinic because they were deemed ineligible for ART upon retesting (11). For individual consistency, CD4 measurements poorly reflect an individual's true immune state and produce significant variability.

As a marker for international guidelines, CD4 counts must also have the same meaning regardless of country. Particularly in Africa, which has the vast majority of people living HIV, there must be consistency in CD4 measurements. When average CD4 counts are compared across Africa, however, there is wide variation. In Uganda, the average CD4 count in a person without HIV is estimated to be 1150 cells/μL, while in Botswana, it is estimated to be 700 cells/μL despite individuals in the two countries experiencing the same average duration of HIV infection (Figure 1) (9). This can be partially explained by differences in HIV subtype, which can cause differences in CD4 counts. ART guidelines, however, do not take these factors into account, and therefore, an individual recently infected with HIV in one country may have a similar need for ART as a recently infected individual in another country, but be required to wait an arbitrary amount of time before initiating ART.

CD4 counts do not facilitate ART scale-up

The current trend in global HIV policy toward expanding ART availability is based on studies demonstrating the substantial benefit to people living with HIV of early ART provision. Individuals face lower probabilities of illness and death, resulting in increases in population-level life expectancy, and experience improved economic outcomes for themselves and their families. The President's Emergency Plan for AIDS Relief (PEPFAR), Global Fund, WHO and the International Association of Providers of AIDS Care (IAPAC) have adopted the new Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 HIV treatment targets (12), which will improve access to ART for all people living with HIV. Despite the fact that achieving 90-90-90 will likely require immediate offer of treatment, only 14 middle- and high-income countries have updated their guidelines to include ART provision for all persons living with HIV. However, those countries only represent 8.5% of the global burden of HIV infection. Therefore, in order to aid the achievement of universal ART coverage, requiring the CD4 cell counts is a barrier to ART scale-up.

Scaling ART provision to reach the 37 million people who need it requires decentralization of HIV care. Using CD4 counts to determine ART

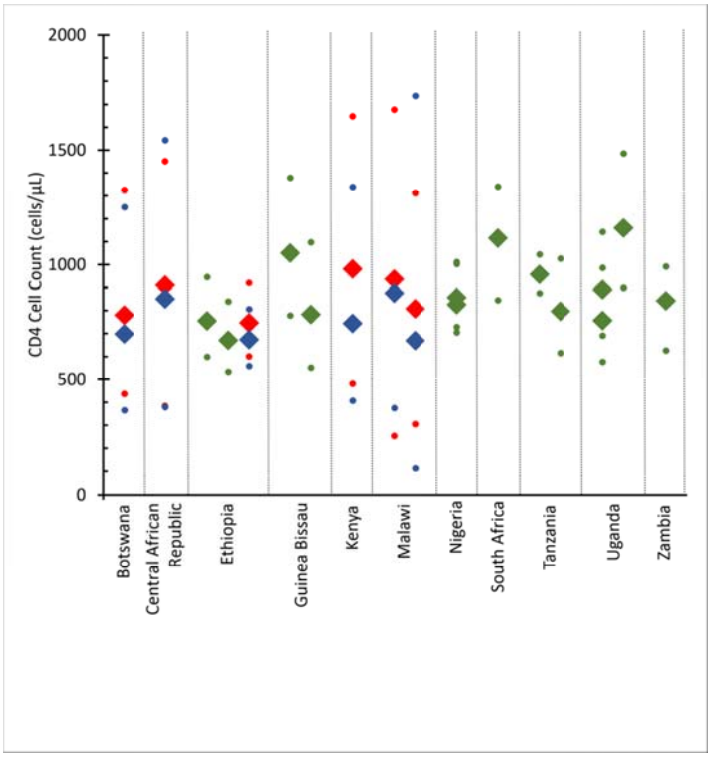

Figure 1. Average CD4 cell count in different countries

eligibility, however, anchors HIV care to the laboratories that are able to process CD4 measurements. Although point-of-care CD4 tests are currently being developed, they are not recommended by the WHO for CD4 measurements. The cost of CD4 counts also detracts from other potential uses of funds such as toward viral load measurements to evaluate response to medication (13). Finally, CD4 counts act as a barrier to accessing life-saving ART. The current process of going from HIV testing to viral suppression requires the many steps including HIV testing, HIV diagnosis, CD4 measurement, ART counselling, and finally, receipt of ART. Removing CD4 measurements would greatly increase the number of individuals receiving ART, and bring us closer to achieving universal ART coverage.

Moving toward universal ART coverage

When global HIV policies were first being developed during the last decade, ART was unaffordable and had substantial side effects. Today, ART is 100 times less expensive, has a vastly improved therapeutic index, and allows people living with HIV to lead normal, healthy lives. Increasing ART coverage requires international funding and support, but also requires that HIV policy does not hinder access to life-saving treatment. The current practice in many countries of requiring repeat CD4 measurements to determine eligibility for ART restricts the progress of ART scale-up. Removing the unnecessary and ineffective CD4 criterion from ART provision will move us closer toward achieving universal ART coverage and living in an AIDS-free generation.

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Table 1: ART policies in 114 countries (Last updated: May 2016). This list is contingent upon publication or published national guidelines.

	2003-05	2006-08	2009	2010	2011	2012	2013	2014	2015
Irrespective of CD4 count						**Netherlands, USA DHHS**	**Australia, Brazil, France, South Korea, Turkey**	**Mexico, Romania, Spain, Thailand**	**Argentina, Britain, Maldives**
≤500 (consider for ≥500)	USA DHHS			**Italy**			**Hong Kong**		
≤500				**Algeria**			WHO, Bolivia, Chile, Colombia, Democratic Republic of Congo, Ecuador, Ethiopia, Fiji, Haiti, Honduras, Madagascar, Mali, Oman, Rwanda, Tunisia, Uganda, Zambia, Zimbabwe	WHO, Bangladesh, Bhutan, Burundi, Nepal, Cameroon, Gabon, El Salvador, Kenya, Lesotho, Malawi, Mauritania, Myanmar, Namibia, Sudan, Poland, South Africa, South Sudan, Sri Lanka, Tanzania, Uruguay, Venezuela	WHO, Cambodia, Pakistan, Swaziland, Viet Nam
≤350 (consider for ≤500)			**Guyana***		**Guinea**	**Belize**		Austria*, Costa Rica, Finland, Germany*, Greece*, Norway*	
≤350		**Burkina Faso, Djibouti, Ghana, Sierra Leone**	**Croatia, Niger, Moldova, Papua New Guinea, Portugal, Nicaragua, Sweden**	WHO, Morocco, Nigeria, Ukraine	WHO, Jamaica, Kazakhstan, Panama, Switzerland, Timor-Leste	WHO, Botswana, Benin, China, Guatemala, Peru	Canada, Cote d'Ivoire, Dominican Republic, India, Paraguay	Angola, Indonesia, Latvia, Malaysia, Mozambique	

≤300		**Macedonia**							
≤200 (consider for ≤350)	**Cape Verde, Estonia**	WHO, Afghanistan, Belarus, Russia	WHO, Cuba						
≤200	WHO, Senegal	Comoros, Lao People's Democratic Republic, Liberia	Philippines						

*Austria, Germany, Greece, Guyana and Norway additionally recommend *considering* ART at CD4 count ≥500 cells/mm^3.

Countries in grey boxes are consistent with WHO guidelines in a given year while countries in bold were recommended early ART compared to WHO recommendation.