INVITED ARTICLE

CD4 Cell Count: Declining Value for Antiretroviral Therapy Eligibility

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Antiretroviral therapy (ART) policy for people living with human immunodeficiency virus (HIV) has historically been based on clinical indications, such as opportunistic infections and CD4 cell counts. Studies suggest that CD4 counts early in HIV infection do not predict relevant public health outcomes such as disease progression, mortality, and HIV transmission in people living with HIV. CD4 counts also vary widely within individuals and among populations, leading to imprecise measurements and arbitrary ART initiation. To capture the clinical and preventive benefits of treatment, the global HIV response now focuses on increasing HIV diagnosis and ART coverage. CD4 counts for ART initiation were necessary when medications were expensive and had severe side effects, and when the impact of early ART initiation was unclear. However, current evidence suggests that although CD4 counts may still play a role in guiding clinical care to start prophylaxis for opportunistic infections, CD4 counts should cease to be required for ART initiation.

Keywords. HIV; ART; CD4 cell count; universal test and treat; care continuum.

Triple-drug therapy was shown to be effective for treating people living with human immunodeficiency virus (HIV) in 1996 [1, 2], and it has been suggested that antiretroviral therapy (ART) can halt the HIV epidemic by preventing HIV illness, transmission, and death [3–6]. To optimize resource allocation and improve health, international health organizations have published guidelines that recommend which individuals should be eligible to initiate ART. Criteria for clinically driven ART initiation have been consistent over time, with World Health Organization (WHO) clinical stages III and IV being indicated for ART initiation in both the 2002 [7] and 2013 [8] WHO guidelines. However, for individuals in WHO clinical stages I and II, ART initiation is based on CD4+ T-cell count thresholds, which have been the subject of considerable debate, with different views being expressed at different times.

When the WHO published its first ART guidelines in 2002, 2 other institutions—the International AIDS Society (IAS) and the US Department of Health and Human Services (DHHS)—had published guidelines 2 years earlier. Despite having access to the same results, the 3 scientific committees reached different conclusions for when adults should start ART. All agreed that people with AIDS-defining illnesses (WHO clinical stages III and IV) should start ART, but in the absence of AIDS-defining illnesses, the WHO recommended ART for persons with a CD4 count ≤200 cells/μL [7], the IAS recommended ART for persons with a CD4 count ≤350 cells/μL or a viral load >30 000 copies/mL while considering ART for persons with a CD4 count 350–500 cells/μL [9], and the DHHS recommended ART for persons with a CD4 count ≤500 cells/μL or a viral load >10 000 copies/mL [10].

Over time, the WHO CD4 count–based ART eligibility criterion has increased, and in 2013 the WHO increased the CD4 count threshold for starting ART to ≤500 cells/μL, closer to the DHHS recommendation 13 years earlier. Despite the WHO's 2013 and now more recent recommendation for "test and treat" [8, 11], global ART guidelines among countries still display marked differences (Table 1), which might be explained by the local context of capacity and resource availability, but begs the question of whether recommendations should represent a higher but potentially unachievable standard of care, or a lesser but potentially achievable standard. In their 2000 guidelines, the WHO, explaining their decision to recommend ART only to those with a CD4 count ≤200 cells/μL, noted that "beginning therapy before the CD4 cell count falls below 200/mm^3 clearly provides clinical benefits," but that treatment should be limited to those with CD4 count <200 cells/mm^3 because "the actual point above 200/mm^3 at which to start therapy has not been definitively determined" [7]. The IAS also conceded that "treatment effects on survival at higher CD4+ cell counts is not documented," but they nevertheless stated that the concerns "should not obscure the dramatic changes in HIV-related morbidity and mortality resulting from therapy in advanced disease" [9]. In the most inclusive guidelines, the DHHS states that their "aggressive approach is heavily based on . . . the principle that one should begin treatment before the

Table 1. Antiretroviral Therapy Policies in 99 Countries

CD4 Count Policy, Cells/μL	2004–2005	2006–2008	2009	2010	2011	2012	2013	2014
Irrespective of CD4 count						**Netherlands, DHHS**	**Australia, Brazil, France, South Korea**	**Spain, Thailand**
≤500 (consider for ≥500)	DHHS			**Italy**		**Argentina**	**Hong Kong**	
≤500				**Algeria**		*WHO, Bolivia, Ecuador, Ethiopia, Honduras, Madagascar, Mali, Oman, Rwanda, Tunisia, Uganda, Zambia, Zimbabwe*	*WHO, Bangladesh, El Salvador, Gabon, Kenya, Lesotho, Malawi, Mauritania, Myanmar, Namibia, Nepal, South Africa, South Sudan, Sri Lanka, Sudan, Venezuela,*	
≤350 (consider for ≤500)			**Guyana**[a]		**Uruguay, Guinea**	**Austria**[a]**, Belize, Germany**[a]**, Mexico**		*Costa Rica*
≤350		**Djibouti, Sierra Leone**	**Burkina Faso, Canada, Moldova, Niger, Papua New Guinea, Nicaragua, Sweden**	*WHO, Burundi, Chile, Democratic Republic of Congo, Ghana, Morocco, Nigeria, Swaziland*	*WHO, Angola, Haiti, Indonesia, Jamaica, Kazakhstan, Malaysia, Panama, Paraguay, Switzerland, Vietnam*	*WHO, Botswana, Benin, Cambodia, China, Guatemala, Peru, Mozambique, Tanzania*	Great Britain, Dominican Republic, India	
≤250 (consider for ≤350)				Colombia				
≤200 (consider for ≤350)	**Cape Verde**	*WHO, Afghanistan, Russia, Ukraine*	*WHO, Cuba*					
≤200	*WHO, Cote d'Ivoire, Pakistan*	Bhutan, Comoros, Lao People's Democratic Republic, Liberia	Philippines			Cameroon		

The list is updated as of April 2015 and is contingent upon publication of national guidelines. Countries listed in italics are consistent with WHO guidelines in a given year; countries listed in bold recommend early antiretroviral therapy (ART) compared with the WHO recommendation.

Abbreviations: DHHS, US Department of Health and Human Services; WHO, World Health Organization.

[a] Austria, Germany, and Guyana additionally recommend considering ART at CD4 count ≥500 cells/μL.

development of significant immunosuppression" [10]. Even after considering the potential toxicity and costs of the early regimens, the disparity in CD4 count criteria over time demonstrates the lack of consensus over CD4 count–based ART initiation. We explore this issue by examining the value of CD4 counts as a reliable marker for ART initiation and prioritization given current scientific evidence.

Suitability of CD4 Cell Counts for Determining Eligibility to Start ART

A surrogate laboratory marker to be used as the primary eligibility criterion to begin ART must satisfy several clinical and public health criteria. From the clinical perspective, the marker must predict disease progression and the risk of transmitting the virus. From the public health perspective, the marker must produce consistent and reliable measurements, and be feasible to scale up as ART access increases (Table 2). Although many possible markers exist, most guidelines were and continue to be based on CD4 counts. Therefore, we will examine how well CD4 count fulfills each criterion for ART initiation, particularly soon after HIV infection, which is the period for which ART guidelines are being debated.

Predict Disease Progression, Response to ART, and HIV Transmission

A useful clinical surrogate marker for disease progression must indicate to healthcare providers and policy makers the current and expected future health states of the patient, as well as provide information regarding the public health and community consequences of clinical decisions. Although low CD4 counts provide a simple and direct measure of a person's prognosis in late-stage HIV, at high CD4 cell counts, the measure has little prognostic value. Furthermore, CD4 cell counts are not associated with a person's infectiousness, so they provide no important information in relation to HIV prevention.

Disease Progression

People living with HIV progress to AIDS an average of 7 years after infection, but there is considerable heterogeneity in time to AIDS [12]. The heterogeneity in HIV progression requires a surrogate marker that predicts one's expected rate of disease progression toward mortality. Studies demonstrate that low CD4 counts predict risk of mortality and opportunistic infection [12]. However, the correlation is weak early in HIV infection when ART initiation has been questioned. A quantitative review of data from 30 studies by Korenromp et al found that early in HIV infection, CD4 counts are poor predictors of clinical progression due to their high variability, even in perfectly healthy HIV-uninfected people, and that when the CD4 count is >625 cells/μL, CD4 counts provide zero prognostic value [13]. In a study of seroconverters in Uganda, Eller et al found that neither activation nor exhaustion of CD4 T cells was correlated with disease progression [14]. Furthermore, an analysis of the Multicenter AIDS Cohort Study found that median CD4 count explained only 29% and 35% of the variability in the probabilities of AIDS and death, respectively, whereas viral load explained 51% and 58%, respectively [15].

Overall, survival after seroconversion appears to be independent of CD4 cell counts [16]. Consequently, CD4 measurements indicate neither one's prognosis nor when retesting should occur, thus providing little information as to when ART should be initiated for those with high CD4 counts. At low CD4 cell counts, people are likely to have shown symptoms of AIDS-related opportunistic infections that are the reason for their presenting to a clinic, and this should always be followed by an HIV test. If a clinician feels it necessary to know how serious the person's condition is, then there may be marginal value for measuring the CD4 count, but as regular HIV testing and immediate treatment, following new WHO guidelines, are made available, the value of CD4 counts is likely to decrease even further.

HIV Transmission

In addition to predicting the health of the patient, the optimal prognostic marker for staging should indicate the individual's risk of transmitting HIV. Studies have demonstrated the strong correlation between HIV RNA load and HIV transmission. Quinn et al found that each 1.0 $\log_{10}$ increase in plasma viral load was associated with a 2.45 rate ratio (95% confidence interval, 1.85–3.26) for sexual HIV transmission [17], similar to a

Table 2. Criteria for Clinical Surrogate Marker for Antiretroviral Therapy Guidelines[a]

Criterion	Specific Outcomes	CD4 Count Suitability	Ideal?
Clinical outcomes	• Predict disease progression	• Poor correlation with disease progression early in HIV infection	No
	• Predict disease transmission	• Poor correlation with HIV RNA load, and thus, HIV transmission early in HIV infection	No
Consistent measurements	• Low variability within individuals	• Variable by time of day, sex, smoking status	No
	• Low variability among populations	• Variable by country and HIV subtype	No
	• Low variability among sites and devices	• Variable by location and measurement method	No
Feasible to implement	• Does not hinder decentralization and large-scale implementation	• Lack of laboratory capacity prevents decentralization and reduces resources for ART monitoring	No
	• Improves HIV care continuum	• CD4 counts are a barrier in the care continuum and prevent successful continuity of care due to logistic barriers	No

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

[a] The ideal clinical surrogate marker would have the following characteristics, none of which are satisfied by CD4 counts and existing CD4 count policy.

study of mother-to-child transmission by Chuachoowong et al, which found a 6.1-fold increased odds of HIV transmission per 1.0 log$_{10}$ increase in plasma viral load [18]. However, CD4 counts have low correlation with viral load and thus do not predict transmission [19]. Furthermore, people with high CD4 counts can also have high viral loads during acute and chronic infection. Kranzer et al found that in a South African township, only 13% of the population had a CD4 count ≤200 cells/µL, but 44% had a viral load >10 000 copies/mL [20]. In a rural Ugandan community, Jain et al found that only 17% of the population had a CD4 count ≤200 cells/µL, but 40% had a viral load >10 000 copies/mL [21]. In such settings, the poor correlation would result in the failure of a CD4 count–based ART criterion to substantially reduce HIV transmission.

Produce Consistent Measurements

To develop recommendations for guidelines, a marker used for ART initiation should produce consistent measurements and have low variability within individuals and among populations. International guidelines that rely on a surrogate marker would ideally be applicable at least in sub-Saharan Africa, which has >70% of the global population of people living with HIV [22]. However, CD4 counts vary greatly within individuals, across populations (Table 3), and among testing centers. As a result, a single CD4 measurement, or even repeated CD4 measurements, on the same day can be misleading because it indicates neither the individual's trajectory nor the individual's baseline CD4 count.

Within Individuals

CD4 counts are highly variable within people living with HIV, and repeat measurements do not produce consistent results. CD4 counts have been shown to vary in people living with HIV by as much as 56 cells/µL (P = .038) [23] and 59 cells/µL (P = .018) [24] between morning and afternoon. Other factors such as body mass index [25, 26], sex [25, 27, 28], illness [31, 32], and smoking status [25] also significantly impact CD4 counts (Table 3). However, these factors associated with variations in CD4 counts are not accounted for in ART initiation criteria, and if patients are given different results on different days, the individual may receive ineffective clinical care. For example, a recent study of community-based HIV testing found that 65%

of patients who were determined to be eligible for ART by point-of-care CD4 tests during home testing and counseling visits did not initiate ART at the local clinic because they were told they were not eligible when retested [33].

Among Populations

Among populations, CD4 measurements are also highly variable. A review of data from 12 observational studies in 8 countries in Africa found that in people without HIV, CD4 counts vary widely within populations (interquartile range, 169–603 cells/µL) and among populations (range, 699–1244 cells/µL) (Figure 1) [16]. This variability can lead both to healthy persons with low CD4 counts initiating ART and to sick persons with high CD4 counts being withheld ART. For example, the average CD4 count among those without HIV was found to be as high as 1150 cells/µL in Uganda and as low as 700 cells/µL in Botswana. CD4 counts also vary significantly by environmental factors, such as pathogen exposure [31, 32], that are country- and context-specific. Finally, Amornkul et al found a difference of 92 cells/µL (P = .02) between subtype C (503 cells/µL) and subtype A (595 cells/µL), 2 common HIV type 1 subtypes in sub-Saharan Africa, at 3 months after HIV infection [48]. With considerable variability across populations, using a global standard for CD4 count levels for initiation without adjusting for population and context does not make sense.

Testing Variability

CD4 measurements conducted in laboratories display substantial variability as well. Among laboratories, Raboud et al estimated that 15% of the variability in CD4 measurements from
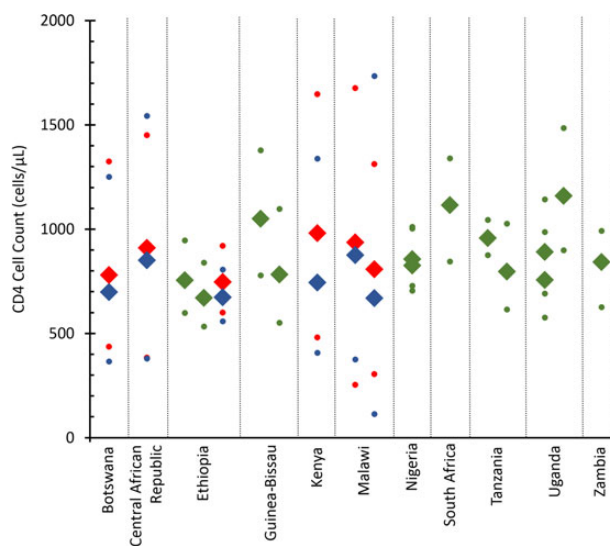
Table 3. Factors Influencing CD4 Cell Count

Factor	Trend
Time of day	Positive correlation [23, 24]
Body mass index	Positive correlation [25, 26]
Sex	Higher in females [25, 27–29]
Smoking	Higher in smokers [25, 27, 28]
Age	Positive correlation [29, 30]
Environment	Exposure to pathogens, acute illness [31, 32]

CD4 counts exhibit significant variability depending on multiple factors that are not accounted for in existing antiretroviral therapy (ART) policies. The variability makes CD4 counts an unreliable marker for ART initiation.

Figure 1. Median CD4 cell counts in African populations (Botswana [34], Central African Republic [35], Ethiopia [36, 37], Guinea-Bissau [38, 39], Kenya [40], Malawi [41], Nigeria [42], South Africa [6], Tanzania [43, 44], Uganda [45, 46], and Zambia [47]). Dots represent 95th percentiles in sample. Blue markers represent males, red markers represent females, and green markers represent both sexes.

the same blood sample could be attributed to laboratory factors [26]. Furthermore, Peeling et al reviewed 32 studies for 16 types of CD4 testing methods and found a variation of −35.2 to 13.1 cells/μL among the testing methods for those with a CD4 count ≤350 cells/μL, and, more important, a variation of −70.7 to 47 cells/μL for those with a CD4 count >350 cells/μL [49], demonstrating the unreliability of tests, particularly at high CD4 counts when staging for ART initiation is being contested.

Implementation for ART Scale-up

In the past, HIV staging for the initiation of ART was justified in relation to the lack of resources and concerns about ART toxicity. However, ART is now well tolerated [50], more potent [51, 52], easier to take [53], less costly [54], and proven to prevent illness, death, and transmission irrespective of CD4 cell count. Although the long-term effects of ART are unknown, it would be irresponsible for the possibility of long-term adverse effects to outweigh the substantial established immediate benefits of ART.

On the individual level, early ART has been found to significantly reduce the risks of AIDS [55], mortality [56], and HIV transmission in both heterosexual couples [57] and men who have sex with men [58], as well as to increase immune recovery [59]. The recent START (Strategic Timing of AntiRetroviral Treatment) [60] and TEMPRANO [61] trials further strengthened the evidence for initiating early ART by finding that individuals who initiated ART early—with CD4 counts >350 cells/μL or ahead of WHO guidelines, respectively—had a 57% and 44% lower probability of serious adverse events, respectively. These individual-level impacts translate into economic benefits [62, 63] and population-level improvements in life expectancy [64] and HIV morbidity [65]. The accumulation of evidence for earlier treatment has prompted shifts in HIV targets such as the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets of diagnosing 90% of all people living with HIV, starting ART for 90% of those diagnosed, and achieving viral suppression in 90% of those on ART [66]. The President's Emergency Plan for AIDS Relief (PEPFAR) goal to use the 90-90-90 targets and new WHO and International Association of Providers of AIDS Care (IAPAC) guidelines for test and start [67] as part of delivering the right interventions at the right time in the right place [68], and the IAPAC Fast Track Cities initiative that focuses on 90-90-90 in urban settings [69], are all examples of expanded HIV treatment targets that call for ART initiation irrespective of CD4 count. In addition to international ART targets, at the end of 2014, 8 high- and middle-income countries, including the United States, Brazil, and Australia, already offered ART irrespective of CD4 cell count (Table 1). However, they only represent 3% of the global HIV burden, whereas the majority of people living with HIV live in low- and middle-income countries that still have an ART eligibility criterion.

Large-scale implementation and access to achieve targets such as 90-90-90 would require integrating a laboratory marker such as CD4 count into primary care settings to decentralize HIV care. The test must not hinder other efforts for providing care and timely initiation of ART. CD4 counts do not fit these criteria, as they require reasonably complex and expensive laboratory equipment, and accompanying maintenance and supply chains. Although CD4 access has expanded, costs and access to functioning equipment have been problematic for people living with HIV and raise questions about the feasibility of providing regular CD4 counts for the nearly 37 million people who require lifelong ART.

Facilitate Decentralization

Decentralizing HIV care is critical to having a global impact on the HIV epidemic, but CD4 counts are a barrier to decentralization. Decentralization of care has been associated with reduced morbidity and mortality and increased linkage to ART [70, 71], with the presence of HIV staging in itself being a barrier to patient care. Although point-of-care CD4 tests have been developed and are consistent with laboratory measurements, the current recommendation by the WHO is to use laboratory CD4 cell counts when available [8]. Relying on laboratory CD4 tests, however, anchors ART initiation to large healthcare facilities to process the tests [72], preventing decentralization of HIV care.

Scaling up the HIV response also requires strategic allocation of resources. One important use of resources is monitoring people on ART—previously achieved with CD4 counts—to ensure response to medication, determine prophylaxis for opportunistic infections, and prevent the development of ART-resistant HIV strains. The WHO currently advises using viral load to monitor patients on ART, and a recent review [73] highlights the future of using viral load rather than CD4 counts for ART monitoring. Although CD4 counts play an important role in estimating risk of mortality and determining prophylaxis against some opportunistic infections such as cryptococcal meningitis late in HIV infection [74], their use for ART initiation detracts from other resources such as viral load for ART monitoring. In some settings where national programs recommend cotrimoxazole prophylaxis for all people living with HIV, CD4 counts may not be necessary for prophylaxis.

Improving the Care Continuum

People living with HIV have many stages to complete before being successfully treated with ART. These steps form the HIV care continuum, which tracks the stages of HIV testing, ART eligibility, ART initiation, and viral suppression [75]. Limiting ART eligibility further reduces the likelihood of viral suppression. To increase access to treatment for the estimated 37 million people who are infected with HIV, ART program design and care delivery will need to remove barriers to treatment such as pre-ART, clinic access, and complex regimens. The existence of such barriers has led to only 55% (range, 42%–95%) of people who test HIV positive receiving repeated CD4 counts and

initiating ART [76]. In South Africa, the country with the highest burden of HIV, only an estimated 45% and 31% of people living with HIV have been tested or are on ART, respectively [77]. The UNAIDS 90-90-90 targets are designed with these challenges in mind and will, in most settings, require significant programmatic changes. Although CD4 staging is only one barrier to ART, removing CD4 staging and all ART prioritization would greatly enhance the global response to HIV.

CONCLUSIONS

Historically, there has been discordance in global ART initiation guidelines based on CD4 counts, suggesting that CD4 counts may not be a reliable surrogate marker for ART initiation. They do not predict disease progression or transmission, produce widely varying results within and among populations, and pose a barrier to scaling up HIV care and decentralization. CD4 counts should be removed for ART prioritization, and in moving forward, ART should be provided to people living with HIV irrespective of CD4 counts. CD4 counts played an important role early in the HIV epidemic as a concrete, biological clinical surrogate marker with which to rationally distribute scarce and expensive medications. If scarcity and cost were currently more severe, then perhaps a clinical marker such as viral load could prioritize those expected to transmit HIV and rapidly progress to AIDS. However, improvements in ART therapeutic profiles, dramatically reduced costs, and increasing evidence for the benefits of early treatment lead to the conclusion that ART prioritization is no longer necessary. Initiating more patients on ART and eliminating the costs of ART staging will create an environment conducive to HIV care decentralization and scale-up that will put the world on track not only to reach UNAIDS' 90-90-90 targets, but to exceed them and achieve an AIDS-free generation.

Notes

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