CD4+ T cell counts in initiation of Antiretroviral Therapy in HIV Infected Asymptomatic Individuals; Controversies and Inconsistencies

Maina EK^{1, 3}, Bonny E¹, Bukusi EA³, Sedegah M⁴, Lartey M² and Ampofo WK¹

¹*Noguchi Memorial Institute for Medical Research, Department of Virology, Ghana*

²*University of Ghana Medical School, Dept of Medicine, Fevers Unit, Ghana*

³*Kenya Medical Research Institute, Centre for Microbiology Research, Kenya*

⁴*Naval Medical Research Centre, Malaria Program, USA*

Corresponding author; Edward K. Maina

Email: emain02@yahoo.com

Tel: +233265154115

ABSTRACT

The primary goal when devising strategies to define the start of therapy in HIV infected individuals is to avoid HIV disease progression and toxicity from antiretroviral therapy (ART). Intermediate goals includes, avoiding resistance by suppressing HIV replication, reducing transmission, limiting spread and diversity of HIV within the body and protecting the immune system from harm. The question of how early or late to start ART and achieve both primary and intermediate goals has since dominated HIV research. The distinction between early and late treatment of HIV infection is currently a matter of CD4+ T cells count, a marker of immune status, rather than on viral load, a marker of virus replication. Discussions about respective benefits of early or delayed therapy, as well as the best CD4+ T cell threshold during the course of HIV infection at which initiate ART is initiated remains inconclusive. Guidelines issued by various agencies, provide different initiation recommendations. This can be confusing for clinicians and policy-makers when determining the best time to initiate therapy. Optimizing ART initiation strategies are clearly complex and must be balanced between individual and broader public health needs. This review assesses available data that contributes to the debate on optimal time to initiate therapy in HIV-infected asymptomatic individuals. We also review available data on CD4+ T cell threshold for guiding initiation of ART and finally discuss arguments for and against early or late initiation of ART.

Keywords; HIV, CD4+ T cell, Antiretroviral therapy, AIDS

1. Introduction

Since the early years of Highly Active Antiviral Therapy (HAART), the debate regarding optimal time to initiate antiretroviral therapy (ART) has continued (Hamilton et al., 1992) and remains active in the current stage of therapies against HIV (Mfinanga et al., 2014; NIAID, 2015). Host immunological and virological factors influence the progression of HIV infection (Choi et al., 1993; Githinji et al., 2011; van Lelyveld et al., 2012; Maina et al., 2014) and holds prognosis value especially in the timing of initiation of HAART (Mfinanga et al., 2014). Although a number of HIV disease progression markers have been reported (Kamat et al., 2012; Margolick et al., 2006; Miedema et al., 1988), CD4⁺ T cell counts are more extensively researched and have become the most commonly used surrogate marker of the health of the immune system of HIV- infected individuals (Kaufmann et al., 2005; Langford et al., 2007; Patten et al., 2013; Venkataramani et al., 2014). Hence, CD4 + T cell counts have been the prime metric for treatment initiation of HIV-infected asymptomatic individuals.

However, the CD4⁺ T cell threshold, during the course of HIV infection, at which ART is best initiated in asymptomatic patients has been controversial and inconsistent. Recommendations regarding the appropriate threshold have changed many times over the years (Choi, et al., 1993; Goldman, 2000; Hughes, et al., 1998; Moreno-Fernandez et al., 2011). , We herein enumerate several evidences for the optimal time to initiate ART in HIV-infected individuals, in the context of CD4⁺ T cell counts, and discuss arguments for and against early or late initiation of ART asymptomatic individuals.

2. CD4⁺ T cell count threshold in ART initiation

Recommendations on the timing for ART initiation have swung back and forth since the advent of antiretroviral therapy. This has led to confusion amongst clinicians and policy-makers

in determining the most favorable point to begin treatment. The advent of HAART by the mid-1990s brought new hopes for the advocates of the “hit early, hit hard” approach (Kassirer and Angell, 1995). However, studies analyzing patient cohorts on earlier HAART regimens versus delayed HAART initiation have suggested immune markers to be considered when deciding on timing of HAART in HIV- infected asymptomatic individuals. Notably, CD4+ T cell count has become the most commonly used surrogate marker of the health of the immune system in HIV- infected individuals, and a key determinant of time to initiate ART. Other factors such as HIV viral load (Kamat et al., 2012), the patient’s potential for adherence (Geng et al., 2012) and total lymphocyte counts (Githinji et al., 2011; Kumarasamy et al., 2002) have also been used to make a decision on initiation of ART. Consensus on CD4+ T cell threshold at which ART should be initiated has swung back and forth and this trend is not about to end in the near future as clinicians, policy makers and governments still debate on appropriate CD4+ T cell threshold at which to initiate HIV therapy. Generally, patients with significant symptoms attributable to HIV infection should be offered HAART as soon as possible. Initiation of therapy for asymptomatic or individuals with mild HIV-related symptoms largely depends upon CD4+ T cell counts. However, some controversy remains as to the optimal CD4+ T cell count threshold to guide initiation of HAART in asymptomatic patients.

On the basis of evidence that clinical progression rates are low when CD4+ T cell counts remain above 200 cells/mm³ most early treatment guidelines recommended treatment when CD4+ T cell counts fall below 200 cells/mm³. Over time, however, most treatment guidelines have recommended treatment with CD4 cell counts below 350 cells/mm³, below 500 cells/mm³, and even above 500 cells/mm³ (Figure 1). From 2013, World Health Organization(WHO) and United States Department of Health and Human Services (USDHHS) guidelines recommend

HIV therapy at CD4+ T cell counts below 500 cells/mm³ (WHO, 2013; USDHHS, 2013), a departure from the previous guidelines that recommended 200 cells/mm³ (WHO, 2006) and 350 cells/mm³ (WHO, 2009) as thresholds. The Strategic Timing of Anti-Retroviral Treatment (START) trial, in 2015, provided the first randomized trial evidence of whether immediate initiation of treatment in patients with CD4 cell counts above 500 cells/mm³ is superior to delaying initiation of HAART until the CD4 cell count falls below 350 cells/mm³ (Lundgren et al., 2015). This study recommends initiation of ART to all HIV infected individuals regardless of their CD4+ T cell counts. USDHHS 2015 recommends initiation of ART even when CD4+ T cell counts are above 500 cells/mm³ (USDHHS, 2015). The European Aids Clinical Society Guideline recommends initiation of ART to all patients when CD4+ T cell count falls below 350 cells/mm³ and treatment at higher CD4+ T cell counts (below 500 cells/mm³) are considered on case by case basis (EACS, 2014). Both the European Union (EU) and WHO guidelines scheduled for release in October and December 2015 respectively are likely to recommending ART initiation even when CD4+ T cell counts are high. Previous studies recommended initiation of therapy before CD4+ T cell counts fall below 200 cells/mm³, a cell count much lower than the current recommendation of 500 cells/mm³. This could have been due to limited studies to support initiation of ART at a higher CD4+ T cell counts and the lack of knowledge of HIV pathogenesis, as HIV infection was relatively new. Observational cohort studies of HIV-infected patients suggested that patients should initiate HAART before their CD4+ T cell count falls to below 200 cells/mm³ (Garcia et al., 2004; Van Griensven and Thai, 2011; Lawn et al., 2009; van Lelyveld et al., 2012; WHO, 2006). Such patients were shown to have a higher likelihood of durable virologic suppression, a lower likelihood of progression of acquired immune deficiency syndrome (AIDS) disease, and more robust immune reconstitution as compared to patients who

initiated HAART after their CD4+ T cell counts have dropped below 200 cells/mm³. For asymptomatic patients with a CD4+ T cell count between 200 and 350 cells/mm³, HAART was generally recommended, recognizing that a better response to HAART is likely if treatment is initiated before the CD4+ T cell count falls to below 200 cells/mm³. Despite numerous findings from these observational cohort studies, the debate on CD4+ T cell count thresholds to inform initiation of ART continues. Randomized clinical trials data are proposed as standard to inform on CD4+ cell count threshold at which ART should be initiation. Apparently, there is lack of evidence from HIV treatment initiation randomized clinical trials, a situation that has continued to fuel debate on when to initiate ART.

3. Clinical trials as modality to inform ART initiation

When HAART first became available with the development of protease inhibitors in the late 1990s, most experts and guidelines advocated aggressive use of HAART, even for patients with relatively high CD4+ T cell counts and low HIV viral load levels (Kassirer and Angell, 1995). However, it was soon discovered that while HAART can suppress HIV replication to undetectable levels, it cannot fully eradicate the virus (Kawado et al., 2006). Furthermore, long-term adverse effects associated with antiretroviral (ARV) agents were increasingly being recognized as individuals continued therapy for several years (van Lelyveld et al., 2012; Uy et al., 2009). These findings prompted most experts to favor a less aggressive approach to HAART than was advocated in the past.

Although clinical trials are touted as the study modality capable of providing the strongest evidence in guiding ART initiation, they are not necessarily the right modality to answer all questions regarding when to start therapy. Clinical trials are usually run within a predetermined short period of time whereas HIV infection persists for a life time with varying

rates of disease progression. Thus, several confounders and limitations exist when using clinical trial data to determine when to start therapy in asymptomatic patients (Miedema et al., 1988). First, the time to development of complications of either viral infection or drug toxicity in patients who have relatively early HIV disease is quite long. Therefore, a few years study is inadequate to answer the question. Also, the impact of ongoing, unchecked viral replication will not become evident until many years later in some HIV infected individuals. It should be appreciated that a small population of HIV infected individuals referred to as elite controllers and long-term non-progressors are clinically stable for over ten years before showing any clinical progression of infection (Okulicz, 2012). Second, although clinical trials have the advantage of randomization, there are inherent limitations in study eligibility criteria and study referral patterns that can limit the generalizability of the findings. In particular, patients referred to a clinical trial study will be only those deemed to have clinical equipoise regarding when to start treatment. Patients unwilling to start therapy or those needing immediate treatment and cannot wait for routine study procedures, including extra time for randomization, are likely not to be referred to the study. With the current HIV pandemic, such patients could represent up to three quarters of potentially eligible patients. So, in essence, some of the same biases present in observation and cohort studies are at play in clinical trials.

If the question is whether to ever have a strong modality to guide initiation of therapy in HIV asymptomatic patients, a clinical trial seems like a great approach to answer the question. However, in defining subtle differences within a narrow window of time, the results do not seem worth the efforts and/or the costs. It is acknowledged that millions of people do not receive ART as recommended by guidelines based on current data. This lack of treatment may be due to fiscal constraints and lack of capacity in the health system. There is a need to identify strategies for

earlier linkage to treatment or for building such capacity rather than investing in clinical trials. Most importantly, sustainable funding for treating people with HIV who we know require such treatment for their health is more urgently needed than an additional randomized, controlled trial on when to start ART. Randomized clinical trials, though proposed as standard to inform ART initiation, are prone to serious ethical issues leaving only observational studies to guide clinicians and policy-makers on ART initiation. In this respect, scientific literature does include observational treatment initiation studies of varying quality that can bring treatment guidelines closer to the best treatment strategy. Therefore, utilizing data generated from observation and cohort studies, and mindful of resources, availability of ART and patient's potential for adherence, therapy may be started safely in asymptomatic individuals regardless of their CD4+ T cell counts. Importantly, because response to HAART correlates strongly with adherence (Bangsberg et al., 2006), and lack of support for fears that expanding treatment to largely asymptomatic patients with higher CD4+ T cell counts will lead to suboptimal adherence (Geng et al., 2012), individual patient's potential for adherence should be assessed carefully and attempts made to address and correct potential obstacles to adherence prior to initiation of therapy.

Many varied recommendations have been presented about the CD4+ T cell count threshold at which to initiate treatment. These can be categorized into two main approaches: the “hit early, hit hard” and the “wait until later” approaches.

4. Early initiation of ART (“hit early, hit hard”)

The dilemma on when to start ART has been raised several times during the decades of ART and recommendations have changed several times in both directions; start earlier and start

later. The main reasons given by the proponents of “Start early” include avoiding the development of AIDS or opportunistic infections (Kawado et al., 2006), better long-term outcome (Sterling et al., 2003a) and induction of better immune control of the virus (Kitahata et al., 2009; Patten et al., 2013). They argue that HIV gradually damages the immune system therefore the earlier the infection can be controlled, the more likely the immune function can be preserved. Similarly, there may be a better chance of restoring immune function if someone starts treatment early (Kaplan et al., 2003). Specifically, the body's immune response to HIV may be preserved or restored by early treatment. Moreover, persons with less advanced HIV infection tend to tolerate antiretroviral therapy more easily than those with an advanced infection (Van Griensven and Thai, 2011). In essence, fewer side effects would mean that a person is likely to adhere to and continue on their drug regimens, which should increase the likelihood of long-term success.

Data showing benefits of early initiation of ART have over the years been generated. There is evidence that initiating ART at CD4+ T cell count levels higher than 200 or 250 cells/mm³ reduces mortality rates in asymptomatic, ART-naive, HIV-infected people (Siegfried et al., 2010). The authors recommend that practitioners and policy-makers consider initiating ART at levels equal or less than 350 cells/mm³ for patients who present to health services and are diagnosed with HIV infection. Data from the North America-AIDS Cohort Collaboration on Research and Design (NA-ACCORD) demonstrated that the adjusted mortality rates are statistically higher among patients who defer therapy until their CD4+ T cell counts fall to below 500 cells/mm³ than in patients who start therapy with CD4+ T cell counts above 500 cells/mm³ (Kitahata et al., 2009). Of note, no cohort study to date has demonstrated any clear evidence of greater harm among those initiating therapy with CD4+ T cell counts above 500 cells/mm³. To

the contrary, most have shown trends toward benefit and as such strengthen the advocacy for initiation of therapy at higher CD4+ T cell counts. In a clinical trial study (Hogan et al., 2012), patients who were within six months of HIV seroconversion were randomly assigned either to receive immediate treatment for 36 weeks or deferred treatment when CD4+ T cell counts were below 350 cells/mm³. The deferred treatment group had a statistically higher risk and needed treatment initiation resulting in earlier discontinuation of the study. These findings illustrates that the time from diagnosis of early infection to the need for initiation of therapy is short, and earlier initiation of ART is paramount. Other studies (Bonnet et al., 2005; Palella et al., 2003; Kaplan et al., 2003; Kawado et al., 2006; Lifson et al., 2012), report a survival benefit when ART is initiated at a CD4+ T cell count above 350 cells/mm³ or above 500 cells/mm³ compared to those initiated at a CD4+ T cell count of below 200 cells/mm³. This reinforces the importance of initiating therapy at relatively higher CD4+ T cell counts. However, these studies caution that there is no statistically significant difference in mortality between starting at 500 or at 350–500 cells/mm³. The authors conclude that initiation of combination ART at a CD4+ T cell count of 500 cells/mm³ increases AIDS-free survival but mortality does not substantially vary with CD4+ T thresholds between 300 and 500 cells/mm³. When patients are initiated on ART at a CD4+ T cells threshold of between 350–500 cells/mm³, the risk of mortality/AIDS is significantly higher than those initiated at greater than 500 cells/mm³ (Kaplan et al., 2003), and risk of poor outcome is reduced significantly (Garcia et al., 2004; Van Griensven and Thai, 2011; van Lelyveld et al., 2012).

The benefits of early treatment go beyond hard immunologic parameters and translate into a higher likelihood of overall treatment success. Chronically infected patients delaying therapy until CD4+ T cells below 350 cells/mm³ have suboptimal CD4+ T cell count recovery

(van Lelyveld et al., 2012). After six years of ARV therapy, those who delay therapy reach a CD4+ T cell count plateau below 500 cells/mm³, which is significantly lower than patients starting therapy earlier (Moore and Keruly, 2007). Earlier initiation of therapy leads to controlled viral replication which prevents the emergence of ARV resistant HIV strains (Uy et al., 2009). Each time HIV replicates, there is a chance of development of viral mutations which may give HIV the ability to multiply in the presence of certain antiretroviral drugs. These resistance mutations can develop even before a person starts antiretroviral therapy. The sooner a person starts therapy, the less likely they are to develop a significant number of resistance mutations and therefore the greater the likelihood that the drug regimen will be able to successfully suppress HIV replication. The implementation of universal treatment of all HIV-infected persons in a large, publicly-funded clinic in San Francisco in 2010 led to a six-fold increase in the probability of viral suppression (Geng et al., 2012). In patients entering the clinic with CD4+ T cell counts above 500 cells/mm³, the one-year incidence of viral suppression increased from 14% to greater than 52% after adopting the approach. These results are complimentary to data from another large outpatient cohort showing that major resistance mutations were 50% less likely in patients starting therapy with CD4+ T cell count above 350 cells/mm³ versus below 200 cells/mm³ despite greater treatment exposure (Uy et al., 2009). These data run counter to the views of the ‘wait until later’ proponents, who predict that resistance would be more common among those who start therapy earlier. Nonetheless, given the concerning reality of the low proportions of treatment success in real life settings, it should be emphasized that when considering initiation of therapy to patients with high CD4+ T cell counts, clinicians should consider individual patient’s characteristics. In addition, availability of resources, relative efficacy, toxicity and convenience of available regimens should be carefully assessed to inform earlier initiation of therapy.

5. Delayed initiation of ART (“wait until later”)

Despite the high-quality, cohort-derived evidence in favor of early treatment, some clinicians and policy makers remain skeptical and reluctant to adopt this strategy. The main reason driving this skepticism has been the lack of clinical trials of early versus delayed therapy. It has long been clear that starting ART before a person's CD4+ T cell count thresholds are low reduces the likelihood of progression to AIDS or death (Sterling et al., 2003a, 2003b). While earlier initiation of ART can preserve immune function (Miedema et al., 1988) and prevent long-term problems related to chronic inflammation (Patten et al., 2013), it involves greater expense (UNAIDS, 2009). It is estimated that increasing the CD4+ T cell count threshold for ART initiation can increase ART cost up to 57% (UNAIDS, 2009). For HIV-infected individuals, the primary question is whether to start ART early and risk possible cumulative drug toxicities (van Leth et al., 2005; Mocroft et al., 2007; Stern et al., 2003), potential viral resistance, and difficulties with long-term adherence (Bangsberg et al., 2006), or to defer ART until later in the course of infection and risk developing irreparable immune system dysfunction or other health issues related to ongoing, uncontrolled HIV replication (Geng et al., 2012).

Some studies reported similar clinical disease rates among those initiating ART with a CD4+ T cell count of below 350 cells/mm³ and above 500 cells/mm³ (Bonnet et al., 2005; Kawado et al., 2006; Kitahata M. M et al., 2009; Lawn et al., 2009; Lifson et al., 2012; Palella et al., 2003; Sterling et al., 2003a). They suggest no benefit of starting ART if CD4+ T cell counts are above 350 cells/mm³. While most studies suggest a benefit associated with initiation of therapy at CD4+ T counts above 200 cells/mm³ (Hogan et al., 2012; Kaplan et al., 2003; Siegfried et al., 2010) they have not consistently shown any significant benefit of initiation of HAART at CD4+ T cell counts above 350 cells/mm³. Hence recommendation that patients who

are asymptomatic and have a high CD4+ T cell count above 350 cells/mm³ should be initiated on HAART may generally be deferred. An HIV-infected individual with a CD4+ T cell count of 500 cells/mm³ and low viral loads is considered healthy enough not to need ART. The risk of progression to AIDS within few years for such an individual is low and is likely to do well on antiretrovirals from the viral load standpoint. However, when a patient's cell count reaches 200 cells/mm³, the immune system is severely weakened (Siegfried et al., 2010) and ART is necessary. Such a patient with advanced symptoms receives treatment regardless of CD4+ T cell count (WHO, 2006, 2013). However, it has been shown that a later start at CD4+ T cell count 350-500 cells/mm³ leads to the same CD4+ T cell count after immune reconstitution in most cases as if started earlier at above 500 cells/mm³ (Garcia et al., 2004; Van Griensven and Thai, 2011; van Lelyveld et al., 2012). Moreover, people who start HAART at a CD4+ T cell counts of 350 cells/mm³ have a similar risk of death due to all causes as those who start at 500 cells/mm³ (Kawado et al., 2006; Lifson et al., 2012). Two large cohort studies, the Antiretroviral Therapy-Cohort Collaborative (ART-CC) and the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration, also did not identify a benefit of earlier initiation of therapy in reducing AIDS progression or death (CASCADE, 2012; Sterne et al., 2009). These studies support deferring ART initiation in patients with high CD4+ T cell counts above 500 cells/mm³.

Effective HAART leads to suppression of viral replication during the course of therapy. If viral replication is completely suppressed, resistance may not develop since replication is required for new mutations to develop. However, it is not known whether complete suppression of replication happens even when viral load is below the limit of detection, since there may be reservoirs of replicating virus which cannot be detected with the available technology. Although

there is reasonable evidence to support the concept that patients with suppressed viral replication are less likely to transmit HIV, reduced transmission has never been demonstrated as a result of antiretroviral therapy outside of mother-to-child transmission studies.

Another concern about early initiation of antiretroviral therapy pertains to the risk of running out of treatment options in the event of failure or adverse side effects of the initial regimen. Although more recently approved ARV have fewer side effects, their less known long-term side effects and perhaps long-term toxicities will be recognized in the future. Additionally, the impact of earlier initiation on adherence is uncertain (Bangsberg et al., 2006); a more challenging issue for someone who has no symptoms to begin with and who may develop side-effects and a reduced quality of life from the medications. If such persons develop resistance, as has been shown previously, (Mocroft et al., 2004) to their initial regimen early in the course of their HIV disease due to poor adherence, there is a risk that they may end up switching to multiple alternate drugs and eventually running out of drugs at a time when they are clinically well, leaving no options for the future until new classes of drugs are developed. Broadening the criteria for treatment may also result in some persons in urgent need of treatment being displaced by persons for whom treatment would be beneficial but not as urgent.

6. Conclusions

Since the advent of ART, policy-makers and clinicians have presented different views on the optimal time to start ART. The lack of consensus on when to start ART for HIV infected individuals is evidenced by the differing guidelines established by various committees of experts. These divergent views affect clinicians, patients and policy makers who keep searching for efficient and effective treatment strategies. Although there are a number of compelling

theoretical reasons to support early initiation of antiretroviral therapy, there are important reasons to consider deferring therapy in healthy persons with low risks of progression to AIDS. Few would argue against the need to start therapy in someone with symptoms or who is at high risk of progression in the short term. Although most experts believe that HIV infected persons should be started on ART at a higher CD4+ T cell counts, the decision need not be rushed. Observing the trend in a person's viral load and CD4+ T cell count over time can be of great help and that a number of other factors have to be weighed and the decision individualized. We would recommend ART for everyone only, if it becomes possible to receive non-toxic antiretrovirals for everyone and for each individual's life-span. As soon as governments, policy makers and clinicians can be sure that an individual starting ART will not have a worse outcome due to drug resistance development or due to treatment toxicity combined with no option to change the regimen, ART may be started early regardless of CD4+ T cell count threshold. In recommending a higher CD4+ T cell count threshold for initiation, a guiding principle is that those most in need of treatment should retain priority access.

Acknowledgment

We acknowledge support by the postdoctoral fellowship program of Noguchi Memorial Institute for Medical Research (NMIMR) with financial support from the Bill and Melinda Gates Foundation (Grant OPP52155).

Author's contribution

EM was responsible for drafting and revising the manuscript. EB assisted in revising the manuscript as well as organizing the content. EAB, MS, ML and WA assisted in revising the manuscript as well as offering expert advice.

References

- Bangsberg, D., EP, A., and Gupta, R. (2006). Adherence-resistance relationships for protease and nonnucleoside reverse transcriptase inhibitors explained by virological fitness. *AIDS* 223–231.
- Bonnet, F., Thiebaut, R., and Chene, G. (2005). Determinants of clinical progression in antiretroviral-naïve HIVinfected patients starting highly active antiretroviral therapy. Aquitaine Cohort, France, 1996-2002. *HIV Med* 198–205.
- CASCADE (2012). Timing of HAART Initiation and Clinical Outcomes among HIV-1 Seroconverters. *Changes* 29, 997–1003.
- Choi, S., Lagakos, S., Schooley, R., and Volberding, P. (1993). CD4+ lymphocytes are an incomplete surrogate marker for clinical progression in persons with asymptomatic HIV infection taking zidovudine. *Ann Intern Med*; 118, 674–680.
- EACS (2014). European Aids Clinical Society Guidelines.
- F. Okulicz, J. (2012). Elite Controllers and Long-term Nonprogressors: Models for HIV Vaccine Development? *J. AIDS Clin. Res.* 01, 8–11.
- Garcia, F., de Lazzari, E., Plana, M., Castro, P., Mestre, G., Nomdedeu, M., Fumero, E., Martinez, E., Mallolas, J., Blanco, J.L., et al. (2004). Long-Term CD4+ T-Cell Response to Highly Active Antiretroviral Therapy According to Baseline CD4+ T-Cell Count. *JAIDS J. Acquir. Immune Defic. Syndr.* 36, 702–713.
- Geng, E.H., Hare, C.B., Kahn, J.O., Jain, V., Van Nunnery, T., Christopoulos, K. a., Deeks, S.G., Gandhi, M., and Havlir, D. V. (2012). The effect of a “universal antiretroviral therapy” recommendation on HIV RNA levels among HIV-infected patients entering care with a CD4 count greater than 500/μL in a public health setting. *Clin. Infect. Dis.* 55, 1690–1697.
- Githinji, N., Maleche-Obimbo, Elizabeth, N., Wamalwa, M., C, D., and Mbori-Ngacha, D. (2011). Utility of total lymphocyte count as a surrogate marker for CD4 counts in HIV-1 infected children in Kenya. *BMC Infect. Dis.* 11, 1–8.
- Goldman (2000). *Cecil Textbook of Medicine*, 21st edition, W.B. Saunders, Inc.
- Van Griensven, J., and Thai, S. (2011). Predictors of immune recovery and the association with late mortality while on antiretroviral treatment in Cambodia. *Trans. R. Soc. Trop. Med. Hyg.* 105, 694–703.

Hamilton J. D et al. (1992). A controlled Trial of Early versus Late Treatment with Zidovudine in Symptomatic Human Immunodeficiency Virus Infection. *N Engl J Med* 326, 437–443.

Hogan, C.M., Degruittola, V., Sun, X., Fiscus, S. a., Del Rio, C., Hare, C.B., Markowitz, M., Connick, E., MacAtangay, B., Tashima, K.T., et al. (2012). The setpoint study (ACTG A5217): Effect of immediate versus deferred antiretroviral therapy on virologic set point in recently HIV-1-infected individuals. *J. Infect. Dis.* 205, 87–96.

Hughes, M., Daniels, M., Fischl, M., Kim, S., and Schooley, R. (1998). CD4 cell count as a surrogate endpoint in HIV clinical trials. *AIDS* 12, 1823–1832.

Kamat, A., Misra, V., Cassol, E., Ancuta, P., Yan, Z., Li, C., Morgello, S., and Gabuzda, D. (2012). A plasma biomarker signature of immune activation in HIV patients on antiretroviral therapy. *PLoS One* 7, e30881: 1–11.

Kaplan, J.E., Hanson, D.L., Cohn, D.L., Karon, J., Buskin, S., Thompson, M., Fleming, P., and Dworkin, M.S. (2003). When to begin highly active antiretroviral therapy? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/microL. *Clin. Infect. Dis.* 37, 951–958.

Kassirer, J.P., and Angell, M. (1995). Redundant publication: a reminder. *N. Engl. J. Med.* 333, 449–450.

Kaufmann, G.R., Furrer, H., Ledergerber, B., Perrin, L., Opravil, M., Vernazza, P., Cavassini, M., Bernasconi, E., Rickenbach, M., Hirschel, B., et al. (2005). Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clin. Infect. Dis.* 41, 361–372.

Kawado, M., Hashimoto, S., Yamaguchi, T., Oka, S., Yoshizaki, K., Kimura, S., Fukutake, K., Higasa, S., and Shirasaka, T. (2006). Difference of Progression to AIDS According to CD4 Cell Count, Plasma HIV RNA Level and the Use of Antiretroviral Therapy among HIV Patients Infected through Blood Products in Japan. *J. Epidemiol.* 16, 101–106.

Kevin, M.D.C., and Wafaa, M.E.-S. (2013). When to Start ART in Africa — An Urgent Research Priority. *N. Engl. J. Med.* 368, 886–889.

Kitahata M. M et al. (2009). Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival. 1815–1826.

Kumarasamy, N., Mahajan, A., Flanigan, T., Hemalatha, R., Mayer, K., Carpenter, C., Thyagarajan, S., and Solomon, S. (2002). Total lymphocyte count (TLC) is a useful tool for the timing of opportunistic infection prophylaxis in India and other resource-constrained countries. *AIDS* 378–383.

Langford, S.E., Ananworanich, J., and Cooper, D. a (2007). Predictors of disease progression in HIV infection: a review. *AIDS Res. Ther.* 4, 1–14.

Lawn, S.D., Little, F., Bekker, L.-G., Kaplan, R., Elizabeth, C., Orrell, C., and Wood, R. (2009). Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. *AIDS* 23, 335–342.

Van Lelyveld, S.F.L., Gras, L., Kesselring, A., Zhang, S., De Wolf, F., Wensing, A.M.J., and Hoepelman, A.I.M. (2012). Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS* 26, 465–474.

Van Leth, F., Andrews, S., and Grinsztejn, B. (2005). The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz- based first-line HAART. *AIDS* 463–471.

Lifson, A.R., Krantz, E.M., Grambsch, P.L., Macalino, G.E., Crum-Cianflone, N.F., Ganesan, A., Okulicz, J.F., Eaton, A., Powers, J.H., Eberly, L.E., et al. (2012). Clinical, demographic and laboratory parameters at HAART initiation associated with decreased post-HAART survival in a U.S. military prospective HIV cohort. *AIDS Res. Ther.* 9, 1–7.

Lundgren, D., Abdel, G.B., Fred, G., Sean, E., Birgit, G., and Shweta, S. (2015). Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N. Engl. J. Med.* 150720091517005.

Maina, E.K., Bukusi E A, Martha, S., Lartey, M., and Ampofo, W.K. (2014). The Relative Balance between Th17 and Regulatory T cell subsets is Critical for Progression of HIV Infection. *J. AIDS Clin. Res.* 5, 1–7.

Margolick, J.B., Gange, S.J., Detels, R., O’Gorman, M.R.G., Rinaldo, C.R., and Lai, S. (2006). Impact of inversion of the CD4/CD8 ratio on the natural history of HIV-1 infection. *J. Acquir. Immune Defic. Syndr.* 42, 620–626.

Mfinanga, S.G., Kirenga, B.J., Chanda, D.M., Mutayoba, B., Mthiyane, T., Yimer, G., Ezechi, O., Connolly, C., Kapotwe, V., Muwonge, C., et al. (2014). Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): A prospective, international, randomised, placebo-controlled trial. *Lancet Infect. Dis.* 14, 563–571.

Miedema, F., Petit, a J., Terpstra, F.G., Schattenkerk, J.K., de Wolf, F., Al, B.J., Roos, M., Lange, J.M., Danner, S. a, Goudsmit, J., et al. (1988). Immunological abnormalities in human immunodeficiency virus (HIV)- infected asymptomatic homosexual men. HIV affects the immune system before CD4+ T helper cell depletion occurs. *J Clin Invest* 82, 1908–1914.

Mocroft, A., Ledergerber, B., and Viard, J. (2004). Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA Study Group. *J Infect Dis* 1947–1956.

Mocroft, A., Staszewski, S., and Weber, R. (2007). Risk of discontinuation of nevirapine due to toxic ities in antiretroviral-naïve and experienced HIV-infected patients with high and low CD4+ T-cell counts. *Antivir. Ther.* 2007 325–333.

Moore, R.D., and Keruly, J.C. (2007). CD4+ cell count 6 years after commencement of highly active antiretroviral therapy in persons with sustained virologic suppression. *Clin. Infect. Dis.* 44, 441–446.

Moreno-Fernandez, M.E., Rueda, C.M., Rusie, L.K., and Chougnet, C. (2011). Regulatory T cells control HIV replication in activated T cells through a cAMP-dependent mechanism. *Blood* 117, 5372–5380.

NIAID (2015). START Trial data support starting antiretroviral treatment for HIV as early as possible; <http://sciencespeaksblog.org/2015/05/27/start-trial-data-support-starting-antiretroviral-treatment-for-hiv-as-early-as-possible/>.

Palella, F., Deloria-Knoll, M., and Chmiel, J. (2003). Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med* 620–626.

Patten, G.E.M., Wilkinson, L., Conradie, K., Isaakidis, P., Harries, A.D., Edginton, M.E., De Azevedo, V., and Van Cutsem, G. (2013). Impact on ART initiation of point-of-care CD4 testing at HIV diagnosis among HIV-positive youth in Khayelitsha, South Africa. *J. Int. AIDS Soc.* 16, 1–6.

Siegfried, N., Uthman, O. a, and Rutherford, G.W. (2010). Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naïve adults. *Cochrane Database Syst. Rev.* CD008272.

Sterling, T., Chaisson, R., Keruly, J., and Moore, R. (2003a). Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. *J Infect Dis* 1659–1665.

Sterling, T., Chaisson, R., and Moore, R. (2003b). Initiation of highly active antiretroviral therapy at CD4+ T lymphocyte counts of >350 cells/mm³: disease progression, treatment durability, and drug toxicity. *Clin Infect Dis* 812–815.

Stern, J., Robinson, P., and Love, J. (2003). A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr* S22–S34.

Sterne JA et al. (2009). Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 373, 1352–1363.

UNAIDS (2009). Cost estimates: AIDS financing and economics.

USDHHS (2013). Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines For the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Department of Health and Human Services.

USDHHS (2015). Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. February 5, 2011. *HIV Clin. Trials* 2, 227–306.

Uy, J., Armon, C., Buchacz, K., Wood, K., and Brooks, J. (2009). Initiation of HAART at higher CD4 cell counts is associated with a lower frequency of antiretroviral drug resistance mutations at virologic failure. *J Acquir Immune Defic Syndr.* 51, 450–453.

Venkataramani, A.S., Thirumurthy, H., Haberer, J.E., Boum, Y., Siedner, M.J., Kembabazi, A., Hunt, P.W., Martin, J.N., Bangsberg, D.R., and Tsai, A.C. (2014). CD4+ cell count at antiretroviral therapy initiation and economic restoration in rural Uganda. *AIDS* 1221–1226.

WHO (2006). World Health Organization and Charles Gilks and Marco Vitorio guidelines development group. Geneva: WHO; Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach-2006 revision.

WHO (2009). Geneva; World Health Organization. (WHO) guidelines; Rapid advice antiretroviral therapy for HIV infection in adults and adolescents.

WHO (2013). World Health Organization, Consolidated Guidelines on the Use of Antiretroviral Drugs For Treating and Preventing HIV Infection, Recommendations for a Public Health Approach, <http://www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html>.

Figure legend

Figure 1. Evolution of CD4+ cell counts criteria for starting antiretroviral therapy in asymptomatic persons with human immunodeficiency virus infection, according to different guidelines. Adapted (Kevin and Wafaa, 2013), and modified.

Figure 1. Evolution of CD4+ cell counts criteria for starting antiretroviral therapy in asymptomatic persons with human immunodeficiency virus infection, according to different guidelines. Adapted (Kevin and Wafaa, 2013), and modified.