Antiretroviral Therapy: When to Start

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Introduction

The development of effective antiretroviral therapy (ART) in response to the emerging epidemic of human immunodeficiency virus (HIV) ranks as one of the most remarkable achievements of modern medicine. However, it was not long after the first of these medications became available that the issue of when is the optimal time in the disease course to use these agents was raised – a question that continues to be asked today. The answer, framed in terms of a balance between the potential benefits of therapy and its risks and costs, has evolved along with HIV therapy and our understanding of its benefits and disadvantages.

At lower CD4+ cell counts, there is irrefutable evidence that the benefits of ART outweigh the harms. For individuals with less advanced infection, the balance between the hazards of unchecked viral replication and the possibility of long term drug toxicities, development of drug resistance and expense of treatment for many years seemed to favor delaying HIV therapy. As the potency, tolerability, and convenience of ART regimens have improved and the deleterious effects of even moderate CD4+ cell depletion have been revealed, the calculus of ART initiation has shifted and the rationale for deferring therapy until a specific CD4+ count threshold has become vulnerable to challenge. Yet, the evidence supporting the

initiation of ART at high CD4+ counts is less robust than that available for those with lower counts, and it is within this data-vacuum controversy has emerged.

Below, we review current expert panels' recommendations on when to start ART, and discuss the strengths and weaknesses of the rationale to treat earlier rather than later in the course of HIV infection.

HIV Treatment Guidelines

Current recommendations by both major U.S. HIV treatment guideline panels, the Department of Health and Human Services (DHHS) and the International Antiviral Society-USA (IAS-USA), call for the initiation of ART in practically all patients with HIV infection willing and able to take these medications. This position abandons any deferral of treatment until a set CD4+ cell count threshold – a substantial departure from earlier recommendations to hold ART until immunosuppression became evident. The history of the evolution of the guidelines from advocating a cautious application of ART to a near universal approach to HIV therapy is also a history of the evolution of HIV therapeutics and our use of these medications (Figure 1).

The first edition of the DHHS guidelines, published in 1998, recommended ART initiation for asymptomatic individuals with CD4+ counts up to 500 cells/mm^3, underscoring the urgency at the time of what was a dire public health emergency. [1] However, the only therapeutic option available at that time, zidovudine, has low potency and high-level toxicity. With data from the Concorde study, a large trial of high-dose zidovudine monotherapy in those with earlier versus more advanced HIV disease, showing no survival or disease progression benefit of this nucleoside,[2] the guidelines downshifted to a more stringent CD4+ count threshold for ART initiation of <200 cells/mm^3. [2,3] And for years a count of 200/mm^3 stood as a tipping point where the benefits of therapy started to outweigh its liabilities. As ART became more effective, durable, and tolerable, this line in the sand began to move. In 2007, the CD4+ cell count criterion at which ART initiation was recommended began a steady climb in both the DHHS [4] and the IAS-USA guidelines, rising to 350 cells/mm^3 after observational cohorts demonstrated an association between deferral of ART until counts below 200 cells/mm^3 and a heightened risk of opportunistic conditions and death. [5–7] Subsequent guideline revisions have seen the initiation of ART grow more inclusive, extending to those with counts of 500 cells/mm^3 or less in 2009 [8] and in 2012 to include all CD4+ counts – a recommendation based on many different lines of evidence discussed below. [9]

The latest DHHS guidelines in explaining the use of ART for all HIV-infected patients regardless of CD4+ count, make clear that the strength of the recommendation increases with decreasing CD4+ cell counts. [10] (Table 1) Additionally, these guidelines introduce the use of ART in HIV-infected individuals to prevent transmission following the announcement of findings from a large randomized clinical trial demonstrating the efficacy of ART as prevention. [11] Importantly, the guidelines advise that "Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence."

As detailed below, several conditions are also specified in the DHHS and IAS-USA guidelines as favoring more rapid or urgent initiation of ART[10] (Table 2). AIDS defining conditions have long been recognized as an indication for prompt ART initiation and joining them are comorbidities, such as co-infection with hepatitis B and hepatitis C and HIV-associated nephropathy (HIVAN), as well as pregnancy, high viral load, and acute HIV infection.

The current U.S. guidelines differ significantly from those from outside the U.S., including those issued by the World Health Organization (WHO), and the British and European guidelines on the timing of ART (Figure 1). The 2013 British HIV Association (BHIVA) guidelines recommend ART initiation at a CD4+ cell count   350 cells/mm^3 in asymptomatic individuals without relevant comorbidities, but suggest offering ART to patients at higher CD4+ cell counts who wish to reduce their risk of transmission to others. [12] Likewise, the European AIDS Clinical Society (EACS) guidelines also published in 2013 recommend ART initiation at CD4+ counts <350 cells/mm^3 and for those with a CD4+ count >350 cells/mm^3, ART can be considered, particularly to reduce infectiousness. [13] The most recent WHO guidelines recommend ART initiation at CD4+ count   500 cells/mm^3, prioritizing those with CD4+ counts   350 cells/mm[3. 14] In contrast, 2013 French guidelines recommend ART initiation regardless of CD4+ count [15] The differences between these guidelines are a reflection of a number of considerations including interpretation of the data regarding the benefits of ART earlier in the HIV disease course as well as regional availability and affordability of ART.

Evidence Informing the When to Start ART Question

The gradual creep in the CD4+ cell count threshold for ART initiation reflects a growing body of data indicating that even modest degrees of immunosuppression and ongoing viral replication carry significant risks to health. However, the strength of any association between adverse outcomes and CD4+ cell count wanes when it comes to the benefits of ART in those with normal or near normal counts. Large randomized trials of ART initiation at such high CD4+ cell counts (i.e., >500 cells/mm^3) have not been conducted. A multinational trial comparing immediate ART versus deferral of treatment until declines in CD4+ cell count to less than 350 cells/mm^3 is ongoing but may face some limitations in fully addressing the essential question of when to start ART if those referred to the study, by virtue of entry viral load or other characteristics, are at low risk for disease progression. [16] Therefore, at present support for the use of ART earlier in the HIV disease course relies on data from alternative sources including observational cohort studies, other types of ART trials, and pathogenesis studies.

Observational Data

Several large HIV cohorts have demonstrated a benefit of modern ART initiated at CD4+ counts between 350 cells/mm^3 and 500 cells/mm^3 in terms of decreased progression to AIDS [17, 18, 19] and lower rates of death [20]. For example, analyses from both the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WHIS) find that individuals initiating ART at CD4+ cell counts above 350 cells/mm^3 have a nearly identical hazard of non-AIDS death as HIV-uninfected individuals (hazard ratio [HR] of 1.01),

whereas HIV positive individuals initiating at CD4+ cell counts 201–350 cells/mm^3 and<200 cells/mm^3 have HRs of 1.66 and 2.15, respectively, compared with HIV-positive early ART initiators. [21]

Investigations of the potential mortality and HIV disease progression benefits of ART initiation at CD4+ counts above 500 cells/mm^3 have been addressed in large cohort studies, producing mixed results and provoking much discussion (Table 3). Analyses of data from two cohorts, the European ART Cohort Collaboration (ART-CC) and the HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data (HIV-CAUSAL), did not show a significant difference in all cause mortality using an ART initiation threshold of 450 cells/mm^3, although both found benefits when death and progression to AIDS were used as a combined endpoint. [18,19] In stark contrast, the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) reported significantly lower adjusted mortality rates in those who initiate ART above a count of 500/mm^3. [20] The Concerted Action on Sero-Conversion to AIDS and Death in Europe (CASCADE) cohort showed slower disease progression when initiating ART at CD4+ thresholds of 500 and lower, but did not demonstrate benefit to starting at counts of 500–799/mm^3. [22] Differences in populations, study design, and analysis techniques can be implicated to account for these discrepant results.

Other observational studies have explored the relationship between CD4+ cell count and well-being. An analysis of over 200,000 individuals enrolled in the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study examined the incidence of the 18 most common AIDS-defining illnesses across the CD4+ cell count spectrum, ranging from 200/mm^3 to >1,000/mm^3. [23] As expected, the incidence rates of AIDS-defining illnesses was highest in those with lower CD4+ cell counts of 200 to 349/mm^3, with the rate of new AIDS-defining illnesses falling as the CD4+ cell count examined increased. However, even at the higher CD4+ cell counts, where in smaller studies such associations often become tenuous, those with a current CD4+ cell count of 750–999 cells/mm^3 had a significantly higher rate of new AIDS-defining conditions compared to those with counts of 500–749 cells/mm^3 (adjusted incidence rate ratio, 1.20 [95% CI, 1.10–1.32], P < .0001). The incidence of these conditions among those with current CD4+ counts of >1,000 cells/mm^3 was not significantly different from those with counts of 750–999 cells/mm^3. Importantly, the relationship between CD4+ cell count and disease development were stronger for malignant than non-malignant conditions. The authors' conclusion that persons with HIV infection are not fully immune reconstituted until the CD4+ count increases to >750 cells/mm^3, although expressly not intended to address the 'when to start ART' question, does suggest that avoidance of even modest levels of immunosuppression can be expected to be beneficial in terms of protection from AIDS-defining conditions, including certain cancers.

Studies of cardiovascular, neurocognitive, and bone health in persons living with HIV also show a link between end-organ damage and reduction of the CD4+ cell count pool. Most have been consistent in identifying nadir (lowest) CD4+ cell count as a marker of increased risk for disease. In a large cohort of patients enrolled in the Kaiser Permanente managed care system in California, lower CD4+ count nadir was associated with a significantly

increased incidence of myocardial infarction (MI); those with counts that never dropped below 500 cells/mm^3 had rates of MI that were similar to patients without HIV infection. [24] Investigators from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) study, a U.S. multi-clinic cohort, presented similar findings of a relationship between CD4+ cell count and cardiovascular disease, especially when the presence of viremia was considered. [25] Those with a recent CD4+ cell count of >500/mm^3 had an increased risk of MI when virus was not controlled compared to those with similar counts and undetectable viremia after adjustment for age, sex, tobacco, injection drug use, diabetes, male sex as HIV risk factor (for men), statin use, treated hypertension, renal function, and ART.

Data from the CHARTER cohort, a longitudinal study of the neurocognition HIV-infected persons, found an association between nadir CD4+ cell count and cognitive impairment. [26] A greater prevalence of impairment was observed among those with nadir counts below 500 cells/mm^3 compared to those with lower nadir counts; there were too few participants with counts above 500/mm^3 to examine trends among those with higher CD4+ cell count. Likewise, studies of bone density also point to deleterious affects of CD4+ cell count depletion on skeletal health, including fracture risk. [27,28]

Observations of an association between abnormal CD4+ cell counts and adverse outcomes are concerning given findings of an attenuated immunologic response to HIV therapy among those initiating ART at lower CD4+ cell counts (Figure 2). Slower and truncated gains in CD4+ cells over time were clearly evident in a recently presented study of over 1,300 participants in the U.S. HIV Outpatient Study (HOPS). [29] In this analysis, the likelihood of achieving a CD4+ cell count above 750/mm^3 (the level above which the COHERE study suggests is protective against AIDS-defining illnesses) by four years after initiation of ART increased with each higher stratum of CD4+ cell count at the start of therapy – ranging from 4.3% for those with nadir CD4+ counts below 50/mm^3 to 83.6% for those with counts above 500/mm^3. However, only 65.8% of those with counts 350–499 achieved immune reconstitution as indicated by a CD4+ cell count of 750/mm^3 or greater.

Observational studies have their inherent limitations. Unmeasured confounding, channeling bias, limited numbers of outcomes of interest in those at higher CD4+ cell counts, and other issues can challenge confidence in the conclusions reached. While the association between undesired outcomes and lower CD4+ cell counts has been strong and is convincing, these limitations and the mixed findings from the larger cohort studies regarding the benefits of ART at high CD4+ cell counts fuel the ongoing when to start ART debate.

Clinical Trials

Given the shortcomings of observational data, well-designed randomized clinical trials are looked at to guide standards of care. While the results of a trial directly comparing the initiation of ART at counts that are nearer to normal versus more profoundly depleted does not exist, examination of 'when to start' trials at lower counts have been used to support a strategy of early HIV therapy. Comprehensive International Program of Research on AIDS (CIPRA) study HT 01 was a randomized controlled trial of immediate ART versus deferral of ART until the CD4+ count fell below 200 cells/mm^3 in patients in Haiti with baseline

CD4+ counts between 200 cells/mm^3 and 350 cells/mm$^{3.}$ [30] This trial found higher rates of death (23 versus 6 deaths; hazard ratio [HR] = 4.0; 95% confidence interval [CI]: 1.6–9.8) and tuberculosis (HR = 2.0, 95% CI: 1.2–3.6) among those who deferred ART compared with those randomized to immediate ART initiation. While far from addressing the timing of ART for those with much higher CD4+ cell counts, the trial demonstrated a striking benefit of HIV therapy that many believe extends to higher counts.

The Strategies for Management of Antiretroviral Therapy (SMART) trial was not designed to address the timing of the initiation of ART but has been important to understanding the potential hazards of uncontrolled HIV infection. This study randomized 5,472 patients with baseline CD4+ counts above 350 cells/mm^3 (median CD4+ cell count at baseline was 597 cells/mm^3) to continuous ART or to a strategy of CD4+ cell count guided ART interruption wherein treatment was stopped, restarted when counts dropped below 250 cells/mm^3, and then withdrawn again when counts rebounded above 350 cells/mm^3. The trial was halted early after a survival benefit of continuous ART quickly became apparent. That the risk of AIDS-related and non-AIDS related adverse events, including cardiovascular, renal, and hepatic events, was increased with withdrawal of ART in this population with relatively high CD4+ cell counts, has been interpreted to suggest a benefit of starting HIV treatment at such counts. A subgroup analysis of the 249 participants (median CD4+ cell count was 437 cells/mm^3) who were ART-naive at entry and randomized to start ART immediately of defer ART until counts reached 250 cells/mm^3 looked at this question more directly. Although uncommon, the rate of serious AIDS- and non-AIDS-related events was higher among the arm randomized to defer ART initiation than among those who started ART immediately (7 versus 2 events, HR: 4.6, 95% CI: 1.0–22.2). [5, 31]

Additional indirect support for earlier initiation of HIV therapy came in 2011, when data from the HIV Prevention Trials Network (HPTN) 052 study were released. [11] In this trial over 1,700 HIV-infected individuals with CD4+ counts of 350–550 cells/mm^3 with HIV-uninfected partners were randomized to immediate ART versus ART initiation when CD4+ cell count decreased to <250/mm^3. ART profoundly reduced transmission of HIV with only one linked transmission in the 886 couples randomized to immediate ART compared to 27 in the arm in which ART was delayed, a hazard ratio in the early-therapy group of 0.04 (95% CI, 0.01 to 0.27; P<0.001) - translating to a 96% reduction in transmission risk. Additional analyses found that the incidence of clinical events during the trial was significantly lower in immediate ART arm (IRR=0.8, *P*=0.02) with the difference driven by HIV clinical events (e.g. TB, herpes simplex infections, zoster, and candidiasis). [32]

Studies of Pathogenesis and End-Organ Disease

A growing body of work explores the very early and persistent effects of HIV infection on activation of the immune system, levels of inflammation, and integrity of the gastrointestinal mucosa. Ongoing viremia itself has been demonstrated in the CNICS cohort to be a risk factor for mortality independent of CD4+ cell count. [33] Similarly, in the COHERE analysis controlled viremia (HIV RNA < 400 copies/mL) was associated with a reduced risk of AIDS-defining illness development. [23]

Other studies have described elevated levels of markers of inflammation and coagulation in patients with uncontrolled HIV infection. In the SMART trial, baseline levels of interleukin-6 (IL-6) and D-dimer were significantly associated with subsequent mortality. [34] This heightened inflammatory state begins soon after infection with HIV and persists if viral replication continues unchecked. ART has been demonstrated to significantly reduce markers of immune activation, inflammation, and coagulation as well as those for endothelial dysfunction and microbial translocation. [35,36] However, studies comparing ART treated patients to HIV-uninfected controls suggest that this improvement may be incomplete and that a residual level of excess inflammation persists. [37] The extent of such residual inflammation during ART may be a function of the nadir CD4+ cell count. [38–40] Therefore, an argument for early initiation of ART holds that on-going inflammation, fed by immune activation and microbial translocation, starts early, is harmful, and is addressed by ART – potentially reducing the risk of subsequent disease.

Treatment as Prevention

Recently, the public health benefits of ART have entered into the when to start ART discussion. The dramatic effect of ART on reducing HIV transmission found in the HPTN 052 study established ART as prevention. [11] Subsequent studies including the results from the PARTNER study, a Western European study of HIV discordant couples that found no linked transmission events when the infected partner's HIV was controlled despite unprotected sex, has further fueled broader use of ART to reduce the spread of the virus. [41]

Modeling of the effects of early ART in sero-discordant couples (including individual benefit and prevention benefits) in South Africa and India has suggested cost saving and cost effectiveness, respectively, over a 5-year period, and cost effective over a lifetime. [42] As with any communicable disease, there is a responsibility for a treating clinician to take into account transmission risks in treating HIV infection, a consideration reflected in recent U.S. and European ART treatment guidelines. While few are advocating universal ART strictly for its public health benefits, the impact of ART on transmission, coupled with the demonstrated and potential personal health benefits of HIV therapy, has strengthened arguments for broader and earlier use of treatment to suppress viral replication.

ART Toxicity

HIV remains incurable and once begun, HIV therapy can be anticipated to be lifelong. As such, there are concerns regarding the long-term effects of ART. Among the antiretroviral agents currently in widespread use, a number of toxicities have been recognized and are discussed in "What to Start". Major concerns center on the effects of ART on major organ systems including the circulatory, renal, and skeletal. The Data Collection on Adverse Events of Anti-HIV Drugs Study (D:A:D), other observational studies and one randomized controlled trial have reported an association between abacavir-containing ART regimens and increased risk of MI, [17,43–45] although other cohort analyses [46], secondary analyses of randomized trials and meta-analyses have not found such an association [47–49] While the relative risk of cardiovascular disease associated with common ART is concerning, it should be recognized that the absolute risk of MI and stroke remains low in the D:A:D and other cohorts. Reassuringly, a recent report from the Kaiser Permanente group found that in recent

years the incidence rates of both MI and stroke in HIV-infected and HIV-uninfected patient members had converged, whereas previously HIV-infected patients had higher rates of both. They attribute the reduced incidence of cardiovascular disease in HIV-infected patients to better lipid management, lifestyle interventions, and, importantly, to earlier use of ART. [50,51]

Tenofovir is an integral component of the most commonly used ART regimens. This nucleotide analogue can produce renal tubular damage, and rarely proximal tubulopathy with features of Fanconi's Syndrome including increasing serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis. It is estimated that less than 2% of treated patients can be expected to develop tubulopathy from tenofovir. [52] The PI atazanavir has also been linked in the D:A:D and EuroSIDA cohorts to renal issues including chronic kidney disease. [53] This drug can crystalize in the urine, causing nephrolithiasis. Recent reports also document atazanavir stones as a cause of cholelithiasis. [54,55]

Decreases in bone mineral density (BMD) are well described following initiation of ART - perhaps a consequence of an immune reconstitution phenomenon. In recent clinical trials, declines in BMD have been observed to be greater for both tenofovir and atazanavir than other antiretrovirals. As of yet, there are limited data suggesting an association between pathological fractures and ART mediated reductions in BMD. [52,56–58]

Additional potential adverse events accompany these and other antiretroviral agents and are detailed in each package insert. However, recent clinical trials of modern ART find relatively low levels of treatment discontinuations due to toxicity or treatment intolerance. [59–61] While the support provided patients within the context of a research study may be more robust than that provided in clinical settings, the overall tolerability of these agents is reassuring and indicative of the dramatic improvement in these therapies from the days of the Concorde trial.

Antiretroviral Resistance

Development of antiretroviral resistance is a well-recognized limitation of HIV treatment. Expanding the number of people receiving ART could result in an at least proportionate increase in the development of drug resistance. There are limited data on whether rates of developing resistance differ depending on CD4+ cell count or HIV disease stage at initiation, though one study has suggested initiation at CD4+ count above 350 cells/mm^3 was associated with a *lower* frequency of resistance mutations. [62] Higher rates of acute illness in those with advanced HIV could plausibly increase likelihood of treatment interruption, poor absorption of ART and might result in an increased need for non-HIV medications with potential for drug-drug interaction.

In addition, advances in ART have not only enhanced potency, tolerability, and convenience but also durability. Drug resistance to PIs boosted with ritonavir or cobicistat is rarely detected. The integrase inhibitor dolutegravir also appears in clinical trials to have a high barrier to drug resistance. [61] Therefore, while the risk of drug resistance will never be completely eliminated, it has been reduced and newer generation agents provide the ability to control even drug resistant strains of HIV.

Conditions Strongly Favoring ART Initiation

Outside the debate over whether or not to start ART at high CD4+ cell counts, are a variety of conditions where the benefit of prompt and in some cases urgent initiation of ART, regardless of CD4+ count, is clear.

Pregnancy

The management of HIV in pregnancy is a major topic in its own right, for which the current U.S. guidelines are a useful starting point [63]. Briefly, ART is indicated in pregnancy due to dramatic and repeatedly demonstrated benefits in reducing perinatal transmission of HIV. [64] Current U.S. guidelines recommend initiation during pregnancy and state that in deciding whether to start during the first trimester should involve weighing risk of potential fetal toxicities of first trimester ART exposure against benefits, with maternal CD4+ cell count, HIV RNA level and other maternal conditions. [63] Lack of early viral control is noted to be a risk factor for perinatal transmission. [65]

Acute Opportunistic Infections (OIs)

Initiation of ART in the setting of OIs is covered more fully in Chapter 8: "Opportunistic Infections". Presence of an acute opportunistic condition is generally an indication for ART initiation, but the urgency, optimal timing of initiation and mechanism of benefit varies by infection. Concern for severe immune reconstitution inflammatory syndrome (IRIS) exists with certain opportunistic conditions, including tuberculosis and cryptococcosis. For tuberculosis, several clinical trials have shown mortality and other health benefits to prompt ART initiation. [66–68] In tuberculous meningitis, there is some evidence to suggest higher rates of adverse events with immediate ART compared to ART delayed 2 months, [69] though the high rate of adverse events in both groups in this international trial has prompted concerns about generalizability. IRIS can also occur with other manifestations of tuberculosis. Current DHHS guidelines recommend close monitoring and caution when initiating ART in patients with tuberculous meningitis, and, for tuberculosis in general, recommend initiating ART within 2 weeks when CD4+ count is $<50/mm^3$ and within 8–12 weeks with counts above $50/mm^3$. For severe cryptococcosis, concern also exists that immediate ART may lead to worse outcomes via IRIS, and these guidelines state that "it may be prudent to delay initiation of ART until induction (the first two weeks) or the total induction/consolidation phase (10 weeks) has been completed." [70]

For most other opportunistic conditions, there is a consensus on the benefits of early ART. For infections such as progressive multifocal leukoencephalopathy (PML) and cryptosporidiosis for which no effective targeted therapy exists, ART is a means to potentially improve outcomes by improving immune function, although IRIS is common among those with PML who receive ART and monitoring for this outcome is recommended. [10] Even for infections with effective treatment, there is often a benefit to ART. The ACTG 5164 study randomized patients to early ART (defined as starting within 14 days of acute opportunistic infection treatment) versus deferred ART given after acute treatment of the infection was completed. There were lower rates of death and progression to AIDS in the early ART arm compared to the deferred ART arm. In that study, tuberculosis

was excluded, pneumocystis was responsible for the majority of infections, and there were very few cases of cryptococcal meningitis. [71]

Other Comorbid Conditions

ART initiation is indicated following the diagnosis of AIDS defining malignancies (ADMs). For HIV-associated lymphomas, higher cumulative HIV viremia in the 6 months following lymphoma diagnosis was associated with increased mortality. [72] Additional observational data suggested a lower CD4+ cell count was predictive of death from ADMs. [6]

Coinfection with hepatitis B and C viruses are also indications for prompt initiation of ART, as discussed in chapter 10. HIV-associated neurocognitive disorders and HIVAN are also indications for ART initiation and are discussed at greater length in chapter 9.

Acute HIV Infection

Acute or primary HIV infection is another indication for rapid ART initiation, for a variety of reasons. There is considerable evidence of immunologic benefits of ART initiated in acute HIV infection, including improved CD4+ reconstitution, [73,74] faster decline of HIV reservoir compared with later ART initiation, [73,75,76] and greater preservation of T cell [77,78] and B cell function. [79] Decreased HIV sequence diversity has also been seen with ART initiation in primary infection. [80,81]

Randomized controlled trials have evaluated whether limited duration courses of ART initiated early in the disease course were of benefit. The ACTG Setpoint Study, the Primo-SHM trial, and the SPARTAC trial found benefits of early HIV therapy including transient lowering of viral set point and delay in initiation of long-term ART. However, CD4+ count decline occurred following cessation of ART in all of these trials. [82–84] Thus, early treatment does not obviate the need for lifelong ART.

The disproportionate contribution of the recently infected to HIV transmission also suggests that treatment in this population could have a significant impact on the prevention of HIV transmission. [85] Therefore, initiation of ART during primary infection appears to provide benefits both to individual and public health.

Challenges and Considerations

A major and often under-acknowledged fact is that the majority of HIV-positive individuals present with CD4+ cell counts well under 500/mm^3. [86] Furthermore, rates of loss to follow up (on and off ART) as well as attrition from routine HIV care are exceedingly high, with recent national estimates showing only 24% and 33% of all HIV-infected persons in the U.S. receiving effective ART. [87, 88]

Adherence to ART is a struggle for many patients. While ART has become simpler and more forgiving of lapses in adherence, mental health and substance abuse disorders, in particular, remain impediments to long-term control of HIV infection and reduced infectiousness. Better tools to assess for risk of non-adherence and improved interventions to enhance adherence and retention in care are critical to decreasing the risks of developing

ART resistance and to reducing the potential harms of erratic and interrupted HIV care. At the same time, expanded mental health and substance abuse treatment will be essential to the success of a substantial proportion of those living with HIV.

An increasing challenge to the use of ART is affordability. Changes to the health care landscape in the U.S. have had ramifications for many HIV-infected individuals with and without insurance. As the Affordable Care Act is implemented, access to health insurance, including via expansion of Medicaid in some states, has provided much needed services to the under- and un-insured. However, for others, insurance companies have responded by increasing ART co-pays and deductibles – a devastating burden for patients struggling with limited resources.

Conclusions

There are many circumstances, including low CD4+ cell count, development of an acute opportunistic condition, and presence of an AIDS defining condition, where the benefits of prompt ART initiation are unambiguous. In contrast, whether to recommend routine ART initiation at CD4+ cell counts that are closer to normal remains a subject of some debate. Despite conflicting cohort data regarding the mortality benefit to ART at CD4+ cell counts above $500/mm^3$, there is evidence to reasonably suggest the existence of harm with untreated HIV - even at high CD4+ cell counts. In contrast, no data, cohort or otherwise, exist that demonstrate harm from earlier initiation of ART. The robust clinical data of the benefits of ART at low CD4+ cell counts and a clear biologic plausibility for benefits that extend to high-count individuals compels many to advocate for ART for all. The reduction in infectiousness with effective ART adds further support to the 'earlier is better' enthusiasts.

Critics of this approach can justifiably point to the notable limitations of the available data. But, perhaps the greater drag on the use of ART at higher CD4+ cell counts is operational. Despite ambitious HIV screening programs, the majority of infected individuals are still diagnosed long after their CD4+ cell counts have declined to 50% or more from normal. Among those who are diagnosed, the massive logistical challenges of diagnosing, retaining in care, and supporting medication adherence remains a major and daunting undertaking, especially in the U.S., where access to healthcare is uneven and, often unaffordable. Until we can identify those who are infected with HIV and support their continued engagement in care, the when to start ART debate will be moot for most affected by its outcome.

Acknowledgments

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- Despite ambitious HIV screening programs, the majority of infected individuals are still diagnosed long after their CD4+ cell counts have declined to 50% or more from normal.

- Among those who are diagnosed, the massive logistical challenges of diagnosing, retaining in care, and supporting medication adherence remains a major and daunting undertaking, especially in the U.S., where access to healthcare is uneven and, often unaffordable.

- Until we can identify those who are infected with HIV and support their continued engagement in care, the when to start ART debate will be moot for most affected by its outcome.
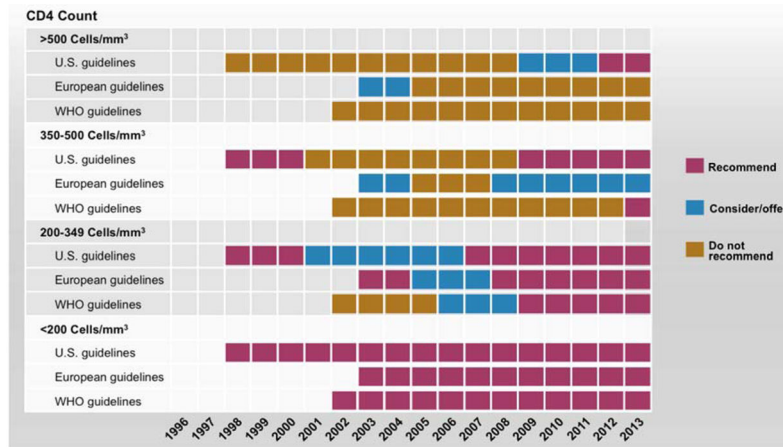
Figure 1.
Evolution of CD4+ Count Criteria for Starting Antiretroviral Therapy in Asymptomatic Persons with Human Immunodeficiency Virus Infection, According to Different Guidelines[89]
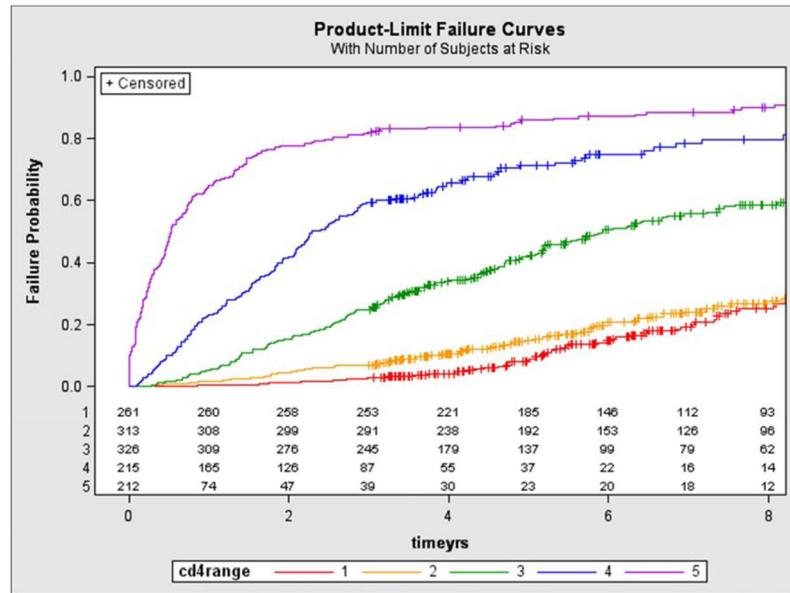
Figure 2.
Years after ART initiation to achieving CD4 > 750 by CD4+ cell count stratum at ART initiation: HOPS Cohort 1996–2012 (N=1,327) [29]

Table 1

2014 DHHS guidelines on initiation of ART in treatment naïve patients[10]

Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression	
Indication	**Recommendation Rating**[*]
Pretreatment CD4+ count (cells/mm^3)	
<350	AI
350–500	AII
>500	BIII
To prevent:	
Perinatal transmission	AI
Heterosexual transmission	AI
Other transmission risk group	AIII

[*] Rating scheme:

Strength of recommendation:

- **A.** Strong recommendation for the statement

- **B.** Moderate recommendation for the statement

- **C.** Optional recommendation for the statement I: One or more randomized trials with clinical outcomes

Evidence of recommendation:

- **I.** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

- **II.** II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes

- **III.** III: Expert opinion

Table 2

2014 DHHS guidelines: Conditions favoring more rapid ART initiation[10]

- Pregnancy (**AI**[*])

- AIDS-defining conditions **(AI)**

- Acute opportunistic infections[†]

- Lower CD4+ counts (e.g. <200 cells/mm^3) **(AI)**

- HIV associated nephropathy (HIVAN) **(AII)**

- Acute/early Infection **(BII)**

- HIV/Hepatitis B virus coinfection **(AII)**

- HIV/Hepatitis C virus coinfection **(BII)**

- Rapidly declining CD4+ counts (e.g., 100 cells/mm^3 decrease per year) **(AIII)**

- Higher viral loads (e.g., >100,000 copies/mL) **(BII)**

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[*] Rating scheme:

Strength of recommendation:

- **A.** Strong recommendation for the statement

- **B.** Moderate recommendation for the statement

- **C.** Optional recommendation for the statement I: One or more randomized trials with clinical outcomes

Evidence of recommendation:

- **I.** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

- **II.** One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes

- **III.** Expert opinion

[†]Recommendation rating varies by specific pathogen and OI disease site. See Chapter 8 for details.

Table 3

Results of major prospective cohort studies on timing of ART initiation[†]

Outcome and CD4+ threshold	NA-ACCORD[20]	HIV-CAUSAL[19]	ART-CC[18]
All-cause mortality			
CD4+ 450 Or 500	**Yes**[*] RR 1.94 (1.37, 2.79)	**No** HR 1.03 (0.92–1.14)[*]	**No** HR 0.93 (0.60, 1.44)
CD4+ 350	**Yes** RR 1.69 (1.26, 2.26)	**No** HR 1.01 (0.84, 1.22)	**No** HR 1.13 (0.80, 1.60)
CD4+ 200		**Yes** HR 1.20 (0.97, 1.48)	**Yes** HR 1.34 (1.05, 1.71)
AIDS-defining illness or death			
CD4+ 450		**Yes** **1.14 (1.07, 1.22)**	**No** **HR 0.99 (0.76, 1.29)**
CD4+ 350		**Yes** HR 1.38 (1.23, 1.56)	**Yes** HR 1.28 (1.04, 1.57)
CD4+ 200		**Yes** HR 1.90 (1.67, 2.15)	**Yes** HR 2.21 (1.91, 2.56)

[*]CD4+ threshold of 500/mm^3 used in NA-ACCORD, 450/mm^3 used in HIV-CAUSAL and ART-CC.

[†]The CASCADE study examined the hazards associated with ART delay vs. initiation, stratified by CD4+ count using a different statistical methodology and reference standard. Results showed benefit to immediate initiation at CD4+ count below but not above 500/mm^{3}.[22]