Current Opinion in Infectious Diseases: Volume 22 (2) April 2009 p 191-197

Should HIV therapy be started at a CD4 cell count above 350 cells/μl in asymptomatic HIV-1-infected patients? [Special commentary]

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Abstract TOP

Purpose of review: The aim is to review the available data that contribute to the debate on the optimal time to initiate highly active antiretroviral therapy (HAART) in HIV-infected individuals with a CD4 cell count more than 350 cells/μl.

Recent findings: Although few randomized data exist that can contribute to this debate, a number of findings from observational studies generally support earlier initiation of HAART. In particular, the findings that death rates remain higher in HIV-infected individuals than in uninfected individuals, even when successfully treated, and that both AIDS and several serious non-AIDS events are more common in those with a lower CD4 cell count (even when this count is above 350 cells/μl), suggest that earlier initiation of HAART may prevent much of the excess morbidity and mortality that remains in this patient group.

Summary: Currently, the data would generally support initiation of HAART in patients with CD4 cell counts more than 350 cells/μl. However, given the strong potential for confounding in observational studies and the lack of adjustment for lead-time bias in many analyses, it is not possible to rule out possible long-term detrimental effects of earlier use of HAART until the results from fully powered randomized trials that directly address this issue become available.

Introduction TOP

Although treatment guidelines currently generally recommend that HIV-infected patients with a CD4 cell count less than 350 cells/μl should receive highly active antiretroviral therapy (HAART), guidelines for those with higher CD4 cell counts are less clear-cut. Apart from analyses on a subset of patients in the Strategies for Management of AntiRetroviral Therapy (SMART) trial, there are no data from randomized trials to inform the optimal time to start HAART in these patients and guidelines are largely based on evidence from observational studies. In this review, we consider recent data to support the arguments for and against earlier initiation of HAART in patients with CD4 cell counts more than 350 cells/μl.

Background and scope of review

Highly active antiretroviral therapy is the mainstay of treatment for those infected with HIV [1]. Since its introduction in 1996, mortality and morbidity rates in HIV-infected individuals in countries with widespread access to HAART have plummeted [2,3]. The main effect of HAART is to suppress viral replication, allowing the individual's immune system to recover and protecting him/her from the development of AIDS and death.

The decision of when to start treatment in an HIV-infected individual has always been problematic. On the one hand, treatment should be initiated at an early point in the individual's course of disease, prior to a time when CD4 cell loss is such that there is substantial risk of clinical progression. On the

other hand, the original antiretroviral drugs were often inconvenient to take, of limited efficacy, and were associated with substantial toxicities. Thus, clinicians balanced the risks of delaying treatment (potentially placing the patient at risk of serious illness and death from AIDS) with the inconvenience and possible long-term effects of taking treatment. On the basis of evidence that clinical progression rates were low while the CD4 cell count remained above 200 cells/µl but increased rapidly at lower levels, most early treatment guidelines recommended that treatment be delayed until the CD4 cell count had fallen below 200 cells/µl. Over time, however, as treatments have improved and the number of treatment options available to patients has increased, this threshold has increased; most treatment guidelines now recommend that all individuals with a CD4 cell count less than 350 cells/µl should be treated [4-7].

For patients with CD4 cell counts in the range 350-500 cells/µl, opinion remains divided as to whether treatment should or should not be started [8,9]. Most treatment guidelines recommend that among patients with CD4 cell counts in this range, treatment be considered in those with high viral loads, those experiencing a rapid drop in CD4 cell count [4-6], or those with low CD4 percentages [7]. The Strategic Timing of AntiRetroviral Treatment (START) trial, due to start enrolling patients in early 2009 (http://www.cphiv.dk/portals/0/files/INSIGHT_feb_2008.pdf), will provide the first randomized evidence of whether immediate initiation of treatment in patients with CD4 cell counts more than 500 cells/µl is superior to delaying initiation of HAART until the CD4 cell count falls below 350 cells/µl. However, there are currently few data from randomized trials to support the earlier initiation of HAART. Thus, treatment guidelines have largely used evidence from observational studies. In this review we re-consider the arguments for and against earlier initiation of HAART in the light of recent data on this topic. Of note, there are groups of patients in whom antiretroviral treatment should be initiated regardless of their CD4 cell count, including patients with clinical AIDS or another serious HIV-related condition (including renal problems) and pregnant women (to prevent transmission to their child). For patients coinfected with hepatitis B virus, there are also strong arguments to starting antiretroviral therapy at higher CD4 cell counts when HAART includes drugs that are active against both viruses. This review will not consider these groups. Furthermore, our review will not consider treatment initiation in children, in whom the arguments for earlier or later initiation of treatment are different.

The current evidence for and against earlier initiation of HAART TOP

Until recently, the main argument for delaying HAART related to the toxicities and inconvenience of these drugs and the fact that treatment was likely to be life-long. It was felt that patients would be unable to maintain the high levels of adherence that are required for successful outcomes [10] and, as a result, would develop resistant strains of HIV, possibly resulting in the exhaustion of treatment options [11,12]. Indeed, Wood *et al.* [13] concluded that starting HAART at higher CD4 cell counts would not provide protection against the effects of nonadherence if patients were not able to maintain these strict regimens. Given the perceived low risk of AIDS and mortality at CD4 cell counts more than 350 cells/µl, it was thought that little would be gained by exposing patients to antiretroviral therapy too soon. There was also a concern that toxicities may differ among those starting HAART at different CD4 levels, possibly resulting in a higher discontinuation rate among those starting with high CD4 cell counts. However, despite some findings of a higher hepatotoxicity rate in individuals starting nevirapine with high CD4 cell counts [14-16], there is limited evidence to support an increased frequency of toxicities in those starting HAART with higher CD4 cell counts [17-21].

Antiretroviral drugs have developed rapidly in the last few years, as has clinicians' ability to manage HIV-infected patients. Not only are the drugs more potent, easier to take, and have fewer and less serious toxicities then those that made up original HAART regimens [1,22-24], but clinicians are aware of the problems associated with incomplete adherence and are better able to prevent and manage toxicities. Improved pharmacokinetic profiles and fixed dose combinations mean that drugs are easier to take and may be more forgiving to minor deviations from full adherence, resulting in less resistance [25,26••,27]. Furthermore, the number and variety of antiretroviral drugs available means treatment options remain even after virological failure on the initial regimen [28]. Thus, complete treatment exhaustion is increasingly unlikely for the majority of patients receiving HAART [29••].

Yet, despite this, death rates in many treated HIV-infected individuals remain higher than those in the general population [30•,31-33,34••,35•,36,37]. For example, among patients in Amsterdam [33], the death

rate for a noninjection drug user aged 25 years with a CD4 cell count of 600 cells/μl was 5.3 times higher than that of men in the Dutch general population, and 10.4 times higher than that of women. Data from the CASCADE collaboration [34••] reported that although the excess mortality rate in HIV seroconverters had dropped by 94% from the pre-HAART era to 2004-2006, an excess mortality remained. Another analysis utilizing the same dataset [35•] found that short-term death rates among those with CD4 cell counts of 200-349, 350-499, and 500 cells/μl or higher were substantially elevated compared to those among individuals of equivalent ages in the general population in England and Wales. A limitation of these studies is that the characteristics of HIV-infected individuals differ from those of the general population, and many risk factors for mortality (e.g. smoking) are more frequent [34••,38,39]. However, the question remains as to whether this excess mortality could be reduced further through earlier use of HAART.

Several large studies have provided important data on the risk of AIDS and death among individuals with high CD4 cell counts. Not only are these events more common than previously thought, but there is a continual increase in the risk of an event as the CD4 cell count declines, even when the count is high. For example, in the CASCADE collaboration [40], although the 6-month risk of AIDS varied according to patient age, a risk factor for disease progression [41], and viral load, it ranged from 2 to 10% in many individuals with a CD4 cell count more than 350 cells/μl. Podlekareva *et al.* [42] described risk factors for the development of opportunistic infections at higher than expected CD4 cell count levels; with the exception of pulmonary and extra-pulmonary tuberculosis, the strongest predictor for other opportunistic infections was a low CD4 cell count, even when the opportunistic infection occurred at a CD4 level previously thought to be protective. Data from the SMART trial, in which patients were randomized to receive either uninterrupted or episodic HAART [43], suggested that episodic treatment was associated with a higher risk of clinical disease at all CD4 levels. Although not designed to answer the question directly, among patients who were antiretroviral-naïve or who had not received HAART for at least 6 months prior to trial entry, major clinical events (opportunistic infections, serious non-AIDS events, and deaths from causes other than opportunistic infections) were more common in those with a lower CD4 cell count [44••], with event rates of 8.4, 5.3, and 0.9 per 100 person-years among those with CD4 cell counts of 250-349, 350-499, and ≥500 cells/μl, respectively. Finally, in the Swiss HIV Cohort Study [45•], the risk of non-Hodgkin's lymphoma was more than twice as high (adjusted hazard ratio of 2.28) in non-HAART users with CD4 cell counts of 200-349 cells/μl compared to those with counts ≥350 cells/μl.

The most surprising finding over recent years, however, has been reports that several clinical outcomes previously thought to be unrelated to HIV infection are more common in those with low CD4 cell counts. Data from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study suggest that the risk of mortality from several non-AIDS causes is increased at lower CD4 cell counts [46], including deaths from liver-related causes [47]. In the SMART trial [43], patients randomized to interrupted treatment had a higher risk of major cardiovascular, renal, and hepatic disease than those randomized to continued treatment, suggesting an impact of HIV on these events (although a possible impact of prior treatment followed by discontinuation cannot be ruled out). In the CPCRA FIRST study [48], each doubling in the latest CD4 cell count was associated with a 20% reduction in the risk of non-AIDS diseases, with similar associations noted between the latest CD4 cell count and renal, cardiovascular, and non-AIDS cancer events. The EuroSIDA study has reported that both pancreatitis [49] and chronic renal failure [50] were less common in those with higher CD4 cell counts.

In contrast, studies have reported conflicting findings regarding the role of the immune system in the development of non-AIDS malignancies. In both the D:A:D [51•] and FIRST [48] studies, an association was noted between the CD4 cell count and non-AIDS malignancies, and the risk of anal cancer dropped by 10% for each doubling in the CD4 cell count in a large French study [52•]. In contrast, no association was found between the CD4 cell count and the development of non-AIDS malignancies in the SMART trial [53], although few events occurred. Although the CD4 cell count was not strongly associated with the risk of lung cancer in one study [54], HIV infection itself was associated with an increased risk. HAART had a substantial impact on the risk of many types of non-AIDS defining malignancies in one US study [55], although the impact on different malignancies was not uniform and the authors concluded that a better understanding was required of the impact of HAART on these events.

The one piece of evidence based on a randomized comparison comes from the subset of patients in the SMART trial (all of whom had a CD4 cell count more than 350 cells/μl at baseline) who were treatment-naïve at baseline or had been off treatment for at least 6 months [56••]. For this subgroup the randomization was effectively to start treatment immediately or defer until the CD4 cell count was below 250 cells/μl. The relative hazard of new AIDS or death was 3.5 (P = 0.02), favouring the immediate arm. The risk of serious non-AIDS diseases was also significantly lower in the immediate arm.

Treatment responses at different CD4 levels TOP

Several observational studies have reported that the probability of attaining elevated CD4 cell count levels are not substantially diminished in those starting HAART at CD4 cell counts less than 200 cells/μl [57•,58,59,60•,61]. In particular, Gras *et al.* [57•] reported that only 20, 26, and 46% of those starting HAART with CD4 cell counts of less than 50, 50-200, and 200-350 cells/μl reached a CD4 cell count more than 800 cells/μl after 7 years of uninterrupted HAART compared to 73 and 87% of those starting HAART with CD4 cell counts of 350-500 and ≥500 cells/μl. In one study [58], compared to those starting HAART with a CD4 cell count ≥500 cells/μl, the probability that the patient's last CD4 cell count was more than 500 cells/μl was substantially reduced in those starting with a CD4 cell count of less than 200 or 200-349 cells/μl, but was not significantly reduced in those starting with a CD4 cell count of 350-499 cells/μl. Moore and Keruly [60•] reported that only patients with baseline CD4 cell counts of more than 350 cells/μl achieved normal CD4 cell counts after 6 years of follow-up compared to those starting HAART at a CD4 cell count of less than 200 cells/μl. Although the time before attaining an elevated level (e.g. >500 cells/μl) will undoubtedly be longer in those starting treatment with a low CD4 cell count, data from the EuroSIDA study [62••] suggest that all patients could eventually experience normalization of their CD4 cell counts, regardless of their starting CD4 cell count.

Care should be taken when interpreting the results on long-term CD4 cell count outcomes on treatment. Firstly, many patients may only have been diagnosed with HIV once their CD4 cell count has already fallen to low levels and factors contributing to late diagnosis [63,64] may also have an impact on an individual's response to HAART. Secondly, and most critically, the results from these studies will depend on the analytical approach taken - where an immunological response is defined as achieving a CD4 cell count above a threshold (e.g. 500 cells/μl), those starting HAART with a higher CD4 cell count are likely to achieve this level sooner than those starting HAART with lower CD4 cell counts. In contrast, studies that consider absolute increases or that estimate CD4 slopes after HAART initiation have not tended to show any marked difference in the CD4 cell count response according to baseline CD4 cell count [57•,62••,65,66]. It is important to consider that there may be a CD4 cell count 'ceiling' above which an individual's CD4 cell count is unlikely to rise - this may result in an inverse association between the pre-HAART CD4 cell count and CD4 increases [61].

Higher clinical progression rates are consistently reported in those starting HAART at CD4 cell counts less than 200 cells/μl [67-74]. At levels above this, however, findings are inconsistent. For example, two studies from the Johns Hopkins HIV Clinic Cohort [75,76] reported similar clinical disease rates among those initiating HAART with a CD4 cell count of 201-350 and more than 350 cells/μl; the authors argued that there was no value to starting HAART if the CD4 cell count was more than 350 cells/μl. In contrast, Palella *et al.* [77] reported that survival benefits were possible if HAART was initiated at a CD4 cell count of 351-500 cells/μl and rates of clinical progression in a French study [78] were halved in those starting HAART with CD4 cell counts ≥350 cells/μl, compared to those starting at lower CD4 cell counts. Among participants in the ALIVE cohort in Baltimore [79], survival of HAART-treated patients approximated that of HIV-seronegative participants only when treatment was initiated at CD4 cell counts more than 350 cells/μl.

The failure of these studies to take account of lead-time bias [80], however, means that although clinical progression rates are certainly higher in those starting HAART with lower CD4 cell counts, these data cannot address the 'when to start' question. Lead-time bias is introduced by the unobserved person-time among individuals who do not present for care until their CD4 cell count has already fallen below the threshold of interest (e.g. 200 cells/μl). These individuals could not have received treatment at higher CD4 cell counts (as they were not diagnosed) but must have survived without clinical progression until the time of their diagnosis. Failure to take account of this bias will

overestimate the potential benefits of earlier treatment [80]. Using methods to account for lead-time bias (as well as the unseen sample of rapid progressors who die before starting treatment), Cole *et al.* [80] concluded that deferring HAART initiation until the CD4 cell count is less than 200 cells/μl is detrimental compared to initiating at a count of 201-350 cells/μl. In contrast, initiation of HAART while the CD4 cell count was in the range 201-350 cells/μl did not increase the risk of AIDS compared to earlier initiation of HAART. Subsequent analyses of the same datasets [81••] revealed that an impact of HAART on the viral load would be present, even if HAART were initiated at CD4 cell counts more than 350 cells/μl. Using a similar approach, Jaen *et al.* [82••] reported that the adjusted hazard of AIDS or death among those starting treatment with a CD4 cell count of 200-350 cells/μl (compared to those starting at a count more than 350 cells/μl) was 1.72, leading the authors to conclude that treatment should be initiated at CD4 cell counts more than 350 cells/μl. Recently, investigators from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) group reported that initiation of HAART at a CD4 cell count between 350 and 500 cells/μl was associated with a 70% improvement in survival compared to starting HAART at lower CD4 cell counts; the authors also used methods to take account of lead-time bias [83].

Final comments TOP

Although the accruing evidence would seem to support earlier initiation of HAART, one limitation of all observational studies is that of unmeasured confounding. Under current treatment guidelines, few patients start HAART at high CD4 cell counts, and those who do generally differ from those who do not in many respects. It is arguable whether any observational study is able to reliably control for the reasons why HAART was initiated at any particular CD4 level, and thus any comparison of treatment outcomes in those starting HAART at different CD4 cell counts is likely to remain biased. Only a randomized controlled trial of earlier versus deferred treatment would be able to eliminate these biases. Mauskopf *et al.* [84] used a Monte Carlo simulation model to track HIV disease progression and to indirectly estimate the outcomes and costs of treatment when initiated at various CD4 cell counts. Using this approach, initiation of HAART at a CD4 cell count more than 350 cells/μl was seen to result in longer quality-adjusted survival compared to starting HAART at lower CD4 cell counts.

Two further points deserve brief comment. Firstly, our arguments for earlier or later initiation of HAART have been based on the benefits to the individual only. However, a potential public health impact of more widespread HAART use, particularly in terms of preventing onward transmission of HIV, cannot be ignored [85], providing further support for earlier initiation of HAART. In contrast, in many countries with widespread access to HAART, the median CD4 cell count at diagnosis of HIV is less than 350 cells/μl due to late diagnosis [86]; recommendations for earlier treatment are therefore unlikely to have any major effect on population-level outcomes, and it is argued that the resources required for earlier treatment may be better used to encourage earlier HIV testing in these countries, or enabling full access to HAART in countries where drugs are less readily available.

Conclusion TOP

In this review we have summarized the evidence for and against earlier initiation of HAART in HIV-infected individuals with a CD4 cell count more than 350 cells/μl. Although the evidence would appear to support earlier initiation of HAART, new data from observational studies may shed further light on this debate. However, it is likely that we will have to wait until the results from the START trial are available before a definitive answer can be obtained to this question.

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Keywords:

antiretroviral therapy; CD4 cell count; HIV infection; when to start treatment