Starting highly active antiretroviral therapy: why, when and response to HAART

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Highly active antiretroviral therapy (HAART) has dramatically improved the prognosis of patients with HIV, although it remains unclear as to the best time to start treatment to reduce the risk of clinical progression. The initial virological response to HAART, by reducing viral load to below the limit of detection, is essential for reducing the risk of drug resistance, which in the longer term may lead to a deterioration in immune function and an increased risk of clinical disease progression. There has been a switch to more conservative therapy recently, given concerns about toxicities and the difficulties of adhering to a complicated regimen long term.

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Why should patients start HAART?

Since the introduction of HAART in 1996 and 1997, there has been a significant decline in mortality and morbidity associated with HIV; following the introduction of HAART across Europe, death rates fell to one-fifth of their level before the introduction of HAART and mortality and morbidity have declined further as experience of treatment has increased (Figure 1). There are a number of problems associated with HAART, including the development of drug resistance, the difficulties of maintaining long-term adherence, and drug-related toxicities, all of which may lead to virological failure, which in turn leads to immunological failure and clinical progression, although there is an unknown lag-time for this sequence of events to occur.

When should patients start HAART?

There has been a move in guidelines from more aggressive therapy, offering HAART at higher CD4 cell counts, to more conservative guidelines, where HAART is deferred until there is an immediate risk of AIDS or death. HAART will not eradicate HIV, and the current goal of therapy is to inhibit viral replication over a long-term period so that immune responses to most common pathogens are restored. There are other potential risks and benefits associated with starting HAART, and these should be considered by both the clinician and patient. Potential benefits of early therapy include preservation of the immune system, a decrease in the risk of HIV transmission, and earlier suppression of viral replication, whereas risks of early therapy include the adverse effects of drugs on quality of life, inconvenience of regimens leading to decreased adherence, potentially serious toxicities and the presently unknown durability of treatment. In contrast, in patients who delay therapy, preservation of future treatment options, waiting for more powerful regimens to be developed and delaying drug resistance are an advantage, whereas the possibility of irreversible damage to the immune system and an increased risk of transmission are disadvantages.

There have been a number of observational studies considering the risks and benefits of HAART according to the CD4 cell count when starting HAART (Table 1). The risk of developing new AIDS-defining diseases and/or death was increased in patients starting HAART at CD4 cell counts below 200 cells/mm3, but these studies have not been able to demonstrate a consistent significant benefit of starting HAART at CD4 cell counts above 350 cells/mm3. In order to minimize the risk of disease progression after starting HAART, it would seem important to start HAART before the CD4 cell count falls below 200 cells/mm3. The data do not indicate that therapy is less effective in patients starting HAART with CD4 cell counts below 200 cells/mm3, as the increased risk of clinical progression occurring after starting HAART in patients with low CD4 cell counts reflects the time for HAART to improve the level of immunodeficiency such that the patient is no longer at risk of disease progression. To address the question of the optimal time to start HAART, one needs to balance the risk of experiencing clinical progression associated with deferring therapy against the likely risk of toxicity and resistance associated with early therapy. Most observational studies have concentrated on the comparison of early versus late HAART by using the CD4 cell

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count or viral load at time of starting HAART, and described clinical progression according to these baseline markers. This analysis does not answer the question of ‘At what CD4 cell count should patients start HAART to minimize the risk of clinical progression?’. This is best answered by comparing the clinical progression of patients from the date of their first CD4 cell count of, for example, 350 cells/mm$^3$. Half of these patients could be assigned to start treatment immediately and half deferred until their CD4 cell count falls to a lower level, say 200 cells/mm$^3$. This analysis not only takes into account the clinical events which happen after the patient has started HAART, but any additional events that might occur in the patient who defers treatment while their CD4 lymphocyte count is in the range 200–350 cells/mm$^3$.

Randomized trials are best suited to answer the question of the optimal time to start therapy. This would require large and lengthy trials, and there are none in progress at present. As an intermediate, one randomized trial is comparing two strategies of using HAART, the drug conservation and the viral suppression strategy. In the drug conservation strategy arm, HAART is used periodically to maintain the CD4 cell count above 200 cells/mm$^3$ whereas in the virological suppression strategy arm, HAART is used at all time points in order to maximize suppression of HIV replication (http://www.smart-trial.org/). This trial will recruit 6000 patients and will be completed when 910 new AIDS events or deaths have occurred, currently estimated to be 2012.

It is important to emphasize that our understanding of the optimal approach to manage patients with HIV remains immature. Should resistance develop, this is an irreversible process because resistant strains will be archived in host DNA. New strategies for treatment, such as the drug conservation strategy discussed above, are currently being developed. In addition, short-term courses of interleukin-2 increase the CD4 cell count by 50–150%, and the absolute increase in CD4 cells is associated with the CD4 cell count before starting HAART. If the ongoing Phase III trials demonstrate that the CD4 cells induced by interleukin-2 are clinically protective, this would be an argument to start HAART with a reasonable immune function.

The drugs used are powerful antiretrovirals, but have a cost in terms of added toxicity. Chronic hyperlactaemia is a rare but potentially fatal toxicity with an incidence of around 1.3 per 1000 person-years exposure to nucleosides. There is an increased risk of hepatotoxicity, particularly among patients infected with hepatitis C, and an increased risk of cardiovascular events associated with longer exposure to HAART.

Two observational studies have considered the risk of toxicities according to CD4 cell count before HAART (Table 1), with conflicting results. Future studies should ensure that events expected to occur in patients with severe immunodeficiency (such as HIV-related neuropathy) are separated from toxicities induced by the therapy provided to such patients.

### Table 1. Evidence from observational studies on risk of disease progression or toxicities according to level of immunodeficiency as determined by CD4+ lymphocyte count before starting HAART

<table>
<thead>
<tr>
<th>Observational cohort (reference)</th>
<th>Number of patients and average follow-up</th>
<th>Endpoint assessed</th>
<th>CD4 cell count when starting HAART (cells/mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART Cohort Collaboration (19)</td>
<td>12 574, 23 months</td>
<td>new AIDS or death</td>
<td>increased risk</td>
</tr>
<tr>
<td>HIV Outpatient Clinic Cohort (20)</td>
<td>1464, 48 months</td>
<td>new AIDS or death</td>
<td>increased risk</td>
</tr>
<tr>
<td>British Columbia Cohort (21)</td>
<td>1219, 28 months</td>
<td>new AIDS or death</td>
<td>increased risk</td>
</tr>
<tr>
<td>John Hopkins Hospital HIV Clinic Cohort (22)</td>
<td>1014, 22 months</td>
<td>new AIDS or death</td>
<td>increased risk</td>
</tr>
<tr>
<td>HIV Outpatient Clinic Cohort (23)</td>
<td>345, 12 months</td>
<td>clinical adverse events</td>
<td>possible increased risk$^a$</td>
</tr>
<tr>
<td>Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study (9)</td>
<td>23 468, 18 months</td>
<td>myocardial infarction</td>
<td>no association</td>
</tr>
<tr>
<td>HIV Outpatient Clinic of the Amsterdam Medical Centre (8)</td>
<td>560, 36 months</td>
<td>hepatotoxicity</td>
<td>no association</td>
</tr>
</tbody>
</table>

$^a$When starting HAART, different categories of CD4 cell count were used making exact comparison difficult.
Response to HAART

Patients who start HAART have a rapid decrease in HIV viraemia to undetectable levels within 6 months of starting HAART and a gradual increase in CD4 cell count to levels approaching those seen among uninfected patients. \(^{10}\) In general, the response to HAART reported from clinical trials tends to be considerably better than that seen in observational studies, and this is due to the selection of patients for clinical trials. \(^{11}\) Patients in clinical trials may be selected for certain characteristics, such as having never received any antiretroviral treatment (treatment naive) or willingness and determination to take HAART, whereas patients from some groups, such as intravenous drug users, migrant populations (where language or cultural differences may play a role) or patients with concomitant infections, such as hepatitis, may be excluded. Whilst the results from clinical trials are essential to establish the efficacy of HAART, results from observational studies of mixed clinic populations may be more representative of the ‘real world’ and give an indication of the efficacy of HAART in a heterogeneous population.

There are several factors commonly reported to be associated with initial virological response to HAART. One of the most important factors related to virological response to HAART is prior treatment; treatment-experienced patients have a poorer response to HAART and are less likely to achieve a viral load of below the limit of detection. \(^{12}\) Treatment-experienced patients may have accumulated drug resistance, which may result in a poorer virological response. Adherence also plays a key role in virological response. Results from both clinical trials and observational studies report an increase in virological response amongst patients who are more adherent, \(^{13,14}\) although it is often difficult to capture accurate data on adherence. Estimates of adherence have used pill counts, electronic monitoring, records of prescription refills, drug-level monitoring and detailed questionnaires, all of which can be time-consuming and impractical within a busy clinic schedule. Failure to adhere to HAART results in low drug levels, which can rapidly lead to the selection of virus with decreased susceptibility. In addition, as different antiretrovirals within the same drug-class are cross-resistant, the number of potential regimens rapidly decreases for the non-adherent patient.

It takes longer for a patient with a high viral load when starting HAART to reduce their viral load to below the limit of detection; some studies also suggest that patients with a higher viral load when starting HAART are less likely to respond with a viral load below the limit of detection. \(^{15,15}\) The viral loads at weeks 4 and 8 after starting HAART are also related to virological outcome at 24 weeks after starting HAART. \(^{16}\) Assessing the reasons for a lack of early response to HAART and addressing problems can improve the longer-term response to therapy, however, it is not known if a change in treatment or intensification of the regimen will improve the clinical outcome. Other factors related to virological response include starting new nucleosides at the time of starting HAART and age. \(^{15,17}\) Among patients with previous nucleoside treatment, those that start HAART with two new nucleosides (i.e. nucleosides that the patient has never taken before) have a better response. The addition of new drugs may increase the genetic barrier of therapy, as the sequential initiation of antiretrovirals impairs drug efficacy because of the failure to overcome drug-resistant mutations. Older patients have been reported to have a better initial virological response to HAART, which may be a marker for greater maturity and reflect a more stable lifestyle, both of which may impact on adherence. Conversely, younger patients have been shown to have an improved immunological response, \(^{18}\) possibly due to preserved thymic function.

It is worth noting that response to HAART is a multifactorial process which depends on many factors in addition to those described above. The availability of emotional and practical support, relationship between the patient and clinical team, the skills and experience of the team treating the patient, presence of concomitant diseases and the possibility of drug interactions should also be taken into account.

Conclusions

As yet, there is no strong evidence for the best time to start HAART. The decision of when to start is clearly a complicated one which must weigh the benefits and disadvantages of immediate treatment against the risks and advantages of delaying treatment. Patients who start HAART with a high viral load, who are poorly adherent, those with prior nucleoside treatment, those with drug resistance or those who do not add new nucleosides to a new HAART regimen are less likely to have a good initial virological response to HAART. Ultimately, failure to suppress viremia may lead to a decrease in CD4 lymphocyte counts and an increase in the immediate risk of AIDS or death.

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References


