Clinical and pharmacological aspects of induction-maintenance therapy in HIV-1 positive patients: the ADAM study
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Chapter 2

Maintenance therapy after quadruple induction therapy in HIV-1 infected individuals: Amsterdam Duration of Antiretroviral Medication (ADAM) study.

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Abstract

Background

Highly active antiretroviral therapy (HAART) has led to health benefits for patients infected with HIV-1. However, long-term use of multidrug regimens is difficult to sustain. Simplifying antiretroviral treatment regimens would increase patients' adherence and minimise toxicity. We investigated the feasibility of a strategy of induction therapy followed by maintenance therapy with HAART in a randomised open-label study.

Methods

From March, 1997, we enrolled patients infected with HIV-1 with at least 200 CD4 cells/μL, at least 1000 HIV-1 RNA copies/mL in plasma, and no previous exposure to antiretroviral drugs. After 26 weeks of induction therapy ( stavudine, lamivudine, saquinavir, and nelfinavir) patients were randomly allocated maintenance therapy (either stavudine and nelfinavir or saquinavir and nelfinavir) or prolonged induction therapy (if the plasma HIV-1 RNA concentration at weeks 24 and 25 was < 50 copies/mL).

Findings

In February, 1998, we discontinued randomisation after an interim analysis. 62 patients had been enrolled. 39 (91%) of the 43 patients who were followed up for at least 26 weeks had an undetectable plasma HIV-1 RNA concentration at week 16. At week 26, 31 patients were randomly allocated treatment. Of these patients 25 had a total follow-up of at least 36 weeks. At week 36, a higher proportion of patients on maintenance therapy (nine (64%) of 14) had a detectable HIV-1 RNA than patients on prolonged induction therapy (one (9%) of 11, p=0.01). The initial virion-clearance rate during induction therapy was higher in five patients on maintenance therapy with a sustained undetectable plasma HIV-1 RNA concentration than in nine patients with recurrence of a detectable plasma HIV-1 RNA concentration at week 36 (0.35 vs 0.19 per day, respectively; p=0.008).

Interpretation

The induction regimen provided a rapid suppression of viral replication to below 50 copies/mL. However, suppression was not sustained in a considerable number of patients who went onto maintenance therapy. It is currently inadvisable to continue attempts at moving from induction to maintenance therapy in day-to-day practice.
Introduction

With a combination of three or more antiretroviral agents, a durable suppression of viral replication in HIV-1 infection can be achieved.\(^1\)-\(^3\) This highly active antiretroviral therapy (HAART) has resulted in clinical benefit in terms of prolonged disease-free survival.\(^4\),\(^5\) However, for sustained clinical benefit, treatment needs to be used for many years, probably for life. The daily burden of taking the pills involved in triple or quadruple antiretroviral regimens is large. Also, a rigid time schedule with complicated dietary prescriptions may interfere with the patient's daily activities. Even in the knowledge of suffering from a life-threatening disease, strict adherence to therapy is difficult for many patients.\(^6\) Unfortunately, adherence is critical for a durable suppression of viral replication, which itself is a prerequisite of avoidance of the development of viral drug resistance.\(^3\),\(^7\) Toxicity, such as lipodystrophy, may also restrict the patient in the chronic use of HAART.\(^8\)

However, HAART has been shown to reduce rapidly the viral burden of plasma, lymphatic tissue, and cerebrospinal fluid,\(^9\)-\(^12\) suggesting that in the near absence of viral replication, maintenance therapy with less antiretroviral agents might be feasible.

In this, the Amsterdam Duration of Antiretroviral Medication (ADAM) study, we explore the feasibility of HAART with a strategy of induction therapy and then maintenance therapy using a quadruple induction regimen followed by maintenance therapy with two drugs. For the induction phase, we added another protease inhibitor to a standard triple regimen to potentially increase the antiviral efficacy. Nelfinavir increases the oral bioavailability of saquinavir about five fold.\(^13\) For the choice of the maintenance therapy, we considered the combination of two nucleoside reverse transcriptase inhibitors less attractive since antiretroviral activity of the various nucleoside reverse transcriptase inhibitors is highly dependent on cellular enzymes, and differs among cell types.\(^14\) Given the lack of experience with maintenance therapy, we decided to study an approach with a combination of a reverse-transcriptase inhibitor and a protease inhibitor versus a double protease-inhibitor combination. Here we present the preliminary results of maintenance therapy after 6 months' induction therapy.
Methods

Patients

The enrolment of HIV-1 infected patients in this open-label randomised controlled study started in March, 1997, and was ended prematurely on April 6, 1998 (see below). Patients, aged 18 years or more, were eligible if they had at least 200 CD4 cells/μL in peripheral blood, 1000 or more HIV-1 RNA copies/mL in plasma, and if they were antiretroviral naïve. Exclusion criteria were the existence of an active opportunistic infection, active hepatitis C or presence of the hepatitis B surface antigen, breastfeeding or pregnancy, and the use of immunomodulatory drugs or investigational drugs up to 1 month before the start of the study medication. Some haematological signs were also exclusion criteria: haemoglobin of less than 7 mmol/L for men or less than 6.5 mmol/L for women; neutropenia of less than 0.75×10⁹/L; aspartate or alanine amino transferase of more than five times upper limit of normal; and serum creatinine of more than 1.5 times upper limit of normal. The study was approved by the institutional review boards of all participating institutions. Informed consent was obtained from all participants.

Study design

All patients started the induction phase with a quadruple therapy consisting of stavudine (d4T, 40 mg twice a day, or 30 mg twice a day if body weight <60 kg), lamivudine (3TC, 150 mg twice a day), saquinavir hard gelatin capsules (saquinavir-HGC, 600 mg three times a day) and nelfinavir (750 mg three times a day, figure 1). When saquinavir soft gelatin capsules (SGC) became available (Nov 1, 1997), all patients on saquinavir-HGC 1800 mg daily switched to saquinavir-SGC 2400 mg daily. Patients were told to take their medication with food.

At week 26, patients with a plasma HIV-1 RNA level below the detection limit of an ultrasense assay (<50 copies/mL) at both week 24 and 25 were randomly allocated prolonged induction therapy or a maintenance regimen: stavudine plus nelfinavir or saquinavir plus nelfinavir. Patients were allocated treatment by a computerised minimisation program, weighting imbalance of allocations according to the CD4 cell count (more or less than 400 cells/μL) and HIV-1 RNA (more or less than 50,000 copies/mL) at screening. Treatment allocation was done in a 2:1:1 ratio of prolonged induction: stavudine plus nelfinavir or saquinavir plus nelfinavir, respectively.
Follow-up

Patients were scheduled to visit the outpatient clinic for clinical assessment and routine laboratory monitoring at the start of treatment and weeks 1, 2, 4, 8, 16, 24, 25 (only plasma HIV-1 RNA concentration assessment) and 26. After randomisation, follow-up of patients on maintenance therapy was scheduled at weeks 27, 28, 32 (only plasma HIV-1 RNA concentration assessment for each follow-up), 36, 48, 60, 72, 84, and 96. Follow-up for patients on prolonged induction therapy was done at weeks 36, 48, 60, 72, 84, and 96. Laboratory monitoring included plasma HIV-1 RNA concentration, and CD4 and CD8 cell count.

HIV-1 RNA plasma concentrations were measured with NASBA and NucliSens HIV-1 RNA QT assays (Organon Teknika, Boxtel, Netherlands). When concentrations declined to less than 400 copies/mL, an ultrasensitive protocol with a quantification limit of 50 copies/mL was used. At week 26 and during further follow-up, the ultrasensitive procedure of the Roche Amplicor assay (Roche Diagnostic Systems, Branchburg, New Jersey, USA) with a variable quantification limit was used (median quantification limit of 24 assays done in plasma: 27 (range 14-79) copies/mL).

After attaining a plasma HIV-1 RNA concentration below the quantification limit of the ultrasensitive assay (<50 copies/mL), a plasma HIV-1 RNA level above 400 copies/mL at two consecutive occasions was originally described in the protocol as a treatment failure. In case of grade 4 toxicity\(^{15}\) or grade 3 toxicity with no improvement after temporary discontinuation (maximum 2 weeks), or recurrence of grade 3 toxicity after rechallenge, permanent discontinuation of the study medication was obligatory. After treatment failure or discontinuation of the study medication, further therapy was given at the discretion of the investigator.

Protocol amendment and stopping of randomisation

Results of the TRILÈGE\(^{16}\) and ACTG 343\(^{17}\) trials regarding induction therapy then maintenance therapy presented at the fifth National Conference of Retroviruses, led to a premature analysis of the ADAM study. Subsequently, the results from this analysis and the above mentioned trials led to an amendment of the protocol and discontinuation of randomisation at week 26 in February, 1988. During this process, the primary endpoint of the study was changed to a detectable HIV-1 RNA copy number with the ultrasensitive assay at a time beyond 26 weeks of induction therapy. What at first seemed a trivial level of viral escape has proven to be relevant. In several studies\(^{18,19}\) it has been shown that maintaining viral replication levels
below the detection limit of ultrasensitive assays (20-50 copies/mL plasma) is essential for a durable effect of therapy.

Patients with detectable HIV-1 RNA concentrations of more than 100 copies/mL or more than 400 copies/mL during maintenance therapy on two consecutive occasions were advised to continue with the original quadruple regimen or advised change their therapy to three completely different antiretroviral agents, respectively.

**Data analysis**

For all patients with a follow-up for at least 26 weeks, plasma HIV-1 RNA concentrations, change in CD4 and CD8 cell count, and occurrence of adverse events during the first 26 weeks of treatment were recorded. The proportion of patients with a plasma HIV-1 RNA level below 50 copies/mL was calculated at each time.

The ability to detect HIV-1 RNA in plasma in the group who had induction therapy followed by maintenance therapy was analysed at week 36. Subsequently, patients on maintenance therapy with and without a detectable plasma concentration of HIV-1 RNA at week 36 were compared for baseline characteristics, the time to an undetectable plasma HIV-1 RNA concentration, the change in CD4 and CD8 cell count, and the initial virion-clearance rate constant in plasma during induction treatment. Statistical comparisons were based on Wilcoxon's rank-sum test.

To calculate the virion-clearance rate constant in plasma an exponential function was used to describe the rate of HIV-1 RNA decline during the first two weeks for each patient. The following function was used to describe the decline of the HIV-1 RNA concentration in plasma (first-order elimination):

\[
V_t = V_0 * e^{-kt}
\]

\(V_t\) represents plasma HIV-1 RNA in copies/mL at time \(t\); \(V_0\) represents the baseline plasma HIV-1 RNA concentration; \(k\) is the elimination-rate constant (per day), and \(t\) is the number of days after the start of treatment. All HIV-1 RNA measurements of 50 copies/mL or more, were used for each patient from the start of treatment until a value of less than 50 copies/mL was reached or until a maximum of 16 days. For each patient the value for \(k\) was estimated by least-squares regression analysis (\(\ln V_0\) vs \(t\)).
Total of patients included at week 0

Patients with a follow-up of at least 26 weeks

Patients not randomised at week 26
- Discontinuation of study medication due to toxicity (n=4)
- Detectable HIV-1 RNA level in plasma at week 24/25 (n=6)
- Due to protocol amendment (n=2)

Patients randomised at week 26
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV
- Patient refused randomisation to maintenance

Patients with a follow-up of at least 36 weeks
- Patients with less than 36 weeks of follow-up (n=4)
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV

Patients with a detectable HIV-1 RNA level at week 36
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV

Figure 1  Trial profile.
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Results

Patients

A total of 62 patients (59 men, 95%) were enrolled before we stopped randomisation at week 26 (figure 1). The baseline characteristics of 43 patients who were followed up for at least 26 weeks are summarised in table 1. Four of these patients stopped taking the study drugs because of adverse events.

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Induction therapy*</th>
<th>Prolonged Induction therapyb</th>
<th>Maintenance therapyb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>43</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Age, Yrs, mean (SD)</td>
<td>40 (8)</td>
<td>43 (6)</td>
<td>39 (10)</td>
</tr>
<tr>
<td>Male, N, (%)</td>
<td>40 (93%)</td>
<td>11 (100%)</td>
<td>12 (86%)</td>
</tr>
<tr>
<td>CDC A</td>
<td>26 (60%)</td>
<td>7 (64%)</td>
<td>9 (65%)</td>
</tr>
<tr>
<td>N, (%)</td>
<td>B</td>
<td>15 (35%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>C</td>
<td>2 (5%)</td>
<td>1 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³</td>
<td>400 (310-510)</td>
<td>420 (310-500)</td>
<td>355 (320-650)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8+ cell count, cells/mm³</td>
<td>1060 (790-1510)</td>
<td>1070 (930-1760)</td>
<td>950 (770-1510)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA, log₁₀ copies/mL</td>
<td>4.53 (4.11-5.04)</td>
<td>4.57 (4.00-5.04)</td>
<td>4.48 (3.85-4.88)</td>
</tr>
<tr>
<td>median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aPatients with at least 26 weeks of follow-up.

*bPatients with at least 36 weeks of follow-up (these patients are included in the 26 weeks follow-up column as well).

Induction phase

Plasma HIV-1 RNA concentrations declined from 4.53 log₁₀ copies/mL at baseline to 1.7 log₁₀ copies/mL at week 26 (figure 2A). At week 8, 48% of the patients had a plasma HIV-1 RNA concentration below 50 copies/mL; at week 16 this proportion had risen to 91%. No treatment failure was observed during the induction therapy according to the protocol definition.

CD4 cell-count response during the first 26 weeks of treatment is shown in figure 2B. The median change from baseline was 200 CD4 cells/µL at week 26. The median CD4 cell count as a percentage of the total lymphocyte count rose from 21.0% at baseline to 29.5% at week 26. A small decrease of the mean CD8 cell count was seen (figure 2C). At week 26, the median change from baseline was -60 CD8 cells/µL.
Figure 2  Plasma HIV-1 RNA level, change in CD4<sup>+</sup>- and CD8<sup>+</sup>- cell count during induction therapy. Bars represent interquartile range (Panel A) or standard error of the mean (Panel B and C).
Panel A: Median log<sub>10</sub> HIV-1 RNA copies/mL in plasma during induction therapy.
Panel B: Mean change in CD4<sup>+</sup> cell count during induction therapy.
Panel C: Mean change in CD8<sup>+</sup> cell count during induction therapy.
33 of the 43 patients suffered from diarrhoea, mostly loose or watery stools, two or three times a day. Loperamide (2-4 mg a day) was used in half of these patients to relieve the diarrhoea. Only one patient discontinued medication because of diarrhoea (week 8). Mild rises of the liver enzymes occurred in ten patients. In three of these patients, the rise of aspartate- or alanine aminotransferase, alkaline phosphatase, or γ-glutamyl transpeptidase led to discontinuation of the study medication (at week 4, 8 and 16, respectively). Other side-effects reported among the 43 patients were: fatigue in 16 patients, raised triglycerides in 15, headache in 16, and abdominal discomfort in nine.

**Maintenance phase**

At week 26, 31 of 39 patients still on induction treatment were randomly allocated to stay on induction therapy or to maintenance therapy (figure 1). One patient subsequently refused maintenance therapy. Eight patients were not randomly allocated treatment: six had detectable plasma concentrations of HIV-1 RNA, albeit without treatment failure (maximum plasma HIV-1 RNA concentration was 76 copies/mL); the remaining two were not randomly allocated treatment because randomisation at week 26 was stopped.

11 of the 25 patients randomly allocated to prolonged treatment and 14 of 16 patients switched to maintenance therapy were followed up for at least 36 weeks. Seven of the 14 were given stavudine plus nelfinavir and seven were given saquinavir plus nelfinavir.

Baseline characteristics were similar in both groups of patients (table 1). At week 36, a difference in the proportion of patients with a detectable plasma concentration of HIV-1 RNA was observed between the treatment arms. One (9%) of the 11 patients in the prolonged-induction group had a detectable plasma concentration of HIV-1 RNA by contrast with nine (64%) of 14 patients in the two maintenance arms (Fisher's exact test: p=0.01). Five (55%) of these nine patients already had a detectable plasma concentration of HIV-1 RNA at week 32. The numbers of patients with detectable plasma concentrations of HIV-1 RNA were evenly distributed between the two maintenance arms; four (57%) of seven and five (71%) of seven patients in the stavudine plus nelfinavir and saquinavir plus nelfinavir arms, respectively. Plasma concentrations of HIV-1 RNA are given in table 2. Treatment failure (>400 HIV-1 RNA copies/mL in plasma on two consecutive occasions) was found in two patients on stavudine plus nelfinavir, and in one patient on saquinavir plus nelfinavir compared to none of the patients continuing quadruple drug therapy.
### Table 2  Characteristics of patients with at least 36 weeks follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Prolonged Induction therapy</th>
<th>Maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Detect.</td>
</tr>
<tr>
<td>Patients, N</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Δ CD4⁺ (cells/mm³) b</td>
<td>200</td>
<td>570</td>
</tr>
<tr>
<td>Mean, SD</td>
<td></td>
<td>(100-290)</td>
</tr>
<tr>
<td>Δ CD8⁻ (cells/mm³) b</td>
<td>-680-220</td>
<td>(-)</td>
</tr>
<tr>
<td>Mean, SD</td>
<td>20</td>
<td>360</td>
</tr>
<tr>
<td>K (day⁻¹) c</td>
<td>0.24</td>
<td>-0.11</td>
</tr>
<tr>
<td>Median, range</td>
<td>(-0.11-0.52)</td>
<td>(-)</td>
</tr>
<tr>
<td>HIV-1 RNA (copies/ml)</td>
<td>-</td>
<td>55 &lt;28</td>
</tr>
<tr>
<td>Median, range</td>
<td>(&lt;15-&lt;79)</td>
<td>(57-3200)</td>
</tr>
</tbody>
</table>

* Comparison of characteristics between patients on maintenance therapy with an undetectable and detectable plasma HIV-1 RNA concentration at week 36 (Wilcoxon rank-sum test). bChange from baseline at week 24. cK = virion clearance rate constant for HIV-1 RNA in plasma. dPlasma HIV-1 RNA concentration at week 36.

Patients on maintenance therapy, with or without a detectable plasma concentration of HIV-1 RNA at week 36, were similar in plasma concentration of HIV-1 RNA at baseline and change in CD4 and CD8 cell-counts during induction therapy (table 2). The time to a plasma concentration of HIV-1 RNA of less than 50 copies/mL differed between patients with or without a sustained viral suppression during maintenance therapy (figure 3, p=0.061). Subsequently, the initial virion-clearance rate (k) was calculated for each patient. The virion-clearance rate was similar for patients on maintenance therapy and on prolonged induction therapy (Wilcoxon's rank-sum test: p = 0.40, table 2). However, in the patients on maintenance therapy, this rate was significantly higher for patients with an undetectable plasma concentration of HIV-1 RNA than for patients with a detectable plasma concentration of HIV-1 RNA at week 36 (k=0.35 vs k=0.19, respectively (p=0.008), table 2).
Figure 3  Kaplan-Meier curve for time to below 50 HIV-1 RNA copies/mL in plasma of patients on maintenance therapy. The thin line represents patients with a detectable plasma HIV-1 RNA concentration at week 36, the bold line represents patients with a undetectable plasma HIV-1 RNA concentration at week 36. Log rank statistic was performed for these two groups. The dashed line represents patients on prolonged induction therapy with an undetectable plasma HIV-1 RNA concentration at week 36.
Discussion

Despite rapid suppression of viral replication during the induction phase, maintenance therapy with two drugs proved to be inferior to prolonged induction therapy. Only 10 weeks after randomisation, plasma concentrations of HIV-1 had become detectable again in 64% of the patients switching to maintenance therapy, versus 9% of those receiving prolonged induction therapy. Our results are supported by those of the Trilège\textsuperscript{16} and ACTG 343 trials.\textsuperscript{17} In these two large randomised trials induction therapy (zidovudine, lamivudine, and indinavir) followed by maintenance therapy with two drugs, or even one drug, was investigated. A higher proportion of patients with measurable recurrence of viral replication was observed in the group of patients receiving maintenance therapy than in the group of patients remaining on the triple drug therapy. Our results and those of the Trilège and ACTG 343 trials led us to amend the protocol and discontinue randomisation at week 26.

Although the results of three randomised trials on induction-maintenance therapy regimens for HIV-1 infection have thus far been disappointing, it is intriguing that not all patients have immediate rebound of viral replication. Moreover, in the unrelated INCAS trial,\textsuperscript{3} five antiretroviral-naive patients who had begun treatment with zidovudine, didanosine, and nevirapine, violated the study protocol and discontinued didanosine for at least 6 weeks after plasma concentrations of HIV-1 RNA below the limit of detection (20 copies/mL) were achieved. They were all documented to have sustained viral suppression at this concentration during the period of ddl interruption.\textsuperscript{22} Just like a small proportion of the patients in our study, these proof-of-concept cases seem to succeed in maintaining viral suppression after a reduction in the number of drugs taken.

Are there specific successful strategies of induction therapy followed by maintenance therapy or are there individual factors in patients that determine whether maintenance therapy is feasible? It has been shown that most cases of lasting viral suppression are only attained in patients whose plasma concentration of HIV-1 RNA can be maintained at very low concentrations (20-50 copies/mL).\textsuperscript{10,23} In our study, randomisation to maintenance therapy was therefore restricted to patients with undetectable HIV-1 RNA plasma concentrations (<50 copies/mL). The ACTG 343 study showed that a rapid reduction of HIV-1 RNA in plasma after the start of treatment may be important as well. The time to an undetectable plasma concentration (<200 copies/mL) of HIV-1 RNA in the induction phase was a predictor of virological failure during maintenance therapy. Likewise, in our study, patients on maintenance therapy with a sustained undetectable plasma concentration...
concentration of HIV-1 RNA at week 36 had a faster reduction to a plasma concentration of HIV-1 RNA of less than 50 copies/mL during induction therapy than those with recurrence of a detectable plasma HIV-1 RNA concentration at week 36. When the initial virion-clearance rate was calculated, a significantly higher clearance rate was found in patients on maintenance therapy with an undetectable plasma concentration of HIV-1 RNA than in patients with a detectable plasma concentration of HIV-1 RNA at week 36. This implies that only patients with a relatively high initial virion-clearance rate succeeded to show a sustained undetectable plasma concentration of HIV-1 RNA during maintenance therapy. In addition, patients on prolonged induction therapy with a sustained viral suppression at week 36 had a virion-clearance rate comparable with the patients on maintenance therapy with a detectable plasma concentration of HIV-1 RNA. Apparently, a less rapid virological control in the first phase of the treatment may allow for viral escape during maintenance therapy and not during prolonged induction therapy. The approach of comparing patients who did or did not succeed to suppress virus replication during maintenance therapy, as regards viral-decay characteristics early in the induction phase, is a hypothesis-generating approach. This subgroup analysis is based on small numbers and should therefore be interpreted with caution. Future trials implementing a prospective approach in a different setting can estimate and therefore validate the prognostic values of these characteristics. The HIV-1 clearance rate might be influenced by the degree of exposure of the virus to antiretroviral agents for each patient. Hoetelmans and colleagues\(^24\) showed that patients with a higher exposure to nelfinavir or saquinavir had a faster initial virion-clearance rate, while Weverling and colleagues\(^25\) showed that five antiretroviral agents were superior to three agents in attaining an undetectable plasma concentration of HIV-1 RNA. The relevance of improving the potency of induction therapy for the feasibility of maintenance therapy may, however, eventually be limited. Tissue characteristics, such as the blood-brain barrier, and the obligate intracellular phosphorylation of the nucleoside reverse transcriptase inhibitors, may prove to be pharmacological limitations that impede the success of maintenance therapy to control replication of HIV-1 in body compartments other than the blood.\(^{26,27}\)

If it is possible for the virus to replicate during maintenance therapy, the virus escape might be aided by the availability of a large pool of target cells. The influence of target cell availability on the rebound of wild-type virus after cessation of therapy and the emergence of resistant mutants during HAART has been described and mathematically modelled.\(^ {28,29}\) This predator-prey phenomenon seems
to be of relevance to induction therapy followed by maintenance therapy because the increase of CD4 cells was a predictor of virological failure of maintenance therapy in the ACTG 343 study. The induction therapy in our study induces a median rise in CD4 cell count of more than 200 cells/µL. Although the small numbers of patients in the different arms were comparable for the change in CD4 cell count, this increase may have adversely affected the suppression of viral replication during maintenance therapy.

We did not observe a difference in CD4 cell counts at week 36 between patients with sustained viral suppression and those with detectable plasma HIV-1RNA. Kaufmann and colleagues\(^30\) have reported that even in individuals who remain viraemic while receiving HAART, a substantial rise in CD4 cells may be seen. The rise, however, appeared to be less than that seen in individuals with undetectable viraemia. Moreover, Li and colleagues\(^31\) have reported that recovery of CD4 T-cell function is dependent on the amplitude and duration of viral-load reduction. This suggests that CD4 cell numbers and the recovery of CD4 T-cell function will eventually be less in the patients with inferior viral suppression during maintenance therapy. The 10-week period between randomisation and virological failure in our study would, however, appear to be too short to detect such differences.

The quadruple drug regimen of stavudine, lamivudine, saquinavir, and nelfinavir provided a potent induction regimen. Nevertheless, only patients with a relatively high initial virion-clearance rate had a sustained suppression of viral replication during maintenance therapy. The initial virion-clearance rate might be used as a parameter for the potency of the antiretroviral regimen used in an individual patient. Our findings, and those reported by others,\(^16\),\(^17\) make it currently inadvisable to continue attempts at induction therapy followed by maintenance therapy in day-to-day practice.
Chapter 2

Acknowledgements

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