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

Reijers, M.H.E.

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Chapter 3

The ADAM study continued: maintenance therapy after 50 weeks of induction therapy.


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Chapter 3

Abstract

Introduction

Several studies have shown an inferior suppression of viral replication during maintenance therapy compared to continued induction therapy in HIV-1 infected patients after three to six months of induction therapy. The ADAM study investigated whether the duration of induction therapy was of importance to the risk of virological failure during maintenance therapy.

Methods

Antiretroviral therapy naive HIV-1 infected subjects were treated with induction therapy ( stavudine + lamivudine + saquinavir + nelfinavir) for either 26 or 50 weeks. Patients were randomised to maintenance therapy (either stavudine + nelfinavir or saquinavir + nelfinavir) or prolonged quadruple therapy at weeks 26 or 50. The patients randomised to maintenance or continued quadruple therapy were compared for the proportion of patients with a plasma HIV-1 RNA concentration > LLQ during follow-up. Subsequently, the time to a viral rebound during maintenance therapy was compared among the patients randomised at week 26 and at week 50.

Results

In total 65 patients were included, of whom 16 were randomised to maintenance therapy at week 26. An interim analysis demonstrated inferior suppression of viral replication during maintenance therapy compared to prolonged induction therapy. Randomisation at week 26 and further enrolment were discontinued. At week 50, 17 of the remaining 49 patients were randomised. Two out of seven patients randomised to continued quadruple therapy at week 50, decided to discontinue their study medication. Two of 10 patients randomised to maintenance therapy, refused maintenance therapy. Treatment failure was observed in 4/8 patients on maintenance therapy compared to only 1/5 patients on continued quadruple therapy (p-value is 0.56). The time to a plasma HIV-1 RNA concentration above the LLQ or above 400 copies/mL during maintenance therapy was comparable among patients randomised after 26 and 50 weeks of induction therapy.
Conclusion

Patients randomised to maintenance therapy after 26 weeks or 50 weeks of induction therapy seem to have an equally rapid rebound to a detectable HIV-1 RNA concentration in plasma. Apparently, a longer period of quadruple drug therapy does not postpone viral rebound.
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Introduction

Induction-maintenance regimens in antiretroviral therapy might improve patient compliance by facilitating drug intake, reducing pill burden and reducing toxicity of antiretroviral drug regimens. The induction-maintenance strategy was investigated in three studies: the ACTG 343, the Trilège, and the ADAM study. These three studies used different periods of induction therapy, patient populations, and antiretroviral agents. Nevertheless, each trial indicated that maintenance therapy with two or one antiretroviral drug could not sustain suppression of viral replication in a significant proportion of patients. Although these results were disappointing, factors associated to treatment failure during maintenance therapy could be identified.

First of all, a lower potency of induction therapy by means of viral decay rate or time to undetectability was associated with virological failure during maintenance therapy. Secondly, the level of increase in CD4+ T-cells was a predictor of virological failure during maintenance therapy in the ACTG 343 study, indicating a role for the 'predator-prey' phenomenon in viral rebound (e.g. a large pool of target cells facilitates the outgrowth of virus). Finally, the presence of drug resistant mutants at the start of therapy increased the risk for virological failure during maintenance therapy.

The duration of the induction therapy varied from three to six months in these three studies. Perhaps this was too short to make maintenance therapy possible. At the time of the design of the ADAM study, it was speculated that with the duration of therapy, the amount of HIV-1 RNA in cellular and anatomical reservoirs would further decrease, reducing the risk of viral escape.

The design of the ADAM study therefore provided the opportunity to investigate whether the duration of induction therapy was of significance for the efficacy of maintenance therapy. Albeit with small patient numbers, we here present the efficacy of maintenance therapy after induction therapy with a quadruple drug regimen for 50 weeks and discuss the effect of the duration of induction therapy on the efficacy of maintenance therapy.
Material and 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 the 6th of April 1998. Patients, aged 18 years or older, were eligible if they had at least 200 CD4+ T-cells per mm$^3$ in their peripheral blood, 1000 or more HIV-1 RNA copies/mL in plasma and if they were naive for antiretroviral therapy. Further exclusion criteria have previously been described. The study was approved by the institutional review boards of all participating institutions.

Study design

All patients started the induction phase with a quadruple drug regimen consisting of stavudine (d4T, 40 mg bid, or 30 mg bid if body weight <60 kg), lamivudine (3TC, 150 mg bid), saquinavir (SQV) hard-gelatin capsules (saquinavir-HGC, 600 mg tid) and nelfinavir (NFV, 750 mg tid). When saquinavir soft-gelatin capsules (saquinavir-SGC) became available (November 1st, 1997), all patients using saquinavir-HGC switched to saquinavir-SGC (800 mg tid). Patients were switched to saquinavir-SGC (1200 mg bid) and nelfinavir (1250 mg bid) on September 1st, 1998, in order to facilitate drug intake. Patients were instructed to take their medication with food. One of the objectives of the trial was to compare patients randomised after 26 weeks of induction therapy with patients randomised after 50 weeks of induction therapy for the efficacy of maintenance therapy. However, further enrolment and the randomisation at week 26 were discontinued on the 6th of April 1998, since the interim analysis showed an inferior suppression of viral replication in the maintenance therapy arms. The trial was continued to investigate the efficacy of maintenance therapy after 50 weeks of induction therapy.

At week 50, patients with a plasma HIV-1 RNA concentration below the lower limit of quantification (LLQ) of an ultrasensitive assay at both week 48 and 49 were randomised to continued quadruple drug therapy or to one of the following maintenance regimens: stavudine + nelfinavir or saquinavir + nelfinavir. Patients were allocated using a computerised minimisation program, weighting imbalance of allocations according to the CD4+ T-cell count (more or less than 400 cells/mm$^3$ ) and HIV-1 RNA (more or less than 50,000 copies/mL) at baseline, and a plasma HIV-1 RNA concentration >LLQ at week 24/25. Treatment allocation was
performed in a 1:1:1 ratio (continued quadruple drug therapy, stavudine + nelfinavir or saquinavir + nelfinavir, respectively).

Follow-up

Patients not yet randomised at week 26 were scheduled to visit the outpatient clinic for clinical assessment and routine laboratory monitoring at the start of treatment and at weeks 1, 2, 4, 8, 16, 24, 25, 26, 36, 48, 49, 50, 51, 52, and every following month. Laboratory monitoring included plasma HIV-1 RNA concentration and CD4+ and CD8+ T-cell count, except for weeks 25, 49, 51, and 52 when only a plasma HIV-1 RNA concentration assessment was done. If patients were not randomised or had discontinued their medication for other reasons, follow-up was continued every three months. Assessment of saquinavir and nelfinavir drug concentrations was done batchwise on stored plasma.

HIV-1 RNA Quantification

During the first 26 weeks, HIV-1 RNA concentrations in plasma were measured using commercially available assays: NASBA and NucliSens HIV-1 RNA QT (Organon Teknika, Boxtel, the Netherlands) with a fixed limit of quantification of 1000 and 400 HIV-1 RNA copies per mL, respectively, or the Amplicor assay (Roche Diagnostic Systems, Inc., Branchburg, NJ, USA) with a variable limit of quantification (median quantification limit: 248 copies/mL, range: 125-755 copies/mL (n=53)). If a plasma HIV-1 RNA concentration below the limit of quantification was reached, a more sensitive assay was used: either the NucliSens HIV-1 RNA QT assay with a fixed limit of quantification of 50 copies/mL or the ultrasensitive procedure of the Roche Amplicor assay with a variable lower limit of quantification (LLQ). At week 26 and during further follow-up, only the ultrasensitive procedure of the Roche Amplicor assay was used with a median LLQ of 22 copies/mL (range: 9-107 copies/mL (n=384)). After July 1999, the COBAS Amplicor assay was used with a fixed quantification limit at 50 copies/mL.

Endpoint definition and discontinuations

During the induction period, treatment failure was defined as two consecutive assessments with a plasma HIV-1 RNA concentration above 400 copies per mL. As outlined before, the primary endpoint after randomisation was a plasma HIV-1 RNA concentration above the LLQ of the ultrasensitive assay at a time beyond week 50. Patients with a detectable HIV-1 RNA concentration 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 to change their therapy to three completely different antiretroviral agents, respectively.

In case of grade 4 toxicity, or grade 3 toxicity\textsuperscript{11} without improvement after temporary discontinuation (max. 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 at the discretion of the investigator.

**Assessment of drug exposure**

The quantification of nelfinavir and saquinavir plasma concentrations was performed using a validated and sensitive reverse-phase high-performance liquid chromatography (RP-HPLC) assay.\textsuperscript{12} To adjust for the time interval between drug ingestion and the drawing of the sample, the drug plasma concentration ratio was calculated for each sample, as described elsewhere.\textsuperscript{8,13} These plasma concentrations ratios were used as a measure for exposure to saquinavir and nelfinavir.

**Analysis**

**Induction phase**

The plasma HIV-1 RNA concentrations and median CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cell counts over time were described for patients on induction therapy. The proportion of patients on quadruple drug treatment, with a plasma HIV-1 RNA concentration below 400 copies/mL and below the LLQ of the used assay was calculated at each time point. The proportion of patients experiencing a certain side effect (severity: \( \geq \) grade 2) was assessed. In addition, the duration of the side effect within 50 weeks of quadruple drug induction therapy was calculated.

**Drug exposure**

The median drug concentration ratio was calculated for each patient. Median drug concentration ratios of saquinavir and nelfinavir during the use of saquinavir-HGC and saquinavir-SCC were compared. To evaluate the effect of time and the effect of the introduction of saquinavir-SCC on the plasma concentration ratios of saquinavir and nelfinavir, an analysis of repeated measures with mixed effects was performed (Mixed Models procedure of the statistical package SAS 6.12 for Windows).
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Maintenance phase

To evaluate the efficacy of maintenance therapy after 50 weeks of induction therapy, the proportion of patients with a plasma HIV-1 RNA concentration above the LLQ of the ultrasensitive assay at week 60 was compared between patients randomised to continued quadruple therapy and to maintenance therapy. In addition, the occurrence of treatment failure (a plasma HIV-1 RNA concentration above 400 copies/mL) during the available follow-up was compared among these same patients (Wilcoxon test).

Subsequently, patients randomised to maintenance therapy at week 26 and week 50 were compared for baseline characteristics, change in CD4+ T-cell count at time of randomisation, initial virion-clearance rate, and median concentration ratio of saquinavir and nelfinavir per patient. Finally, to compare the efficacy of maintenance therapy after 26 and 50 weeks of induction, the time to a plasma HIV-1 RNA concentration above the LLQ of the ultrasensitive assay and above 400 copies/mL during maintenance therapy was compared for patients randomised at week 26 and at week 50. Statistical comparisons were based on the Wilcoxon test.
Results

Patients

A total of 65 patients (61 males, 94%) was enrolled (Figure 1). Baseline characteristics have already been reported. The median age at baseline was 39 years. The CD4$^+$ T-cell count at baseline was 410 cells/μL and the median plasma HIV-1 RNA concentration 4.51 log₁₀ copies/mL. Three patients were lost to follow-up (see also Figure 1).

Induction phase

Efficacy

The response of the CD4$^+$ T-cell count during 50 weeks of quadruple drug therapy is shown in Figure 2A. The median CD4$^+$ T-cell count rose from 410 cells/μL at baseline to 560 cells/μL at week 24 and to 680 cells/μL at week 48. The median CD4$^+$ T-cell count as a percentage of the total lymphocyte count rose from 21% at baseline to 30% at week 24 and 32% at week 48. The mean CD8$^+$ T-cell count was 1050 cells/μL at baseline and 950 cells/μL, and 940 cells/μL at weeks 24 and 48, respectively. The median CD8$^+$ T-cell count as a percentage of the total lymphocyte count showed a decrease from 61% at baseline to 49% and 46% at weeks 24 and 48, respectively. The decline in plasma HIV-1 RNA concentration during treatment with the quadruple drug regimen is depicted in Figure 2B. Two patients had treatment failure on quadruple drug therapy before randomisation at week 50. The percentage of patients with a plasma HIV-1 RNA concentration below the LLQ of the ultrasensitive assay during quadruple drug therapy was 69% at week 24 and 71% at week 48. The proportion of patients with a plasma HIV-1 RNA concentration below 400 copies/mL was higher (96% and 97%, respectively).

Toxicity and discontinuations

Side effects with a severity grade 2 or more were reported in 44 out of 65 patients. Of the ten patients who discontinued their study medication for reasons of toxicity, seven patients stopped the medication within the first 26 weeks as described previously (Figure 1). The remaining three patients complained about general malaise, depression or lipodystrophy as the reason for discontinuation. Toxicity during 50 weeks of induction therapy mainly concerned gastro-intestinal complaints and fatigue. Twenty-seven of the 65 patients had diarrhoea (median duration 56 days (interquartile range (IQR): 18-153 days), and eight patients had complaints of abdominal pain (median duration 50 days (IQR 7-100 days)).
**Total of patients included at week 0**
- Toxicity (n=7)
- Lost to follow-up (n=2)
- Treatment failure (n=1)

**Patients on quadruple induction therapy at week 24**
- Randomised to maintenance at week 26 (n=16)
- Toxicity (n=3)
- Lost to follow-up (n=1)
- Treatment failure (n=1)

**Patients on quadruple induction therapy at week 48**
- HIV-1 RNA concentration >LLQ at week 48/49 (n=9)
- Patient request (n=8)

**Patients randomised at week 50**
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV
- Patient refused randomisation
- Discontinuation due to toxicity

**Patients with a follow-up of 60 weeks**
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV

**Patients with HIV-1 RNA >LLQ at week 60**
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV

**Patients with treatment failure during follow-up**
- Prolonged induction therapy
- Maintenance therapy
  - d4T + NFV
  - SQV + NFV

**Figure 1** Trial profile. The numbers in shaded boxes indicate patients who discontinued the study medication.
Fatigue occurred in eight patients and was usually quite persistent (median duration 83 days (IQR 41-224)). Laboratory monitoring revealed raised liver enzymes in 8/65 patients. Cholesterol levels in plasma were elevated in 28/65 patients. However, in only 6/65 patients cholesterol temporarily rose above 7.7 mmol/L. Triglyceride elevations in plasma were observed in 13/65 patients, of whom only two were found to have triglyceride levels above 8.4 mmol/L in plasma.

Drug exposure

The median plasma drug concentration ratio per patient (n=56) was 0.78 for saquinavir (IQR: 0.42-1.25) and 0.61 for nelfinavir (IQR: 0.45-0.83). Median plasma concentration ratios of saquinavir were lower during the use of saquinavir-HGC than during the use of saquinavir-SGC (0.56 (IQR 0.28-1.28) and 0.81 (IQR 0.41-1.67) respectively, p=0.002). Median nelfinavir ratios were comparable among the two treatment periods (0.61 (IQR 0.41-0.89) and 0.60 (IQR 0.37-0.85), respectively; p=0.46). These findings were confirmed, using repeated measures analysis with mixed effects to investigate the effect of time and the use of saquinavir-SGC. High plasma concentrations of saquinavir were associated with the use of saquinavir-SGC (test of fixed effects, p=0.03 and p=0.27 for saquinavir and nelfinavir, respectively). No change in plasma drug concentration ratios could be found over time (test of fixed effects; p=0.53 and p=0.09 for saquinavir and nelfinavir, respectively).

For the evaluation of the period that saquinavir-SGC and nelfinavir were used in a bid regimen, not enough data were available at the time of analysis.

Maintenance phase

Patients

At week 50, 17 of the 65 patients were randomised (Figure 1). Reasons for not randomising at week 50 were: lost to follow-up (3), prior randomisation to maintenance therapy (16), treatment failure (2), toxicity (10), a plasma HIV-1 RNA concentration above the LLQ at week 48 and 49 (9) or at the request of the patient (8). One of the seven patients randomised to continued quadruple therapy decided to take a 'drug holiday' and another patient experienced lipodystrophy, leading to a switch of therapy. Ten patients were randomised to maintenance therapy with either stavudine + nelfinavir (n=6) or saquinavir + nelfinavir (n=4). One patient in each maintenance arm refused maintenance therapy (Figure 1).
Figure 2  Median CD4\(^+\) T-cell count and plasma HIV-1 RNA concentration during the induction therapy. The dashed line represents 50 copies/mL or 1.69 log\(_{10}\) copies/mL; Bars represent interquartile ranges.

Panel A: Median CD4\(^+\) T-cell count;
Panel B: Median log\(_{10}\) HIV-1 RNA copies/mL in plasma.
Efficacy

At week 60, no difference was observed between the randomisation arms regarding the proportion of patients with a quantifiable plasma HIV-1 RNA concentration (Figure 1). One out of five patients in the continued quadruple drug therapy arm had a plasma HIV-1 RNA concentration above the LLQ compared to 3 out of 8 patients on maintenance therapy. After a median follow-up of 34 weeks in the quadruple therapy arm and 46 and 40 weeks in the two maintenance therapy arms ( stavudine + nelfinavir and saquinavir + nelfinavir, respectively), treatment failure had occurred in one out of five patients (20%) using quadruple drug therapy, and in four out of eight patients (50%) using maintenance therapy (Fisher exact: p=0.56; Figure 1).

Table 1 The characteristics of patients randomised to maintenance therapy after 26 or 50 weeks of induction therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Week 26 (n=16)</th>
<th>Week 50 (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4(^+) T-cell count (x10(^6)cells/L)(^a)</td>
<td>360 (320-570)</td>
<td>370 (320-440)</td>
<td>0.71</td>
</tr>
<tr>
<td>CD8(^+) T-cell count (x10(^6)cells/L)(^a)</td>
<td>950 (750-1490)</td>
<td>103 (970-1760)</td>
<td>0.16</td>
</tr>
<tr>
<td>Log(_{10}) HIV-1 RNA (copies/mL)(^a)</td>
<td>4.69 (4.09-5.04)</td>
<td>4.32 (3.99-4.57)</td>
<td>0.15</td>
</tr>
<tr>
<td>At randomisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Delta)CD4(^+) T-cell count (x10(^6) cells/L)(^a)</td>
<td>200 (120-310)</td>
<td>280 (100-470)</td>
<td>0.33</td>
</tr>
<tr>
<td>(\Delta)CD8(^+) T-cell count (x10(^6) cells/L)(^a)</td>
<td>-30 (-290-250)</td>
<td>40 (-290-320)</td>
<td>0.86</td>
</tr>
<tr>
<td>Virological decline during induction therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial virion-clearance rate (days(^{-1}))(^a)</td>
<td>0.31 (0.25-0.34)</td>
<td>0.30 (0.28-0.34)</td>
<td>0.81</td>
</tr>
<tr>
<td>Median drug concentration ratio in plasma within the first 26 weeks of induction therapy(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saquinavir(^a)</td>
<td>0. 0.18-0.74</td>
<td>0.86 0.62-1.51</td>
<td>0.03</td>
</tr>
<tr>
<td>nelfinavir(^a)</td>
<td>0. 0.41-0.75</td>
<td>0.62 0.46-0.74</td>
<td>0.88</td>
</tr>
</tbody>
</table>

\(^a\) Values are median (interquartile range); \(^b\) For the patients randomised at week 50: n=8.

Subsequently, we compared patients randomised to maintenance therapy at week 26 (n=16) and week 50 (n=10, Table 1). Patients were comparable for their baseline characteristics and change in CD4\(^+\) and CD8\(^+\) T-cell counts at time of randomisation. Compared to patients randomised at week 26, patients randomised at week 50 had significantly higher plasma concentration ratios of saquinavir and were more often treated with saquinavir-SGC during the first 26 weeks of induction therapy (p=0.03 and p<0.001, respectively; Table 1).
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The time to a plasma HIV-1 RNA concentration above the LLQ of the ultrasensitive assay or above 400 copies/mL during maintenance therapy was comparable among patients randomised to maintenance therapy after 26 or 50 weeks of induction therapy, as is illustrated in the Kaplan Meier plots (Figure 3A and 3B, respectively).

**Figure 3** Kaplan Meier curve for the time to a plasma HIV-1 RNA concentration above the variable lower limit of quantification of the ultrasensitive assay (median quantification limit: 22 copies/mL; panel A) or above 400 copies/mL (panel B) during maintenance therapy. The solid line represents the patients \( n = 14 \) randomised to maintenance therapy at week 26, the dashed line represents the patients \( n = 10 \) randomised to maintenance therapy at week 50. The P-value was calculated using Log-Rank testing.
Discussion

Maintenance therapy in HIV-1 infected patients, even after an induction therapy for 50 weeks, seemed not efficacious. Four out of eight patients randomised to maintenance therapy were found to have a rebound of viral replication in contrast to one out of five patients randomised to continued quadruple drug therapy. Although the difference was not statistically significant, prolonging the induction therapy from 26 to 50 weeks does not seem to contribute to the efficacy of the maintenance regimen, since patients randomised after 50 weeks of induction therapy had an equally rapid rebound of the plasma HIV-1 RNA concentration to >400 copies/mL than patients randomised after 26 weeks of induction therapy.

The switch from saquinavir-HGC (600 mg tid) to saquinavir-SCC (800 mg tid) did result in a higher drug exposure during induction therapy in patients randomised to maintenance therapy at week 50. However, this did not result in differences in the viral decline of these patients compared to patients randomised to maintenance therapy at week 26 (Table 1), nor did it result in improved suppression of viral replication during maintenance therapy.

Although only two patients discontinued the study medication for reason of virological failure during the induction therapy, it is remarkable that a considerable proportion of the patients who discontinued medication was not available for randomisation at week 50. Besides a drop-out of patients due to toxicity (mostly within the first 26 weeks), a considerable amount of patients refused study medication for personal reasons, both before (n=8) and after (n=2) randomisation. It is likely that the negative results of the interim analysis have influenced patients to abandon randomisation at week 50. This is in line with results of the quality of life study indicating that the knowledge of an incomplete suppression of the viral load was of significance to the quality of life of the patients randomised to maintenance therapy. Finally, the lower limit of detection was set to 50 copies/mL at week 24/25 but was lower and variable at week 48/49. We therefore may have been more stringent in selecting patients for randomisation at week 50.

With the low number of patients randomised at week 50, it is difficult to demonstrate a statistically significant difference in virological failure between patients randomised to maintenance therapy and to continued quadruple drug therapy. A population of 80 patients would be needed to show statistical significance for the difference observed (50% vs. 20%), with 80% power. This,
however, seems not realistic, since patients already tended to discontinue the study at the knowledge of results from earlier publications, as discussed above.

Since the design of the study, several studies have indicated that even after long-term suppression of viral replication below 50 copies/mL, low level replication remains present.\textsuperscript{15-18} It is therefore not surprising, that viral replication can expand when the antiviral potency is reduced during maintenance therapy. In the ACTG 343 and Trilège studies, failure during maintenance therapy indeed appeared to be highly attributable to insufficient potency of the maintenance regimen.\textsuperscript{19,20}

Target cell availability was already suggested to be of significance to failure of induction-maintenance regimens.\textsuperscript{2} In our study, no difference in the increase of CD4\textsuperscript{+} T-cell count was observed among the patients randomised at week 26 or at week 50 (Table 1). Fleury et al. recently showed, that the pool of proliferating CD4\textsuperscript{+} T-cells was found to be enlarged for at least 48 weeks after the start of antiretroviral treatment, suggesting that randomisation after 50 weeks of induction therapy was still accompanied by increased target cell availability.\textsuperscript{21} Maybe future induction-maintenance strategies could decrease target cell availability by the use of agents that selectively suppress the activation of CD4\textsuperscript{+} T-cell counts.\textsuperscript{22}

With the increasing awareness of the disadvantages of antiretroviral therapy, strategies reducing pill burden, toxicity and complexity of regimens are needed more than ever. Unfortunately, we here again show that induction-maintenance strategies with the currently available classes of agents are not successful.\textsuperscript{24} In future studies targeting induction-maintenance therapy in HIV-1 infected patients, more benefit may be expected from an increase in the antiretroviral efficacy of the maintenance regimen, or a reduction of the required antiretroviral efficacy during maintenance therapy than from a prolongation of the induction phase beyond 26 weeks.
Appendix

In the ADAM Study Team participated:
M. Roos, P. van Swieten, S.M. Bruisten, and H. Schuitemaker, Dept. of Clinical Viro-Immunology, CLB, Sanquin Blood Supply Foundation, Amsterdam; F. de Wolf, and S. Jurriaans, Dept. of Human Retrovirology, Academic Medical Centre, University of Amsterdam, Amsterdam; R.M.W. Hoetelmans, and R.P.G. Van Heeswijk, Dept. of Pharmacy and Pharmacology, Slotervaart Hospital, Amsterdam, the Netherlands; F. de Wolf, Dept. of Human Retrovirology, Academic Medical Centre, University of Amsterdam, Amsterdam; R.M.W. Hoetelmans, and R.P.G. Van Heeswijk, Dept. of Pharmacy and Pharmacology, Slotervaart Hospital, Amsterdam, the Netherlands; P. Portegies, Dept. of Neurology, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; G.J. Weverling, Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam; H.M. Weigel, K. Brinkman, and P.H.J. Frissen, Dept. of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam; R.W. Ten Kate, Kennemer Gasthuis, Haarlem; J.W. Mulder, and P.L. Meenhorst; Dept. of Internal Medicine, Slotervaart Hospital, Amsterdam; H. Sprenger, and G. Law, Dept. of Internal Medicine, Academic Hospital Groningen, Groningen; H.J.M. ter Hofstede, Dept. of Internal Medicine, Academic Hospital Nijmegen, Nijmegen; C. Richter, Dept. of Internal Medicine, Hospital Rijnstate, Arnhem; J.M.A. Lange, P. Reiss, M.H.E. Reijers, F.W.N.M. Wit, and R. van Leeuwen, National AIDS Therapy and Evaluation Centre, Amsterdam, Academic Medical Centre, University of Amsterdam, Amsterdam; the Netherlands.

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