Comparison of Two Once-Daily Regimens with a Regimen Consisting of Nelfinavir, Didanosine, and Stavudine in Antiretroviral Therapy–Naïve Adults: 48-Week Results from the Antiretroviral Regimen Evaluation Study (ARES)

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Background: To improve the dosing frequency and pill burden of antiretroviral therapy, we compared two once-daily dosed regimens to a twice-daily dosed regimen. **Method:** HIV-1–infected, antiretroviral drug–naïve adults were randomized to either twice-daily nelfinavir and stavudine and once-daily didanosine (regimen A) or simplified once-daily dosed antiretroviral regimens consisting of nevirapine, didanosine, and lamivudine (regimen B) or saquinavir, ritonavir, didanosine, and lamivudine (regimen C). **Results:** At 48 weeks of therapy, the proportion of patients with a blood plasma HIV-1 RNA concentration (pVL) <50 copies/mL by intention-to-treat analysis was 42.3%, 50.0%, and 56.5% for regimens A (n = 26), B (n = 22), and C (n = 23), respectively. The time to a pVL <50 copies/mL for the first time was significantly shorter in regimen C, and there was significantly more progression to CDC events in regimen B. These differences are possibly due to differences in baseline characteristics. Adverse events were lowest for regimen C; more signs associated with mitochondrial toxicity occurred in regimen A. Increase in CD4 count was comparable between arms. **Conclusion:** No statistically significant difference in efficacy was found between the two investigated once-daily dosed treatment regimens (B and C) and the reference (A). Regimen C possibly had a better virological response and less toxicity than regimens A and B. **Key words:** *antiretroviral therapy–naïve, human immunodeficiency virus type 1, once-daily dosed highly active antiretroviral therapy*

The aim of highly active antiretroviral therapy (HAART) given to previously untreated individuals infected with the human immunodeficiency virus type 1 (HIV-1) is to achieve a maximal and durable viral suppression. At present, a blood plasma HIV-1 RNA concentration (plasma viral load [pVL]) below the limit of detection of 80 copies/mL is considered appropriate for this goal.[1–3] Several factors have been associated with the virological response to initial HAART.[4] Of these factors, the adherence to therapy is one of the most important.[1–4] The dosing frequency and pill burden are important factors for adherence to therapy.[1–6]

To investigate options for improvement of the

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dosing frequency and pill burden of HAART in previously untreated HIV-1–infected adults, the Antiretroviral Regimen Evaluation Study (ARES) was performed. The objective of this study was to compare the antiviral efficacy and tolerability of once-daily dosed (qd) regimens with a frequently used twice-daily dosed (bid) regimen. At the time of development and implementation of the protocol, the protease inhibitor (PI) nelfinavir in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) was considered one of the standard initial HAART regimens.

METHOD

Study Design

This was a randomized, parallel arm, open-label, multicenter study comparing the efficacy and safety of three antiretroviral regimens: a once-daily dosed (qd) nonnucleoside reverse transcriptase inhibitor (NNRTI)–based (regimen B) or qd PI-based (regimen C) or bid NNRTI plus PI-based regimen (D) with a frequently used twice-daily dosed PI-based regimen (A, the reference regimen). The regimens were:

- A: nelfinavir 1250 mg bid, didanosine 400 or 250 mg qd, and stavudine 40 or 30 mg bid
- B: nevirapine 400 mg qd, didanosine 400 or 250 mg qd, and lamivudine 300 mg qd
- C: saquinavir soft gelatin capsule (sgc) (Fortovase®) 1600 mg qd, ritonavir 100 mg qd, didanosine 400 or 250 mg qd, and lamivudine 300 mg qd
- D: nelfinavir 1500 mg bid, nevirapine 200 mg bid, didanosine 400 or 250 mg qd, stavudine 40 or 30 mg bid, and abacavir 300 mg bid

The dose of didanosine and stavudine depended on whether the body weight was below (250 mg and 30 mg, respectively) or above 60 kg (400 mg and 40 mg, respectively). Up to October 2000, didanosine chewing tablets were used and thereafter the enteric-coated capsules were used. Didanosine was administered in a fasting state, defined as minimally 1 hour before or 2 hours after a meal. Nelfinavir and saquinavir sgc were administered with food. Nevirapine had a lead-in dose of 200 mg qd during the first 14 days.

There were three randomization strategies: patients could choose to be randomized to one of these four antiretroviral regimens or to regimens A, B, and C or to regimens A and D. This strategy was chosen to give patients the opportunity either to avoid the intensive, high pill burden and more toxic regimen D or to increase their chance to be randomized to regimen D.

The primary study objective was to compare the proportion of participants with a pVL below the level of detection between the bid PI-based reference regimen and the other three regimens after 48 and 96 weeks of treatment. Secondary objectives were to compare with the reference regimen (a) the time to the pVL lower limit of detection (50 copies/mL) for the first time, (b) virological failure, (c) treatment failure, and (d) changes in the CD4+ T-lymphocyte (CD4) count.

Seven hospitals in The Netherlands participated in the ARES study. The study was approved by the institutional review board of each participating site. All participating patients gave their written informed consent.

Study Patients

Patients were eligible for the study if they were naïve for antiretroviral drugs and had an indication to start antiretroviral therapy. Other inclusion criteria were an age of 18 years or older, a pVL ≥5,000 copies/mL, and, for women of child-bearing potential, a negative urine pregnancy test within 28 days of baseline assessment and use of contraception with a barrier method. Exclusion criteria were an expected noncompliance with the protocol; excessive alcohol and elicit drug use; a history of pancreatitis, grade 3 or 4 hyperbilirubinemia, and/or elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) according to the AIDS Clinical Trial Group (ACTG) toxicity grading scale (7); a hemoglobin level <6.3 mmol/L for men and <5.7 mmol/L for women; a neutrophil count $<1.0 \times 10^9$/L; a platelet count $<75 \times 10^9$/L; pregnant and/or breast-feeding women; presence of a severe medical condition; and concomitant use of drugs that are contraindicated with use of PIs and/or NNRTIs.

Assessments

Visits according to the protocol were screening (up to 28 days before baseline); baseline; weeks 2, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, and 96; at virological failure; and at premature discontinuation of the

study medication. At all these visits, blood was drawn for pVL measurement. Except for weeks 2, 12, and 20, blood was drawn for CD4 count; except for weeks 2, 16, and 20, blood was drawn for standard hematology and chemistry; and except for screening, baseline, and weeks 2, 16, and 20, blood was drawn for PI or NNRTI blood plasma concentrations. At baseline and weeks 24, 48, 72, and 96, blood was drawn in a fasting state, which was defined as an interval of at least 6 hours after the last meal.

The pVL was measured with a local assay at screening and from baseline onward with the Amplicor HIV-1 Monitor 1.5 and ultra-Amplicor Cobas reverse transcriptase polymerase chain reaction assay (Roche Molecular Systems, Inc., New Jersey, USA) with a lower limit of detection of 50 copies/mL.

Virological failure was defined as one of the following: (a) a pVL >50 copies/mL and having a drop of the pVL <2 $\log_{10}$ at week 12 of treatment, (b) not achieving a pVL <200 copies/mL within 24 weeks of treatment, (c) not achieving a pVL <50 copies/mL within 48 weeks of treatment, (d) a pVL rebound from <50 copies/mL to ≥200 copies/mL on two consecutive measurements within 6 weeks or (e) after an initial decrease a pVL increase of ≥0.5 $\log_{10}$ on two consecutive measurements.

Treatment failure was defined as a composite of virological failure and/or change of the allocated regimen, whichever came first. Adverse events were graded according to the ACTG toxicity grading scale.[7]

Change of Randomization Procedure and Termination of the Study

In March 2000, the first patient was enrolled in the study. Because inclusion lagged behind and another study already had demonstrated an improved virological response with intensified treatment,[8] randomization to treatment arm D was discontinued in November 2000. At discontinuation of the randomization to arm D, 21 patients were included in the study. Nine, eight, and four patients had then chosen randomization strategies 1, 2, and 3, respectively, and seven, five, six, and three patients were randomized to regimens A, B, C, and D, respectively. In November 2002, the steering committee decided to stop enrollment in the study and in August 2003 they decided to discontinue the study prematurely. The reasons for these decisions were, first, the expectation that the desired goal of 90 (30 in each arm) eligible patients would not be achieved within a proper period of time; second, the results of the ACTG 384 study[9,10]; third, the indication from the interim analysis that statistically significant differences were not likely to be found; and, fourth, the concern of the Independent Data Monotoring Committee (IDMC) about different rates of treatment failure. In the ACTG 384 study, there was significantly more severe or dose-modifying toxicity in the regimen containing didanosine and stavudine compared to the regimen containing lamivudine and zidovudine.[9,10] At the moment of discontinuation of the study, all patients had a follow-up of at least 48 weeks.

Statistical Analysis

A sample size of 90 HIV-1–infected patients, 30 in each study arm, was estimated to be sufficient to demonstrate a 30% difference in the proportion of participants with an undetectable viral load between arms B and C and arm A, a two-sided significance level of .025, and a power of 0.80.

Interim analyses were performed on week 12 and 24 data, respectively, and were presented to an IDMC. At both occasions, the IDMC concluded that the data gave no reason to prematurely discontinue the study. However, the IDMC had concerns about different, but not statistically significant, rates of treatment failure; therefore, after the second interim analysis, they recommended that the analysis of the events be continued sequentially.

A sequential analysis is a continuous interim analysis of the available data. After each new treatment failure, the cumulative data are tested for evidence to stop or continue the study. The stopping rule can be that (1) enough evidence is reached to demonstrate a significant difference in failure rates or (2) enough evidence is reached to make it likely that the anticipated difference will not be found when the study is continued. On average, a sequential analysis requires fewer patients to come to a decision than an analysis based on fixed sample size design with the same characteristics (alpha, power, and expected difference). A sequential design guarantees the type 1 error (alpha) and the power whenever a decision to stop the study is made. After stopping the study, the effect estimate (e.g., the odds ratio [OR]) and its confidence interval (CI) have to be adjusted for the sequential

monitoring of the data, because after a sequential analysis both the parameter estimate (i.e., the logarithm of the OR) and its standard error are biased.[11] The computer program PEST was used to perform the sequential analysis.[12]

Sequential Analysis of Week 24 Data

Two parallel sequential analyses (regimen A vs. B; regimen A vs. C) were performed using a double triangular test at each time point when a treatment failure was observed before or at week 24. The design for the sequential analyses was based on the same assumptions as for the original trial, that is, assumed proportions of treatment failures of 40% for regimen A and 10% for regimens B and C, respectively, a two-sided alpha of 0.25, and a power of 0.80. Based on stopping rule 2, the comparison of regimen A versus B could be stopped after the evaluation of 49 patients (18 in A and 14 in B) and the comparison of regimen A versus C could be stopped after the evaluation of 67 patients (24 in A and 23 in C). Both sequential analyses (A vs. B; A vs. C) of the observed data could be stopped with acceptance of the null hypothesis, meaning that the hypothesized treatment difference of 30% was not found. At the time the sequential analyses indicated that the study could be stopped (for A vs. B after evaluation of, in total, 49 patients and for A vs. C after evaluation of, in total, 67 patients), 4 more patients had been included in the trial. These patients were incorporated into the final study evaluation. Thus, the odds ratios are estimated based on the data from 71 patients: 26 in arm A, 22 in arm B, and 23 in arm C. The estimated adjusted OR for treatment failure for regimen A versus B was 1.53 (97.5% CI, 0.33–8.99; the unadjusted OR was 1.44). For regimen A versus C, the adjusted OR was 3.15 (97.5% CI, 0.80–12.92; the unadjusted OR was 2.59). Therefore follow-up of the participating patients for longer than 48 weeks was discontinued.

Analysis of Week 48 Data

Data are presented as means and standard deviations or medians with interquartile range. Comparisons were made between the two once-daily regimens (B and C) versus regimen A. The intention-to-treat (ITT) population was used for the analyses, with missing data equals failure wherever applicable.

Chi-square tests and Kruskal-Wallis tests were performed on categorical and continuous data, respectively. Time to undetectability was tested by the log rank test. Data on CD4 count were tested by repeated measurements using a generalized linear model (PROC MIXED of SAS software [SAS version 8.02; SAS Institute, Cary, North Carolina, USA]). The safety analyses were performed for the ITT population, but only adverse events that occurred while the patient was using the allocated treatment were considered. Taking into account multiple testing by Bonferroni, a two-sided p value <.025 was considered statistically significant.

RESULTS

Baseline Characteristics and Follow-Up

From March 2000 until October 2002, 71 patients were randomized. In **Table 1**, the baseline characteristics are given. Remarkably, the median CD4 count in arm B was lower than in arms A and C (115 vs. 190 and 300 cells/μL), but this was not statistically significant. In arm C, the pVL was lowest (median 4.8 $\log_{10}$ copies/mL) and the percentage of asymptomatic patients was relatively high (70%).

Virological and Immunological Efficacy

Effect on HIV Load

In ITT analysis of 48-week data, the proportion of patients with a pVL <50 copies/mL was 42.3%, 50.0%, and 56.5% for regimens A, B, and C, respectively (**Table 2**; **Figure 1**). The OR (and CI) for regimen A versus B and A versus C was 1.57 (0.49–5.05) and 2.06 (0.65–6.51), respectively. For virological failure, the proportion was 50%, 45.5%, and 39.1%, respectively; for treatment failure, the proportion was 65.4%, 54.6%, and 47.8%, respectively (**Table 2**). These proportions were not statistically significantly different between regimens B and C and regimen A. However, the time to first measurement of a pVL <50 copies/mL in ITT analysis was statistically significantly different between regimens A and C (p = .01) but not between regimens A and B (p = .68) (**Figure 2**).

Table 1. Baseline characteristics of patients randomized to arms A, B, and C

Characteristic	Treatment arm		
	A	B	C
Number of patients	26	22	23
Mean age, years (*SD*)	42.3 (9.8)	35.8 (5.5)	37.4 (11.6)
Number male/female (%)	20/6 (77/23)	18/4 (82/18)	21/2 (91/9)
Number with CDC A/B/C (%)	16/5/5 (62/19/19)	12/5/5 (54/23/23)	16/3/4 (70/13/17)
Median plasma HIV-1 RNA (log_{10} copies/mL) (IQR)	5.1 (4.7–5.4)	5.0 (5.0–5.3)	4.8 (4.5–5.0)
Median CD4 (cells/μL) (IQR)	190 (110–261)	115 (20–210)	300 (120–460)

Note: arm A: nelfinavir, didanosine, stavudine; arm B: nevirapine, didanosine, lamivudine qd; arm C: saquinavir sgc, ritonavir, didanosine, lamivudine qd; CDC = Centers for Disease Control and Prevention; IQR = 25%–75% interquartile range.

Effect on CD4 Cell Count

The mean increase of the CD4 count from baseline to week 48 of therapy in ITT analysis was 117 cells/μL, 196 cells/μL, and 168 cells/μL for regimens A, B, and C, respectively, and was not statistically significantly different between regimen B or C and regimen A (**Table 2**). The increase in CD4 count was mainly within the first 12 weeks of therapy (**Figure 3**). At 24 weeks of therapy, the absolute mean CD4 count was 326, 278, and 481 cells/μL for regimens A, B, and C, respectively; at 48 weeks, it was 333, 352, and 456 cells/μL, respectively (**Figure 3**).

Serious Adverse Events

Serious Clinical Adverse Events

In arm A, seven serious clinical (grade 3 or 4) events occurred in six patients. In four patients, these adverse events were related to mitochondrial toxicity (peripheral neuropathy, 1; pancreatitis, 1; lactic acidosis, 1; lipodystrophy, 1). The fifth patient had recurring sickle cell bone crisis and has been described in a case report.[13] The sixth patient had general malaise and a pneumonia. In arm B, 12 serious clinical adverse events occurred in eight patients. These adverse events concerned rash (3 patients), fever (3), dyspnea (1), dyspepsia (1), a process in the right cerebrum (1), pneumonia (1), general malaise (1), and an elective abortion (1). Of the three cases with rash, two were related to use of nevirapine and one to clindamycin. In arm C, six serious clinical events occurred in three patients and these concerned one each of rash, epigastric pain, pancreatitis, insomnia, fatigue, and general malaise.

The proportion of patients with at least one serious clinical adverse event during 48 weeks of treatment with regimens A, B, or C was 23.1% (6/26), 36.4% (8/22), and 13.0% (3/23), respectively (**Table 2**). All adverse events were ACTG grade 3, except for the case of pancreatitis in arm C. The differences between regimen B or C and regimen A were not statistically significant.

Serious Laboratory Adverse Events

In arms A, B, and C, 8, 10, and 3 grade 3 or 4 laboratory adverse events occurred, respectively, in seven, five, and two patients, respectively. The serious laboratory adverse events were anemia, neutropenia, thrombocytopenia, and increases in liver biochemistry. All serious laboratory adverse events occurred within the first 24 weeks of therapy. The proportion of patients with at least one serious laboratory adverse event was 26.9%, 22.7%, and 8.7% for regimens A, B, and C, respectively (**Table 2**). The differences between regimen B or C and regimen A were not statistically significant.

Overall, 8 (30.8%), 12 (54.6%), and 4 (17.4%) patients in arms A, B, and C, respectively, had at least one serious clinical or laboratory adverse event. The differences were not statistically significant compared to arm A (**Table 2**).

Table 2. 48-week results: efficacy (virological and immunological), severe adverse events, new CDC events, and permanent change of allocated regimen (ITT)

	Treatment arm			*p* value comparison with A
	A (*n* = 26)	B (*n* = 22)	C (*n* = 23)	
Virological efficacy				
Percentage with pVL <50 copies/mL	42.3	50.0	56.5	A vs. B: .25 A vs. C: .33
Virological failure, number (%)	13 (50.0)	10 (45.5)	9 (39.1)	A vs. B: .75 A vs. C: .45
Treatment failure, number (%)	17 (65.4)	12 (54.6)	11 (47.8)	A vs. B: .44 A vs. C: .22
Immunological efficacy				
Mean increase CD4 count (cells/μL)	117	196	168	A vs. B: .41 A vs. C: .21
Serious adverse events				
Number serious clinical adverse events	7	12	6	
Number of patients with one or more serious clinical adverse events (%)	6 (23.1)	8 (36.4)	3 (13.0)	A vs. B: .31 A vs. C: .37
Number serious laboratory adverse events	8	10	3	
Number of patients with one or more serious laboratory adverse events (%)	7 (26.9)	5 (22.7)	2 (8.7)	A vs. B: .74 A vs. C: .10
Number of patients with one one more serious adverse events (%)	8 (30.8)	12 (54.6)	4 (17.4)	A vs. B: .10 A vs. C: .28
New CDC events				
Number of new CDC category B events	0	9	5	
Number of new CDC category C events	2	6	0	
Number of patients with one or more new CDC events (%)	2 (7.7)	9 (40.9)	4 (17.4)	A vs. B: .02 A vs. C: .55
Change of allocated therapy				
Number of patients with permanent change of allocated regimen (%)	15 (57.7)	11 (50)	7 (30.4)	A vs. B: .81 A vs. C: .10
Reason for change of regimen, number	15	13[a]	7	
Virological failure	1	7[a]	0	
Adverse events	9	5[a]	3	
Clinical progression of HIV	1	1[a]	0	
Low drug levels	2	0	0	
Lost to follow-up	1	0	2	
Patient withdrawl	1	0	0	
Interaction with comedication	0	0	1	
Start with different regimen	0	0	1	

Note: arm A: nelfinavir, didanosine, stavudine; arm B: nevirapine, didanosine, lamivudine qd; arm C: saquinavir sgc, ritonavir, didanosine, lamivudine qd; CDC = Centers for Disease Control and Prevention; ITT = intention to treat.

[a]One patient had clinical progression of a HIV-related disease, hepatitis, and virological failure at the same time.

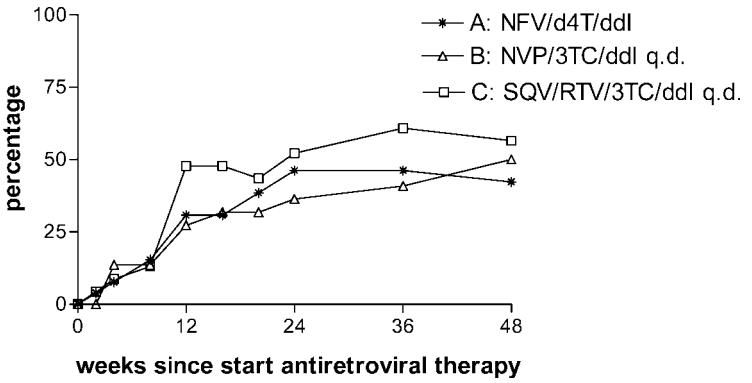

Figure 1. Percentage of patients with plasma viral load <50 copies/mL (ITT). NFV = nelfinavir; NVP = nevirapine; SQV = saquinavir; RTV = ritonavir; ddI = didanosine; d4T = stavudine; 3TC = lamivudine; qd = once daily; ITT = intention to treat.

New CDC Events

New CDC (Centers for Disease Control and Prevention) B or C events that occurred after 8 weeks of antiretroviral therapy were 2, 15, and 5 for regimens A, B, and C, respectively (**Table 2**). According to ITT analysis, the incidence of patients with at least one new CDC event was 7.7%, 40.9%, and 17.4% for regimens A, B, and C, respectively (**Table 2**). The difference between regimen B and regimen A was statistically significant (p = .02). The new CDC events emerged predominantly within the first 24 weeks of therapy. The most common CDC B event was oral candidiasis (8 cases, 6 of which were in arm B). There was no predominant CDC C event.

Change of Allocated Therapy

The percentage of patients in whom the initial therapy was changed during the period of follow-up were not statistically significantly different between study groups (57.7%, 50%, and 30.4% for regimens A, B, and C at 48 weeks, respectively; **Table 2**). It is important to note that therapy was not changed in all cases of virological failure, adverse event, or new diagnosed CDC event.

DISCUSSION

The main purpose of this study was to examine the efficacy and tolerability of once-daily dosed NNRTI (nevirapine) or PI (saquinavir/ritonavir)–based regimens compared to a frequently used HAART regimen. The combination of nelfinavir, didanosine, and stavudine would not be used anymore, but at the time this study was started, this regimen was considered as an adequate standard and reference regimen. No statistically significant differences were found in the percentages of patients with a pVL <50 copies/mL at 48 weeks between both once-daily dosed regimens and the control regimen. However, because of the small sample size, the randomization strategy, and the discontinuation of arm D, relevant differences between the groups might exist. The time to achieve a pVL <50 copies/mL was statistically significantly shorter in the once-daily dosed PI-based regimen (C) than in the control regimen. Further, we observed more CDC events in arm B. This might be explained by the fact that patients randomized to arm B had a more progressive HIV infection at baseline than those randomized to arms A and C. Cohort studies have shown that virological failure and progression of CDC events are found more frequently in patients with a baseline CD4 count of <200 cells/μL compared to those with a higher CD4 count.[2–4,14] In addition, a higher baseline pVL might be associated with more virological failure.[4] There were possibly more adverse events associated with mitochondrial toxicity in regimen A. The limited size of the study did not allow for a valid statistical analysis between arms B and C.

Although this study is hampered by its small size, the efficacy results of the three different regi-

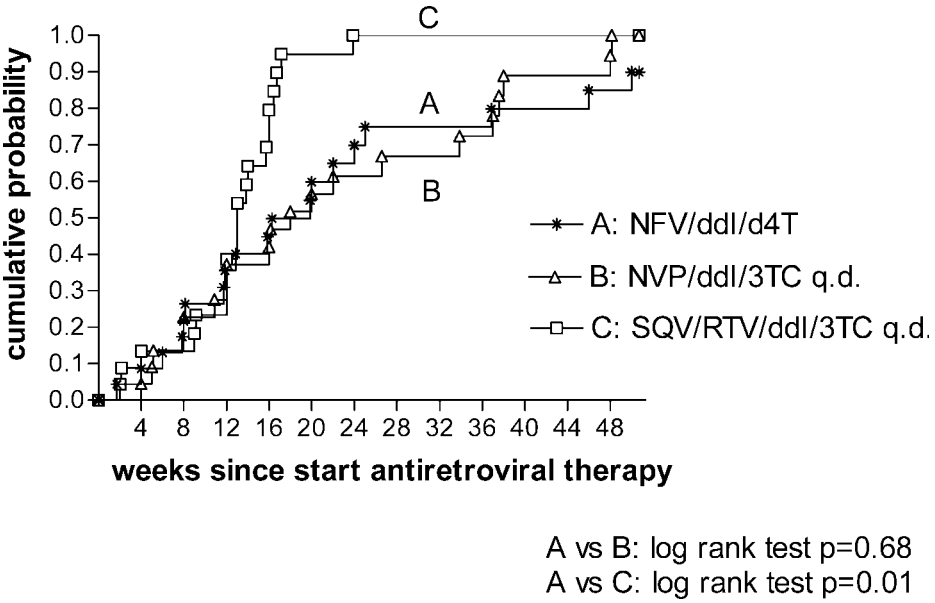

Figure 2. Time to first achieve a plasma viral load of <50 copies/mL (ITT). NFV = nelfinavir; NVP = nevirapine; SQV = saquinavir; RTV = ritonavir; ddI = didanosine; d4T = stavudine; 3TC = lamivudine; qd = once daily; ITT = intention to treat.

mens are comparable to those observed in other (randomized) prospective studies.[4] The virological success to initial HAART as defined by a pVL <50 copies/mL after 48 weeks of therapy according to an ITT analysis varies between 20% and 88%.[4–6,15–17] The older studies demonstrate a virological success of about 50%,[4,5] whereas the more recent studies demonstrate a virological success of 70%–80%.[4,6,17]

In our study, the virological success of regimen A was 42.3%. The ITT virological success of nelfinavir-containing HAART regimens varies between 32% and 65.2% of cases.[3,4,18–24] For the combination of nelfinavir (750 mg three times a day), didanosine, and stavudine, a 48-week response of 32%–39% has been reported.[21,22] In these two studies, the median baseline CD4 count and pVL was >340 cells/mm^3 and >4.74 $\log_{10}$, respectively.[21,22]

We observed a virological success of regimen B of 50.0%. For nevirapine-containing HAART, the ITT virological success varied between 20% and 73%.[3,4,15,25–33] In the study with the least virological success, the median baseline CD4 count was 37.5 cells/μL and the pVL ≥250,000 copies/mL.[15] In studies in which nevirapine once daily was used, the ITT virological success varied between 40% and 70%.[26,28,31–33] In these studies, the dual NRTI backbone was not didanosine and lamivudine and the median baseline CD4 count and pVL were ≥200 cells/μL and >4.34 $\log_{10}$, respectively. In the largest study performed, the 2NN Study, in ITT analysis a pVL <50 copies/mL after 48 weeks of therapy was achieved in 70% of cases with the combination of nevirapine once daily and stavudine and lamivudine twice daily. In this treatment arm, the baseline CD4 count and pVL were 200 cells/μL and 4.7 $\log_{10}$ copies/mL.[33]

Published prospective studies with once-daily ritonavir-boosted saquinavir and two NRTIs as initial antiretroviral therapy and with a follow-up of at least 48 weeks are limited.[34,35] Preliminary results of a randomized, prospective study, the FOCUS study, involving 75 patients in the treatment arm with saquinavir 1600 mg qd, ritonavir 100 mg qd, and two NRTIs, demonstrated in ITT analysis at 24 and 48 weeks of therapy that 60% and 51% of the patients had a pVL <50 copies/mL, respectively.[36,37] In this treatment arm, the median baseline CD4 count and pVL were 322 cells/μL and 4.70 $\log_{10}$ copies/mL, respectively. In the FOCUS study, the compared regimen consisting of efavirenz and two NRTIs was probably more effective at 48 weeks than the saquinavir treatment. In this efavirenz-containing treatment arm, 77 patients were included with a baseline CD4 count and

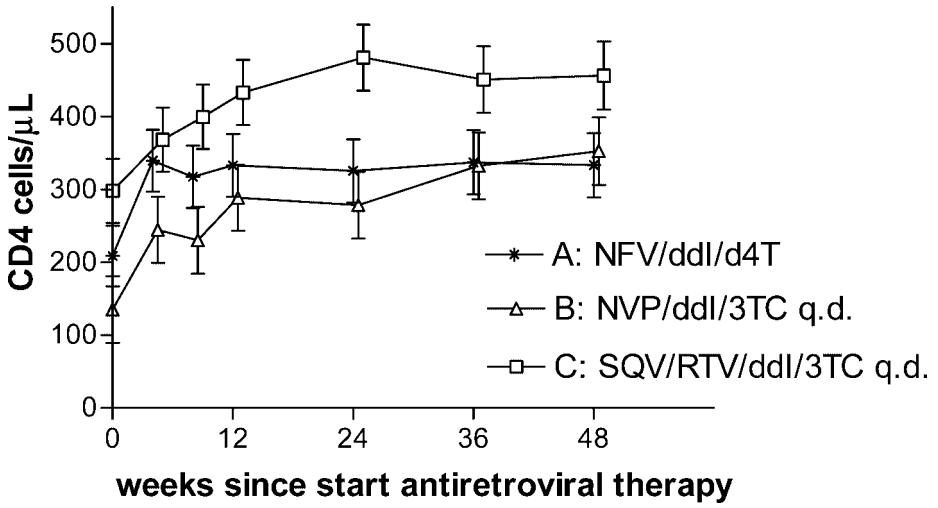

Figure 3. Course of mean CD4 count uncorrected for baseline (ITT). The bars represent the standard errors. NFV = nelfinavir; NVP = nevirapine; SQV = saquinavir; RTV = ritonavir; ddI = didanosine; d4T = stavudine; 3TC = lamivudine; qd = once daily; ITT = intention to treat.

pVL of 326 cells/µL and 4.77 $\log_{10}$ copies/mL, respectively, and the ITT virological success (pVL <50 copies/mL) was 71%.[36] In our study, the baseline CD4 count and viral load and ITT virological success at 24 and 48 weeks of therapy (52.2% and 56.5%, respectively) were comparable to the FOCUS study. With saquinavir hard gelatin capsules (hgc), the virological success at 24 weeks was even better (92%).[38]

In conclusion, the two investigated once-daily dosed treatment regimens (B and C) did not statistically significantly differ in efficacy from the reference regimen (A), and the virological response rate (50%) of this reference regimen was comparable to that reported in literature. However, because of the small sample size, differences between the treatment arms might still exist, although they may be smaller than expected. The efficacy was possibly better and toxicity less in arm C, but this arm had better baseline characteristics. In arm A, there was possibly more mitochondrial toxicity. In arm B, there was statistically significantly more progression to CDC events, which might be related to the worse baseline characteristics. It is possible that the efficacy of arm A and B would be better and progression of CDC events in arm B would be less if treatment was started at a baseline CD4 count of >200 cells/µL, as current guidelines recommend.[1–3,14] One could question whether the efficacy of the once-daily dosed regimens used in this study, regimens B and C, is good enough, taking into account the much better virological success that can be achieved with the more recent HAART regimens.[4,6,17,39] However, regimen C performed well in our study, and this regimen can be further improved. For instance, saquinavir hgc of 500 mg will soon become available. A once-daily dosed regimen consisting of saquinavir 2000 mg boosted with low dose ritonavir (100 mg) may have a greater efficacy than regimen C and comparable toxicity.[40]

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