

Outcome and Predictors of Failure of Highly Active Antiretroviral Therapy: One-Year Follow-Up of a Cohort of Human Immunodeficiency Virus Type 1–Infected Persons

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The outcome and predictors of virologic treatment failure of highly active antiretroviral therapy (HAART) were determined for 271 human immunodeficiency virus (HIV)–infected protease inhibitor–naïve persons. During a follow-up of 48 weeks after the initiation of HAART, 6.3% of patients experienced at least one new AIDS-defining event, and 3.0% died. Virologic treatment failure occurred in 40% (indinavir, 27%; ritonavir, 30%; saquinavir, 59%; ritonavir plus saquinavir, 32%; χ^2 , $P = .001$). Risk factors for treatment failure were baseline plasma HIV-1 RNA (odds ratio [OR], 1.70 per \log_{10} copies increase in plasma HIV-1 RNA), baseline CD4 cell count (OR, 1.35 per 100 CD4 cells/mm³ decrease), and use of saquinavir versus other protease inhibitors (OR, 3.21). During the first year of treatment, 53% of all patients changed (part of) their original HAART regimen at least once. This was significantly more frequent for regimens containing saquinavir (62%; 27% for virologic failure) or ritonavir (64%; 55% for intolerance) as single protease inhibitor.

Several trials have shown that highly active antiretroviral therapy (HAART) with triple-drug combinations containing a protease inhibitor and two nucleoside analogue reverse transcriptase inhibitors may lead to sustained suppression of plasma human immunodeficiency virus type 1 (HIV-1) RNA levels to below the lower limits of quantification and is associated with improved clinical outcome [1, 2]. On the basis of these results, treatment guidelines for HIV-1 infection have been revised in many countries [3–6]. Since the introduction of these guidelines in clinical practice, observational studies from Switzerland, Germany, France, Canada, and the United States [7–13] have revealed a dramatic reduction in morbidity and mortality in patients with HIV infection and AIDS. Achieving sustained suppression of HIV replication is one of the best predictors of clinical outcome, and therefore monitoring of HIV-1 RNA levels in plasma has become a crucial tool in judging and safeguarding the success of HAART [14, 15]. Given the increasing number of available antiretrovirals, various combination regimens may be used as HAART, each with its own characteristics

with respect to toxicity and ease of administration. For the practicing clinician, there is a need for further information concerning differences in the longer-term effectiveness of various HAART regimens and the factors underlying such differences. In The Netherlands, HAART was introduced on a large scale in clinical practice as of 1 July 1996, when the HIV protease inhibitors indinavir, ritonavir, and saquinavir became widely available. Nelfinavir became available in The Netherlands in early 1998, so it was not included in this study. Herein we report on our first year's experiences concerning tolerance, efficacy, and predictors of virologic treatment failure of different HAART regimens incorporating these protease inhibitors in the treatment of HIV-1–infected adults.

Materials and Methods

Patients

Consecutive HIV-1–infected adults of the outpatient clinic of the Academic Medical Center of the University of Amsterdam, who started treatment with antiretroviral combination therapy containing at least one protease inhibitor between 1 July 1996 and 1 March 1997, were included in this study. As the review of medical records for this analysis ceased on 1 March 1998, all patients had a potential follow-up of at least 48 weeks. For inclusion in this study, patients could be either antiretroviral-naïve or -experienced but had to be protease inhibitor–naïve. Patients participating in an antiretroviral drug trial were excluded from the analysis. Patients were also excluded if no plasma HIV-1 RNA load measurement was available at the time treatment with a protease inhibitor was started.

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Study Site

The Academic Medical Center of the University of Amsterdam, where the study was done, is a large teaching hospital and serves as a reference center for care of HIV-infected patients for The Netherlands. Its outpatient clinic is staffed by 7 internists who are infectious diseases specialists. These physicians follow the HIV treatment guidelines drawn up by the Dutch association of HIV-treating physicians. Prophylaxis for *Pneumocystis carinii* pneumonia is started when the patient's CD4 cell count drops below 200 cells/mm³. Much emphasis is placed on continuous patient education, in which nurses specialized in HIV disease play a major role.

Data Collection

Data collection started in the beginning of 1997; thus, for the patients who had already started using a protease inhibitor-containing regimen, some of the data were collected retrospectively. From early 1997 onward, the data have been collected prospectively.

Clinical data. Patients' medical records were reviewed for information on body weight, the use of antiretroviral medication, and history of HIV-related diseases. HIV-related events were diagnosed according to the Centers for Disease Control and Prevention (CDC) 1993 guidelines [16]. Toxicity data were recorded only if toxicity led to modification of HAART. Information on patients' adherence to their regimens was not collected. Data were collected on standardized case record forms. Source document and data entry verification were done for a randomly selected group of patients, ~25% of the total population.

Plasma HIV-1 RNA load. HIV-1 RNA levels were measured in plasma samples by use of the NASBA HIV-1 RNA QT technique (Organon Teknika, Boxtel, The Netherlands). The lower limit of quantification of this assay was 1000 copies/mL (3.0 log₁₀ copies/mL). As of September 1997, this assay was replaced for routine purposes by the NASBA Nuclisens technique (Organon Teknika, Boxtel, The Netherlands), with a lower limit of quantification of 400 copies/mL (2.6 log₁₀ copies/mL). For a small group of patients, the Amplicor assay (Roche, Nutley, NJ) was used, for which the variable lower limit of quantification is ~250 copies/mL. However, for analysis purposes, the lower limits of quantification for both the NASBA Nuclisens and Roche Amplicor assays were set at 1000 copies/mL. Of a total of 1609 evaluated plasma HIV-1 RNA load results, 259 were obtained with the NASBA Nuclisens and 125 with the Roche Amplicor assay.

Lymphocyte subsets. CD4 and CD8 T lymphocyte counts were determined by flow cytometry. These subset counts were rounded off to the nearest multiple of 10 per cubic millimeter.

Analysis

Efficacy analysis. The primary objective was to compare the virologic suppression of combination therapy regimens containing either indinavir, zidovudine, zalcitabine, and zalcitabine, or zidovudine, zalcitabine, and zalcitabine plus zalcitabine. The protease inhibitors were prescribed in dosages according to national consensus treatment guidelines [17]: indinavir, 800 mg three times daily; zidovudine, 600 mg twice

daily; saquinavir, 1200 mg three times daily, which is the recommended dose in The Netherlands; and the double protease inhibitor combination of zalcitabine plus saquinavir, 400 mg each twice daily. Data were analyzed by an intent-to-treat approach, with patients categorized according to their first protease inhibitor used, irrespective of changes in (part of) their HAART regimen.

For the analysis, observation started when treatment with a protease inhibitor was first initiated, irrespective of the date on which the concomitantly used antiretrovirals were started. Time points used for analysis were as follows: baseline (with a window interval of 8 weeks before the start of the protease inhibitor), week 4 (with a window interval of weeks 2–6), week 8 (window interval, weeks 6–10), 12 (window interval, weeks 10–18), 24 (window interval, weeks 18–30), 36 (window interval, weeks 30–42), and 48 (window interval, weeks >42). Whenever more than one laboratory result was available, the one closest to the particular time point was used for the analysis.

A virologic treatment response was defined as a decrease in plasma HIV-1 RNA load from baseline to below the lower limit of quantification (1000 copies/mL) after the initiation of the protease inhibitor. Subsequently, the definition of virologic treatment success was a continued virologic treatment response during follow-up. Consequently, virologic treatment failure was defined as the opposite: not having reached a decrease in plasma HIV-1 RNA load to below the lower limit of quantification at any time between the moment the protease inhibitor was initiated and 48 weeks of follow-up or having an increase in plasma HIV-1 RNA load to above the limit of quantification at any time during the 48 weeks of follow-up after an initial virologic treatment response. Patients with a plasma HIV-1 RNA load below the lower limit of quantification at baseline were included in the analysis of virologic efficacy. They were considered as having a virologic response if their plasma HIV-1 RNA load remained below the lower limit of quantification during the 48 weeks of follow-up and as having virologic treatment failure if their plasma HIV-1 RNA load rose to above the lower limit of quantification at any time during the 48 weeks of follow-up. Patients who died during follow-up were regarded as having virologic treatment failure. Patients who were lost to follow-up for reasons other than death were excluded from the main analysis but were considered as representing treatment failure in an additional analysis.

Data were analyzed with SAS version 6.12 (SAS Institute, Cary, NC). Group comparisons were made with the Wilcoxon rank sum test for continuous data and the χ^2 statistic for categorical data. Differences between groups were considered significant at $P < .05$. All reported P values are two-sided. Clinical and laboratory data were censored at 48 weeks of follow-up. Univariate logistic regression models were constructed with virologic treatment failure as the dependent variable to determine which variables could be important in relation to virologic treatment failure. Baseline parameters considered as possible predictors of virologic treatment failure were age, sex, HIV transmission category, plasma HIV-1 RNA load, CD4 cell count, stage of HIV disease (AIDS vs. non-AIDS), the specific protease inhibitor(s) used, prior reverse transcriptase inhibitor treatment, number of previously used antiretroviral drugs, number of new (not previously used) antiretrovirals concomitantly prescribed, previous use of nonnucleoside reverse transcriptase inhibitors, and the quarter in which HAART was

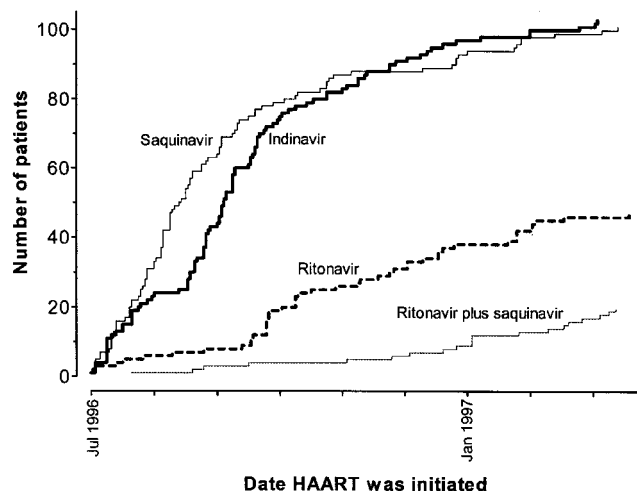


Figure 1. Enrollment of patients into the different protease inhibitor groups between 1 July 1996 and 1 March 1997.

initiated. Variables with $P < .15$ in the univariate model were entered in the multivariate model.

Analysis of tolerance. The tolerability of HAART was analyzed by determining the proportion of patients who discontinued the original drug regimen because of adverse effects. Subsequently, the number of documented adverse events was described for each protease inhibitor group and compared between these groups.

Results

Patients

Baseline characteristics. Between 1 July 1996 and 1 March 1997, a total of 274 protease inhibitor-naïve HIV-1-infected

adults started a combination regimen containing at least one protease inhibitor. From 3 patients, no plasma HIV-1 RNA load data at baseline were available; thus, data from 271 patients (99%) were used (figure 1). Fifty-nine patients (22%) were antiretroviral therapy-naïve at baseline, whereas the remaining 212 patients (78%) had been pretreated with reverse transcriptase inhibitors but were protease inhibitor-naïve. The baseline characteristics of the 271 patients are listed in table 1. There were no significant differences between the protease inhibitor categories with regard to age, sex, mode of HIV infection, stage of HIV disease, pretreatment with nonnucleoside reverse transcriptase inhibitors, baseline HIV-1 RNA levels, and baseline CD4 cell counts. Patients in the ritonavir group were significantly more often antiretroviral therapy-naïve than were patients in the other protease inhibitor groups. Patients in the saquinavir group had significantly more often been pretreated with three or more reverse transcriptase inhibitors than had patients in the other protease inhibitor groups.

Follow-up. Not all of the 271 patients completed a follow-up of 48 weeks: 10 patients were lost to follow-up and 8 died (2 used indinavir, 1 ritonavir, 4 saquinavir, and 1 ritonavir plus saquinavir).

Concomitant antiretroviral medication. The concomitantly used nucleoside analogue reverse transcriptase inhibitors are listed in table 2. Patients in the ritonavir and ritonavir plus saquinavir group added significantly more new antiretroviral drugs to their regimens at the time HAART was started than did those in the other two protease inhibitor groups. Patients in the ritonavir plus saquinavir group more often used reverse transcriptase inhibitors other than zidovudine plus lamivudine,

Table 1. Baseline characteristics of patients in study of HAART.

Characteristic	All	Indinavir	Ritonavir	Saquinavir	Ritonavir + Saquinavir	P^a
Number (%)	271 (100)	103 (38)	47 (17)	101 (37)	20 (7)	
Age, median, years (IQR)	38 (33–45)	38 (33–44)	36 (32–41)	40 (34–46)	39 (34–46)	.11
Male, no. (%)	229 (85)	84 (82)	42 (89)	86 (85)	17 (85)	.67
Mode of infection, no. (%)						.61
MSM	174 (64)	60 (58)	34 (72)	70 (69)	10 (50)	
Heterosexual	42 (16)	18 (17)	6 (13)	15 (15)	3 (15)	
Injecting drug use	23 (9)	10 (10)	3 (6)	7 (7)	3 (15)	
Other	32 (12)	15 (14)	4 (9)	9 (9)	4 (20)	
AIDS, no. (%)	124 (46)	51 (50)	17 (36)	49 (49)	7 (35)	.31
Pretreatment, no. (%)						.011
Naïve	59 (22)	23 (22)	18 (38)	13 (13)	5 (25)	
Used 1 or 2 antivirals	114 (42)	48 (47)	18 (38)	41 (41)	7 (35)	
Used 3 or more antivirals	98 (36)	32 (31)	11 (23)	47 (47)	8 (40)	
Pretreatment, no. (%)						
Zidovudine	208 (76.8)	77 (74.8)	29 (61.7)	87 (86.1)	15 (75.0)	.011
Didanosine	65 (24.0)	21 (20.4)	9 (19.2)	32 (31.7)	3 (15.0)	.14
Zalcitabine	105 (38.6)	41 (39.8)	11 (23.4)	46 (45.5)	7 (35.0)	.08
Stavudine	8 (3.0)	3 (2.9)	0 (0.0)	4 (4.0)	1 (5.0)	.56
Lamivudine	119 (43.9)	41 (39.8)	16 (34.0)	52 (51.5)	10 (50.0)	.16
Pretreatment with NNRTIs, no. (%) ^b	13 (5)	8 (8)	1 (2)	4 (4)	0	.27
HIV RNA load, median, \log_{10} copies/mL (IQR)	4.5 (3.7–5.0)	4.5 (3.7–4.9)	4.7 (3.9–5.0)	4.6 (3.7–5.2)	4.5 (3.5–5.0)	.66
CD4 cell count, median, $\times 10^6/L$ (IQR)	140 (50–260)	110 (50–270)	160 (90–270)	130 (40–250)	150 (20–235)	.40
CD4 cell count ≤ 50 cells $\times 10^6/L$, %	30.0	31.6	18.6	31.3	40.0	.28
CD8 cell count, median, $\times 10^6/L$ (IQR)	700 (400–1050)	690 (380–1140)	820 (550–1200)	690 (390–980)	620 (345–890)	.15

NOTE. IQR, interquartile range; MSM, men having sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor.

^a For comparisons across the 4 protease inhibitor groups, χ^2 was used for categorical data, Kruskal-Wallis for continuous data (HIV-1 RNA load, CD4 cell count).

^b Nevirapine ($n = 7$), loviride ($n = 8$).

Table 2. Concomitant antiretroviral medications received by patients in study of HAART.

Medication	All	Indinavir	Ritonavir	Saquinavir	Ritonavir + Saquinavir	P ^a
Concomitant nucleosides						.001
AZT/3TC	97 (36)	53 (51)	18 (38)	26 (26)	0	
d4T/3TC	87 (32)	33 (32)	15 (32)	39 (39)	0	
d4T/ddI	32 (12)	8 (8)	7 (15)	17 (17)	0	
Other ^b	55 (20)	9 (9)	7 (15)	19 (19)	20 (100) ^c	
Number of new antivirals ^d						.001
1	43 (16)	16 (16)	5 (11)	22 (22)	—	
2	91 (34)	43 (42)	8 (17)	37 (37)	3 (15)	
3	137 (51)	44 (43)	34 (72)	42 (42)	17 (85)	

NOTE. Data are no. (%). AZT = zidovudine, 3TC = lamivudine, d4T = stavudine, ddI = didanosine.

^a For comparisons across the 4 protease inhibitor groups, χ^2 was used.

^b No reverse transcriptase inhibitor (2), AZT (2), zalcitabine (ddC) (1), d4T (20), 3TC (4), AZT/ddI (7), AZT/ddC (9), d4T/ddC (3), AZT/ddI/3TC (1), d4T/ddI/3TC (6).

^c 18 of these 20 patients used d4T as sole reverse transcriptase inhibitor in combination with ritonavir plus saquinavir; other 2 patients did not use any reverse transcriptase inhibitor.

^d Including protease inhibitor(s).

stavudine plus lamivudine, or stavudine plus didanosine (18 of the 20 patients treated with ritonavir plus saquinavir used stavudine as the sole reverse transcriptase inhibitor).

Virology

A virologic treatment response was noted in 246 (94%) of 261 patients. Fifteen patients did not have a virologic treatment response (13 saquinavir, 1 ritonavir, 1 ritonavir plus saquinavir; χ^2 , $P = .001$).

Virologic treatment failure occurred in 104 (40%) of 261 patients (95% confidence interval [CI], 34%–46%): for those receiving indinavir, 26 (27%) of 97 (95% CI, 18%–37%); for the ritonavir group, 14 (30%) of 46 (95% CI, 18%–46%); for the saquinavir group, 58 (59%) of 99 (95% CI, 48%–68%); and for those receiving ritonavir plus saquinavir, 6 (32%) of 19 (95% CI, 13%–57%) (χ^2 , $P = .001$). Table 3 summarizes these results for each protease inhibitor group and subsequently for pretreated and naive subgroups, respectively. Overall, pretreated patients were more likely to have treatment failure than were treatment-naive patients (43% vs. 27%; χ^2 , $P = .02$). At baseline, 46 patients had a plasma HIV-1 RNA load below the lower limit of quantification. These patients had a lower virologic treatment failure rate than did the patients with a detectable baseline plasma HIV-1 RNA load (28% vs. 42%), although this difference was not statistically significant (χ^2 , $P = .08$).

The proportion of patients with a plasma HIV-1 RNA load below the lower limit of quantification during the first 48 weeks after starting a protease inhibitor-containing regimen is shown in figure 2A. After 48 weeks of treatment, 75% (95% CI, 69%–80%) of patients overall had a plasma HIV-1 RNA load below the lower limit of quantification: for indinavir, 84% (95% CI, 75%–91%); for ritonavir, 89% (95% CI, 76%–96%); for saquinavir, 56% (95% CI, 45%–66%); and for ritonavir plus saquinavir, 89% (95% CI, 65%–99%) (χ^2 , $P = .001$).

Immunology

The median overall CD4 cell count increased from 140 cells/mm³ (intraquartile range [IQR], 50–260) at baseline to 320 cells/mm³ (IQR, 210–450) at week 48 (figure 2B). The median CD8 cell count increased from 700 cells/mm³ (IQR, 400–1050) at baseline to 1010 cells/mm³ (IQR, 740–1390) at week 48 (figure 2C). There were no significant differences between the protease inhibitor groups with respect to the CD4 and CD8 cell response.

Predictors of Virologic Treatment Failure

A univariate logistic regression analysis showed the following parameters to be predictors for treatment failure (table 4): baseline plasma HIV-1 RNA load (odds ratio [OR], 1.62 per log₁₀ increase in plasma HIV-1 RNA load), baseline CD4 cell count

Table 3. Patients experiencing virologic treatment failure after 48 weeks of treatment.

Patient Group	All	Indinavir	Ritonavir	Saquinavir	Ritonavir + Saquinavir	P ^a
All (no.)	261	97	46	99	19	
Failure (no.)	104	26	14	58	6	.001
Percentage (95% CI)	40 (34–46)	27 (18–37)	30 (18–46)	59 (48–68)	32 (13–57)	
Pretreated (no.)	205	76	29	86	14	
Failure (no.)	89	22	10	51	6	.001
Percentage (95% CI)	43 (37–50)	29 (19–41)	35 (18–54)	59 (48–70)	43 (18–71)	
Naive (no.)	56	21	17	13	5	
Failure (no.)	15	4	4	7	0	.06
Percentage (95% CI)	27 (16–40)	19 (5–42)	24 (7–50)	54 (25–81)	—(0–52)	

NOTE. 95% CI = 95% confidence interval.

^a For comparisons across 4 protease inhibitor groups, χ^2 statistic was used.

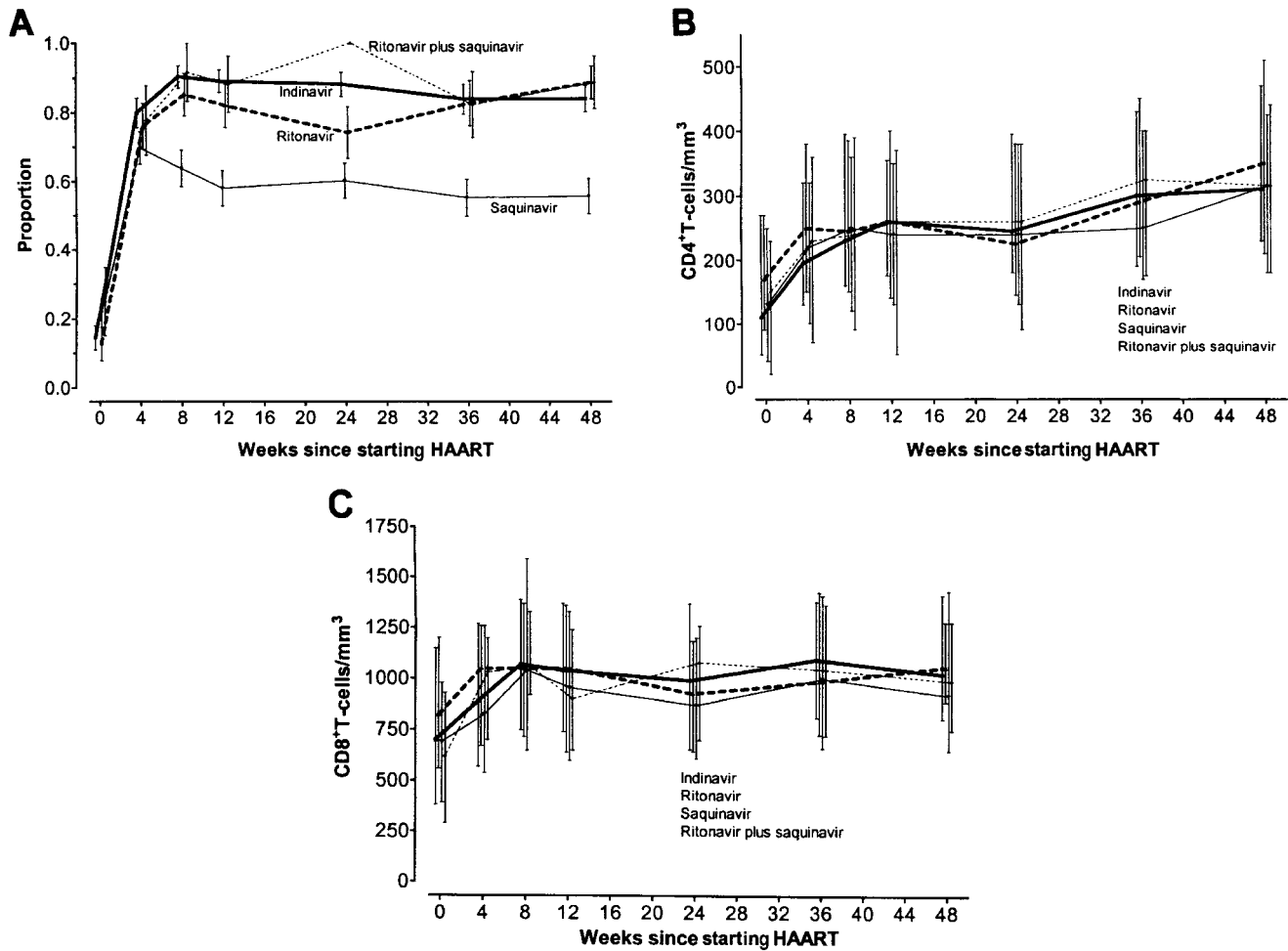


Figure 2. *A*, Percentage (bars, 95% confidence intervals) of patients with virus load below lower limit of quantification per protease inhibitor group during first 48 weeks after initiation of HAART. At baseline, total of 48 patients (18%) had virus load below lower limit of quantification (<1000 copies/mL): indinavir, 15 (15%); ritonavir, 6 (13%); saquinavir, 22 (22%); ritonavir plus saquinavir, 5 (25%). *B*, *C*, Median CD4 cell and CD8 cell counts (bars represent interquartile range) per protease inhibitor group during first 48 weeks after the initiation of HAART. Treatment groups are indicated by lines as labeled in *A*.

(OR, 1.53 per 100 CD4 cells/mm³ decrease), stage C according to CDC guidelines (OR, 2.12), the use of saquinavir (OR, 3.86), the concomitant use of the reverse transcriptase inhibitor combinations stavudine plus didanosine (OR, 2.64) or stavudine plus lamivudine (OR, 2.20), having initiated treatment with a protease inhibitor within the first 3 months after they became available in The Netherlands (July 1996 through September 1996; OR, 3.70), treatment with a protease inhibitor without the addition of other not previously used antiretrovirals (OR, 1.98), and prior treatment with three or more antiretroviral agents versus no antiretroviral pretreatment (OR, 3.43). No relation was found between virologic treatment failure and age, sex, HIV transmission category, and the prior use of non-nucleoside reverse transcriptase inhibitors (table 4).

When the parameters with $P \leq .15$ were entered in the multivariate logistic regression analysis, only the following param-

eters remained predictive for virologic treatment failure (table 4): baseline plasma HIV-1 RNA load, baseline CD4 cell count, and use of saquinavir as single protease inhibitor versus the other protease inhibitor-containing regimens.

To account for a potential bias that may have been introduced by 10 patients who were lost to follow-up, the univariate and multivariate logistic regression analyses were repeated including these 10 patients and considering them as having had virologic treatment failure. This did not change the results dramatically, although in this model, the use of protease inhibitors without concomitant addition of new antiretroviral agents was now found to be a more significant predictor for virologic treatment failure (OR, 2.83; 95% CI, 0.96–8.31; $P = .059$) than in the model without these 10 patients.

Since the extent of nucleoside reverse transcriptase inhibitor pretreatment was associated with virologic treatment failure,

Table 4. Predictors for virological failure after 48 weeks of follow-up in study of HAART.

Predictor	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age	0.98 (0.96–1.02)	.37		
Female	0.77 (0.39–1.49)	.44		
Risk factor for HIV transmission				
MSM	1			
Heterosexual	1.29 (0.65–2.58)	.47		
Injecting drug use	1.27 (0.53–3.07)	.60		
Other	1.26 (0.57–2.77)	.56		
Stage of HIV disease				
Non-AIDS (CDC A or B)	1			
AIDS (CDC C)	2.12 (1.28–3.51)	.004	1.20 (0.64–2.25)	.57
Period HAART was initiated				
3 rd quarter 1996	1		1	
4 th quarter 1996	0.55 (0.29–1.05)	.069	0.92 (0.43–1.99)	.83
1 st quarter 1997	0.27 (0.10–0.75)	.012	0.36 (0.10–1.25)	.11
Pretreatment				
Naive	1		1	
Used 1 or 2 antvirals	1.31 (0.64–2.68)	.39	0.60 (0.21–1.72)	.34
Used 3 or more antvirals	3.43 (1.68–7.01)	.0007	1.15 (0.34–3.88)	.82
Pretreated with nonnucleoside RT inhibitors	1.71 (0.48–6.05)	.41		
Used protease inhibitor				
Indinavir	1		1	
Ritonavir	1.19 (0.55–2.59)	.65	1	
Saquinavir	3.86 (2.12–7.05)	.0001	3.21 (1.75–5.89) ^a	.0002
Ritonavir plus saquinavir	1.26 (0.43–3.66)	.67	1	
Used RT inhibitor combination				
AZT/3TC	1		1	
d4T/3TC	2.20 (1.18–4.09)	.012	2.00 (0.86–4.65)	.11
d4T/ddI	2.64 (1.15–6.10)	.022	2.61 (0.80–8.52)	.11
Other	1.76 (0.87–3.57)	.12	2.47 (1.00–6.14)	.05
Number of new antvirals ^b				
1	1.98 (0.98–3.99)	.057	2.65 (0.89–7.90)	.08
2	1.77 (1.01–3.09)	.044	1.55 (0.64–3.73)	.33
3	1		1	
Baseline HIV-1 RNA ^c	1.62 (1.20–2.19)	.0018	1.70 (1.16–2.50)	.007
Baseline CD4 cell count ^d	1.53 (1.24–1.89)	.0001	1.34 (1.05–1.73)	.02

NOTE. 95% CI, 95% confidence interval; MSM, men having sex with men; RT, reverse transcriptase; AZT, zidovudine; 3TC, lamivudine; d4T, stavudine; ddI, didanosine.

^a Considering indinavir, ritonavir, and ritonavir plus saquinavir as reference group.

^b Including protease inhibitor(s).

^c Per log₁₀ increase in HIV-1 RNA.

^d Per 100 cells/m³ decrease.

we performed a subanalysis including only the pretreated patients to investigate the relative predictive value for virologic treatment failure of pretreatment with a specific nucleoside reverse transcriptase inhibitor. In a univariate logistic regression analysis, lamivudine was the strongest predictor for virologic failure (OR, 2.78; 95% CI, 1.55–4.99). However, when an adjustment was made for having been pretreated with one or two nucleoside reverse transcriptase inhibitors, the predictive value disappeared. Pretreatment with lamivudine was highly associated with having been pretreated with three or more nucleoside reverse transcriptase inhibitors (OR, 14.7).

Changes of Initial Combination Regimen (Including Tolerance)

After 48 weeks of follow-up, 144 patients (53%; 95% CI, 47%–59%) had changed (part of) their regimen at least once (not necessarily the protease inhibitor); 42% did so because of

toxicities and 24% because of an increase in plasma HIV-1 RNA levels. Patients receiving ritonavir or saquinavir had changed their original regimens significantly more often than had patients in the indinavir or the ritonavir plus saquinavir group: for indinavir, 44% (95% CI, 34%–53%); for ritonavir, 64% (95% CI, 49%–77%); for saquinavir, 62% (95% CI, 53%–72%); and for ritonavir plus saquinavir, 30% (95% CI, 12%–54%) (χ^2 , $P = .003$; figure 3). Figure 3 clearly shows more change of regimen in the ritonavir group plus stabilization after 16 weeks. Regimens containing saquinavir were changed more often because of a high plasma HIV-1 RNA load (27% of the total saquinavir group; 95% CI, 18%–35%) than were those including either indinavir (7%; 95% CI, 3%–14%), ritonavir (2%; 95% CI, 0–11%), or ritonavir plus saquinavir (0; 95% CI, 0–17%) (χ^2 , $P = .001$).

Regimens containing ritonavir as the only protease inhibitor were changed more often because of toxicity (55% of the total

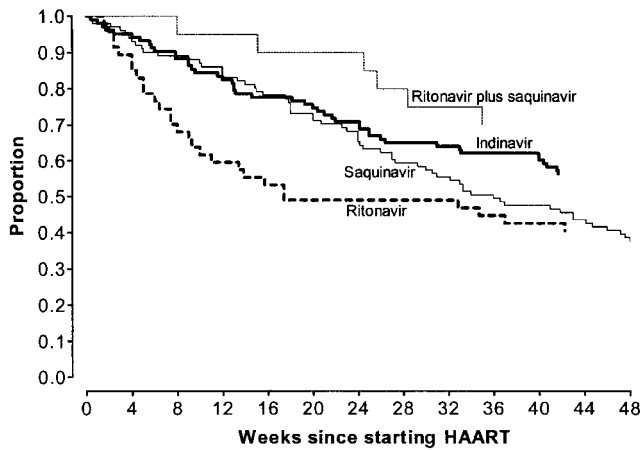


Figure 3. Proportion of patients remaining on original combination regimen per protease inhibitor group during first 48 weeks after initiation of HAART.

ritonavir group; 95% CI, 40%–70%) than were those including either indinavir (29%; 95% CI, 20%–38%), saquinavir (22%; 95% CI, 14%–30%), or ritonavir plus saquinavir (20%; 95% CI, 6%–44%) (χ^2 , $P = .001$). More-detailed information about these toxicities is listed in table 5. Nausea was by far the most common toxicity responsible for the first change in the regimen, occurring in 11% of patients, followed by peripheral neuropathies (3.0%) and anemia (2.2%). Patients receiving ritonavir changed more often because of nausea and vomiting (30% of all patients receiving ritonavir; 95% CI, 17%–45%) than did patients receiving indinavir (13%; 95% CI, 6%–19%), saquinavir (3.0%; 95% CI, 1%–8%), or ritonavir plus saquinavir (5.0%; 95% CI, 0–25%) (χ^2 , $P = .001$).

Data on the syndrome of HIV-1 protease inhibitor-associated peripheral lipodystrophy, hyperlipidemia, and insulin resistance [18] were not collected on our case record forms because the syndrome was not recognized at the time we designed this study in 1996. Serum triglycerides were routinely measured in all patients, although mostly in a nonfasted state. At baseline, 15.5% of all patients had a grade 1 or higher elevation in triglycerides (>3.0 mmol/L); for the indinavir group, 14.7%; for the ritonavir group, 11.1%; for the saquinavir group, 19.0%; and for those receiving ritonavir plus saquinavir, 11.1%. In a during-treatment analysis, after 48 weeks of HAART, the proportion of patients with elevated triglycerides had increased to 37.9%: for the indinavir group, 28.0%; for the ritonavir group, 60.0%; for the saquinavir group, 20.8%; and for those receiving ritonavir plus saquinavir, 66.7% (χ^2 , $P < .001$). The proportion of patients with a grade 2 or higher elevation in triglycerides (>4.9 mmol/L) increased from 3.0% at baseline (indinavir, 4.9%; ritonavir, 0; saquinavir, 2.0%; and ritonavir plus saquinavir, 5.6%) to 10.8% at week 48 (indinavir, 7.5%; ritonavir, 25%; saquinavir, 3.8%; and ritonavir plus saquinavir, 18.8%; χ^2 , $P = .011$).

New AIDS-Defining Events

After 48 weeks of follow-up, 19 new (nonrecurrent) AIDS-defining events (AIDS dementia complex, 1 patient; *Candida* esophagitis, 2; cytomegalovirus disease, 4 [retinitis, 2]; cryptosporidial diarrhea, 3; Kaposi's sarcoma, 2; and one each of non-Hodgkin's lymphoma, microsporidial diarrhea, disseminated *Mycobacterium avium* or *Mycobacterium kansasii* infection, recurrent bacterial pneumonia, progressive multifocal leukoencephalopathy, extrapulmonary tuberculosis, and cerebral toxoplasmosis) had occurred in only 17 patients: in the indinavir group, 4 (3.9%; 95% CI, 1%–10%); in the ritonavir group, 5 (11%; 95% CI, 4%–23%); in the saquinavir group, 8 (7.9%; 95% CI, 3%–15%); and for those receiving ritonavir plus saquinavir, 0 (95% CI, 0–17%) (χ^2 , $P = .23$). Eight (47%) of these 17 patients had virologic treatment failure. Eleven of the 19 events occurred within 3 months after initiation of the protease inhibitor-containing regimens. All but 1 of these 17 patients had experienced at least one HIV-related event prior to the start of the protease inhibitor; 12 of them had a prior AIDS diagnosis. Eleven of the 17 patients had a baseline CD4 cell count $<100/\text{mm}^3$.

Body Weight

The mean body weight at baseline was 69.7 kg (SD, 11.5) and was equal for all protease inhibitor groups (Kruskal-Wallis, $P = .9$). After a follow-up of 48 weeks, the mean body weight did not differ from baseline and between protease inhibitor groups. There were also no differences in body weight after 48 weeks between the patients who were regarded as having virologic treatment failure or success (Kruskal-Wallis, $P = .22$).

Discussion

An important finding of the present study is a relatively high virologic success rate in a fairly advanced and considerably pretreated patient population. The high proportion (75%) of patients in whom plasma HIV-1 RNA became undetectable can partially be explained by the relatively high cutoff value of the assay for plasma HIV-1 RNA load quantification that was used (1000 copies/mL). In addition, we consider it to be the result of the guidelines in our hospital to use, whenever possible, at least two and preferably three new drugs when antiretroviral therapy is initiated or modified because of virologic treatment failure. Another factor could be that our center is staffed by doctors and nurses with much experience and working full-time in the field of HIV disease. It should be realized, however, that 48 weeks of follow-up is a relatively short time in the view of the lifetime of the patients.

The overall rate of virologic treatment success, defined as a sustained suppression of the plasma HIV-1 RNA load below the lower limit of quantification (61%), was considerably lower than the proportion of patients with undetectable plasma HIV-

Table 5. Reasons for first change in regimen in study of HAART.

Reason	All	Indinavir	Ritonavir	Saquinavir	Ritonavir + Saquinavir
No change	127 (46.9)	58 (56.3)	17 (36.2)	38 (37.6)	14 (70.0)
All toxicities ^a	82 (30.3)	30 (29.1)	26 (55.3)	22 (21.8)	4 (20.0)
Nausea, vomiting	31 (11.4)	13 (12.6)	14 (29.8)	3 (3.0)	1 (5.0)
Peripheral neuropathy	8 (3.0)	2 (1.9)	1 (2.1)	4 (4.0)	1 (5.0)
Anemia ^b	6 (2.2)	4 (3.9)	0	2 (2.0)	0
Diarrhea	5 (1.8)	0	2 (4.3)	2 (2.0)	1 (5.0)
Rash	3 (1.1)	1 (1.0)	1 (2.1)	1 (1.0)	0
Myalgia	3 (1.1)	2 (1.9)	1 (2.1)	0	0
Raised liver enzymes ^c	3 (1.1)	0	1 (2.1)	1 (1.0)	1 (5.0)
Nephrolithiasis	2 (0.7)	2 (1.9)	0	0	0
High HIV-1 RNA load	35 (12.9)	7 (6.8)	1 (2.1)	27 (26.7)	0
Other reason	27 (10.0)	8 (7.8)	3 (6.4)	14 (13.9)	2 (10.0)

NOTE. Data are no. (%).
^a All toxicities responsible for first change of (part of) regimen that occurred in >0.5% of total patient population.
^b Anemia as judged clinically significant by treating physician. Observed range for hemoglobin: 3.9–5.6 mmol/L (normal, 8.0–10.0).
^c Raised levels of liver enzymes; clinically significant increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and/or γ glutamyl transferase, as judged by treating physician. Observed ranges: AST, 109–117 U/L (normal, <47); ALT, 159–214 U/L (normal, <37); alkaline phosphatase, 96–132 U/L (normal, 26–103); γ glytamyl transferase, 88–384 U/L (normal, <68).

1 RNA at week 48 (75%). The difference of 14% between the overall rate of virologic treatment success and proportion undetectable at week 48 is caused by the fact that patients who have virologic failure at some point during the follow-up period are usually switched to another antiretroviral regimen, after which their plasma HIV-1 RNA load may once again decrease to below the lower limit of quantification, potentially rendering them with an undetectable result at the 48-week time point. Conversely, HIV-1 replication in a relatively high percentage of patients (39%) was not fully suppressed during the entire period of follow-up; these patients were thus regarded as having virologic treatment failure. Independent predictors for virologic treatment failure were plasma HIV-1 RNA load and CD4 cell count at the start of HAART and the use of saquinavir as the initial protease inhibitor. Having initiated treatment with the protease inhibitor without adding any other new antiretroviral agents to the regimen was borderline significantly associated with virologic treatment failure. These data are consistent with results from previous studies [7, 8, 10]. However, one should be careful when interpreting these results, because this was not a randomized study and the protease inhibitor groups were not completely comparable at baseline (e.g., patients in the saquinavir group were more frequently pretreated than were patients in the other groups).

The high percentage (53%) of patients who changed (part of) their original HAART regimens highlights the difficulties HIV-infected patients and their treating physicians encounter in maintaining therapy with these regimens. Drug-related toxicities are a frequent cause of modification of the original HAART. In this study, drug-related toxicity was probably underestimated, since these data were recorded only when toxicity was the main reason for a change in antiretroviral medication. More patients in the ritonavir group changed their original HAART regimen for reasons of toxicity. Saquinavir appeared to be best-

tolerated. Elevation of triglycerides after initiation of HAART occurred in more than half of the patients who were treated with a ritonavir-containing regimen.

Remarkably few new AIDS-defining events (in only 6.3% of the patients) occurred during the follow-up period. Most of these events occurred within the first 3 months after initiation of the protease inhibitor, so clinicians should be vigilant for these events in this period. The initial rapid increases in CD4 cell counts may have been caused by the redistribution of trapped memory T cells from the lymph nodes into the peripheral blood, followed by a slower repopulation of newly produced naive T cells [19]. The CD4 and CD8 cell counts continued to increase during the entire follow-up period in all protease inhibitor groups, even in the saquinavir group, which did not show as much virologic success as the other groups. Incomplete suppression of HIV-1 replication apparently does not preclude an improvement in immunologic parameters. It has been speculated that small reductions in plasma HIV-1 RNA load, together with reduced cytopathicity and decreased fitness of mutated HIV-1, could explain this phenomenon [20, 21]. However, in a recent study, looking in more detail at immune function, an immunologic response to recall antigens was seen only in persons with sustained virus suppression [22]. We expect that a prolonged follow-up of these patients will eventually show a loss of immunologic and clinical benefit compared with that in patients with a continued suppression of HIV-1 RNA levels.

Clearly, a lot of improvement is still needed in the field of antiretroviral therapy. To obtain sustained suppression of HIV-1 replication in a higher proportion of patients, antiretroviral therapy should cause less toxicity and adherence should become easier. There also seems to be a need for even more-potent regimens, particularly for certain groups of patients, such as those with a high plasma HIV-1 RNA load before therapy.

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