Predictors of Virological Success and Ensuing Failure in HIV-Positive Patients Starting Highly Active Antiretroviral Therapy in Europe

Results From the EuroSIDA Study

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Background: Predictors of virological response to highly active antiretroviral therapy (HAART) have never been systematically evaluated in a large continental multicenter cohort of unselected human immunodeficiency virus (HIV)–infected people.

Objective: To determine the factors related to achieving and maintaining undetectable plasma HIV-1 RNA levels among HIV-1–infected patients first starting protease inhibitor– or nonnucleoside retrotranscriptase inhibitor–containing HAART in Europe.

Design: Prospective multicenter cohort study.

Setting: Fifty-two clinical centers in 17 European countries included in the EuroSIDA Study Group, from August 1996 to April 1999.

Patients: A total of 1469 HIV-positive patients first starting HAART recruited from an unselected cohort of more than 7300 HIV-positive patients.

Main Outcome Measure: Detection of factors related to virological success after first starting HAART (baseline) and ensuing failure by standard survival techniques, including Kaplan-Meier techniques and Cox proportional hazards models. All analyses were intention to treat.

Results: Most patients (80%) achieved plasma HIV-1 RNA levels of less than 500 copies/mL during follow-up (60.4% at 6 months from the onset of HAART). Patients with higher baseline HIV-1 RNA levels (relative hazard [RH], 0.76 per log higher; 95% confidence interval [CI], 0.69-0.84; $P<.001$) and those taking saquinavir mesylate hard gel as a single protease inhibitor (RH, 0.62; 95% CI, 0.47-0.82; $P<.001$) were less likely to reach undetectable HIV-1 RNA levels. Conversely, higher $CD4^+$ lymphocyte counts (RH per 50% higher, 1.09; 95% CI, 1.02-1.16; $P = .008$) and the initiation of 3 or more new antiretroviral drugs (RH, 1.29; 95% CI, 1.03-1.61; $P = .02$) were independent predictors of higher success. Once success was achieved, HIV-1 RNA levels rebounded in more than one third of all patients during follow-up (24% at 6 months). Antiretroviral-naive patients (RH, 0.50; 95% CI, 0.29-0.87; $P = .01$), older patients (RH, 0.86 per year older; 95% CI, 0.75-0.99; $P = .04$), and those starting a protease inhibitor other than saquinavir hard gel (RH, 0.66; 95% CI, 0.44-0.98; $P = .04$) were at decreased hazard for virological failure. Higher baseline HIV-1 RNA level (RH, 1.18 per log higher; 95% CI, 0.99-1.40; $P = .06$) and a longer time to achieve virological success (RH per 12 months, 1.53; 95% CI, 0.99-2.38; $P = .06$) were marginally significant predictors of a decreased hazard of ensuing virological failure.

Conclusions: HAART is associated with a favorable virological response if started when the baseline HIV-1 RNA level is low, if at least 2 new nucleoside retrotranscriptase inhibitors are added, and if standard doses of saquinavir hard gel capsule are avoided as a single protease inhibitor. Older patients are more likely to achieve virological success. Thereafter, the higher durability of virological response is predicted by an antiretroviral-naive status and by the use of specific regimens. Lower baseline HIV-1 RNA levels and rapid maximal viral suppression seem to be other important factors in the durability of virological response.

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AN APPROPRIATE comprehension of the factors that affect the virological response to antiretroviral treatments is warranted to improve the clinical treatment of human immunodeficiency virus (HIV)–infected patients. It is important, as well, to expand the rational basis for the accurate design of effective therapies and to reduce the duration and complexity of clinical trials. Formerly, the natural history of HIV infection was invariably unidirectional, progressively leading to acquired immunodeficiency syndrome (AIDS) and death,

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PATIENTS AND METHODS

PATIENTS

The EuroSIDA study is a prospective European study of more than 7300 HIV-positive patients recruited from 52 centers across Europe (including Israel; see the boxed list on page 1125). Details of the study have been previously published.[19] Briefly, centers provided data on consecutive patients seen in the outpatient clinic from May 2, 1994, until a predefined number of patients were enrolled from each center. This cohort of 3120 patients was defined as the EuroSIDA I cohort. Enrollment of an additional 1367 patients began in December 1995; this cohort was defined as the EuroSIDA II cohort. Enrollment of 2844 patients into the EuroSIDA III cohort began in February 1997. Eligible patients had a $CD4^+$ lymphocyte count below 0.50×10^9/L in the previous 4 months, were older than 16 years at the time of enrollment, and had a scheduled outpatient clinic visit. Information was collected from patient case notes onto a standardized data collection form at baseline and every 6 months thereafter. Members of the coordinating office visited all the centers to ensure correct patient selection and accurate data provision. Dates of diagnosis of all AIDS-defining diseases were recorded using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention, as were dates of stopping and starting all antiretroviral drug treatments, $CD4^+$ lymphocyte counts, and measures of viral load. The analyses presented herein include all follow-up to April 1999.

STATISTICAL METHODS

For descriptive purposes, Europe was arbitrarily divided into 3 regions, as described previously[20]: north (Denmark, United Kingdom, North Germany, Ireland, the Netherlands, Norway, Scotland, and Sweden), central (Belgium, France, South Germany, Luxembourg, and Switzerland), and south (Greece, Italy, Portugal, Spain, and Israel). Continuous variables, such as age and $CD4^+$ lymphocyte count at study recruitment, were generally not normally distributed. To compare differences across groups, we used nonparametric tests, such as the Wilcoxon signed rank test, or a logarithmic transformation of the data to restore normality; we also used parametric methods to test for differences.

Predictors of Progression to HIV-1 RNA Levels Below 500 Copies/mL

We defined HAART as a treatment regimen including a minimum of 1 PI or nonnucleoside in combination with 2 or more other antiretroviral drugs. Our inclusion criteria were starting HAART after enrollment in the EuroSIDA study, a $CD4^+$ lymphocyte count and viral load measure in the 3 months preceding start of treatment, and at least 1 $CD4^+$ lymphocyte count and viral load measure after the start of HAART. Virological success was defined as a single HIV-1 RNA measure of less than 500 copies/mL; this level was chosen because different European centers used different assays for plasma HIV-1 RNA quantification. Eligible patients were followed up from the date of starting HAART to the date of their first HIV-1 RNA level of less than 500 copies/mL or until the last viral load measurement for those patients who did not achieve undetectable HIV-1 RNA levels through follow-up. All analyses were intention to treat; thus, no account was taken of subsequent stopping or switching antiretroviral treatment. Kaplan-Meier analyses were used to determine the proportion of patients who achieved a viral load of less than 500 copies/mL. Cox proportional hazards models were used to further investigate the prognostic factors for virological success. We investigated demographic factors, such as age and sex; treatment-related factors, such as the initial HAART regimen, the number of new antiretroviral drugs added at the date of starting the HAART regimen, and whether a patient was previously treatment naive; and clinical factors, such as the previous diagnosis of an AIDS-defining illness and the $CD4^+$ lymphocyte count ($\log_2$) and viral load ($\log_{10}$) at the date of starting HAART. All multivariate analyses were stratified by center and calendar time (divided into quartiles) of starting HAART.

Predictors of Virological Failure Among Patients Who Initially Achieved an HIV-1 RNA Level Below 500 Copies/mL

Patients who achieved a viral load of less than 500 copies/mL in the analysis described above were included in a further analysis to determine factors associated with virological failure, defined as a rise in viral load to greater than 1000 copies/mL. Patients whose viral load did not decrease below 500 copies/mL were excluded from this analysis, as were patients with no further viral load measures after achieving undetectable levels. Patient follow-up was measured as the time between the first HIV-1 RNA level determination below 500 copies/mL and the date of the first HIV-1 RNA level detected to be greater than 1000 copies/mL, or the last virological follow-up for patients who did not experience such rebound. Similar statistical techniques as described above were used to assess the factors associated with virological rebound.

All tests of significance in this analysis were 2 sided. Tests of the proportional hazards assumption revealed that there was no evidence for nonproportionality. All statistical analyses were performed using SAS statistical software.[21]

and the efficacy of therapy was determined by its ability to delay this fatal progression. Therefore, predictors of clinical progression have been extensively studied and precisely determined in HIV-infected patients.[1-8] Today, the clinical prognosis of HIV infection has radically changed because of the widespread use of highly active antiretroviral therapy (HAART), including protease inhibitors (PIs).[9-11] Partly because these studies link plasma HIV-1 RNA levels with risk of clinical progression, the positivist goal of antiretroviral therapy is now to reduce and maintain HIV-1 RNA levels below the lowest detectable.[12]

However, predictors of short-term virological response to treatments should be considered apart from predictors of clinical progression. Different pathogenic mechanisms probably determine viral dynamic responses to treatments and clinical disease progression. Low baseline $CD4^+$ T-cell counts undoubtedly deter-

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mine the risk of death in HIV-infected people.[13] But do they affect the initial decay of plasma HIV-1 RNA levels after the start of an intense triple therapy containing PIs or nonnucleoside reverse transcriptase inhibitors (NNRTIs)? In addition, it is uncertain whether short-term plasma HIV-1 RNA responses reflect the long-term clinical prognosis of HIV-infected patients.[14] Results of recent studies[15] have shown that the minimum HIV-1 RNA levels achievable are required to obtain durable virological responses. Durability of virological response should be understood as the major goal to improve the clinical prognosis of patients. However, discrepant virological and immunologic responses to antiretroviral regimens[16,17] indicate that not only plasma HIV-1 RNA level plays a role in this clinical prognostic improvement. Because an appropriate definition for treatment success and failure abides for consensus,[16] authors can usually define failure of therapy in terms of lack of "sufficient" suppression of viral replication.

It is important to assess the impact of HAART in unselected HIV-infected patients because the efficacy of therapy in daily clinical practice clearly differs from the high rates of success seen in clinical trials.[18] The main purpose of the present study is to properly define predictors of virological success in a large European cohort of 1469 unselected HIV-positive patients who start a HAART approach for the first time and predictors of eventual failure once success has been accomplished. This is the first report assessing this issue in a large prospective multinational multicenter study that includes all major risk groups.

RESULTS

PATIENTS

A total of 1469 of 7331 patients in the EuroSIDA cohorts met the inclusion criteria for this analysis. **Table 1** presents patient baseline characteristics. Baseline was defined as the date of first starting a PI or an NNRTI in combination with 2 or more nucleosides. Most patients were white (87%), were men (79%), and had no previous diagnosis of AIDS (79%) at the time of starting the study. Almost 46% were homosexual or bisexual men, 24% were heterosexual, and 24% had been infected via intravenous drug use. The median $CD4^+$ cell count at baseline

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Table 1. Demographic Characteristics*

Characteristic	No (%) of Patients
Sex	
Male	1153 (78.5)
Female	316 (21.5)
Cohort	
I	553 (37.6)
II	362 (24.6)
III	554 (37.7)
Race	
White	1276 (86.9)
Other	193 (13.1)
Region	
South	480 (32.7)
Central	473 (32.2)
North	516 (35.1)
Risk	
Homosexual	670 (45.6)
Intravenous drug user	352 (24.0)
Heterosexual	355 (24.2)
Other	92 (6.3)
AIDS at HAART	
No	1158 (78.8)
Yes	311 (21.2)
Drugs at HAART, No.†	
3	1249 (85.0)
4	175 (11.9)
5	42 (2.9)
6	3 (0.2)
Treatment naive at HAART‡	
No	1221 (83.1)
Yes	248 (16.9)
New drugs at HAART, No.§	
1	495 (33.7)
2	426 (29.0)
≥3	548 (37.3)
PI-NNRTI regimen	
Ritonavir	235 (16.0)
Saquinavir	231 (15.7)
Indinavir	651 (44.3)
Dual PI	97 (6.6)
Nelfinavir	129 (8.8)
NNRTI	126 (8.6)
Total	1469 (100)

*AIDS indicates acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; PI, protease inhibitor; and NNRTI, nonnucleoside retrotranscriptase inhibitor.

†Number of drugs being taken at the date of starting HAART.

‡Exposed to all drugs for the first time at starting therapy with a PI or an NNRTI.

§The number of new drugs started at study onset.

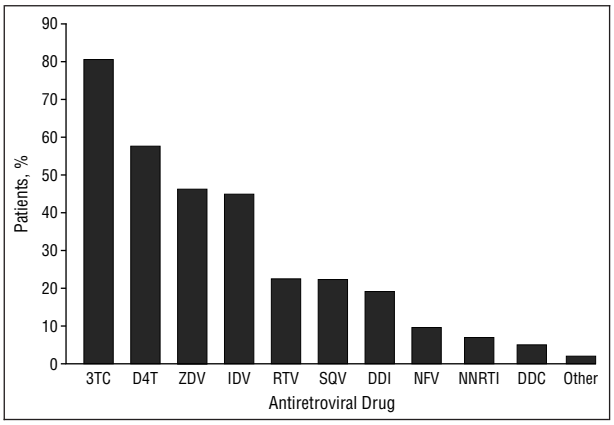

Figure 1. *Patients using antiretroviral drugs at the start of highly active antiretroviral therapy. 3TC indicates lamivudine; D4T, stavudine; ZDV, zidovudine; IDV, indinavir; RTV, ritonavir; SQV, saquinavir; DDI, didanosine; NFV, nelfinavir; NNRTI, nonnucleoside reverse transcriptase inhibitors; and DDC, zalcitabine.*

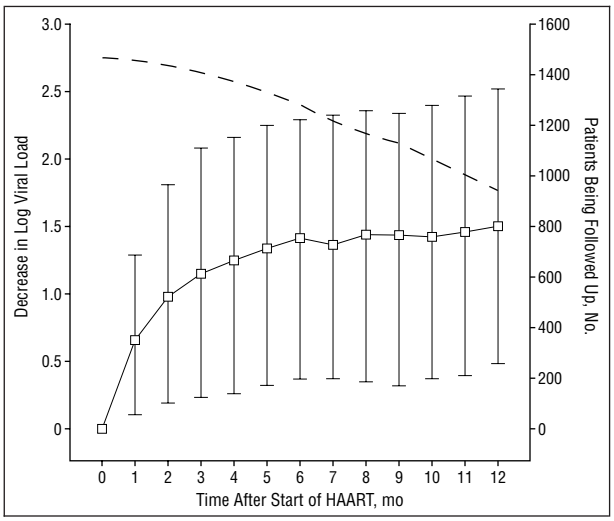

Figure 2. *Overall changes in median plasma human immunodeficiency virus 1 (HIV-1) RNA levels after starting highly active antiretroviral therapy (HAART). Median and interquartile (25%-75%) HIV-1 RNA values are shown. The number of patients under follow-up at each time point is represented by the dotted line.*

was 0.23 × 10^9/L (interquartile 25%-75% range [IQR] = 0.12-0.34 × 10^9/L) and median baseline HIV-1 RNA levels were 20 659 copies/mL (IQR = 3410-89 000 copies/mL) or 4.32 log (IQR = 3.53-4.95 log). A low correlation index between $CD4^+$ counts and HIV-1 RNA plasma levels was found at baseline (r = –0.18). The median date of starting HAART was May 1997 (IQR = January 1997 to November 1997) and patients had a median follow-up of 16.0 months (IQR = 9.0-20.0 months).

Only 17% of patients were naive for any antiretroviral drug treatment. Three-, 4-, 5-, and 6-drug HAART regimens were prescribed to 85.0%, 11.9%, 2.9%, and 0.2% of patients, respectively. At the onset of the study, 33.7% of patients simply added a PI or an NNRTI, 29.0% started taking 2 new drugs (1 NRTI + 1 PI or NNRTI), and 37.3% started taking 3 or more new drugs (including at least 1 PI or NNRTI). The most frequently prescribed drugs when first starting HAART (**Figure 1**) were lamivudine (81%), stavudine (58%), zidovudine (47%), and indinavir (45%). Ritonavir was given to 22% of patients, saquinavir mesylate hard gel to 22%, nelfinavir to 10%, and NNRTIs to only 7%.

OVERALL RESPONSE TO HAART

One hundred forty-six of 1469 patients had undetectable HIV-1 RNA levels at baseline and were therefore excluded from the analysis of the risk of progression to virological success. Of the remaining 1323 patients, 1054 (80%) achieved HIV-1 RNA levels below 500 copies/mL. **Figure 2** displays the evolution of median HIV-1 RNA values through follow-up.

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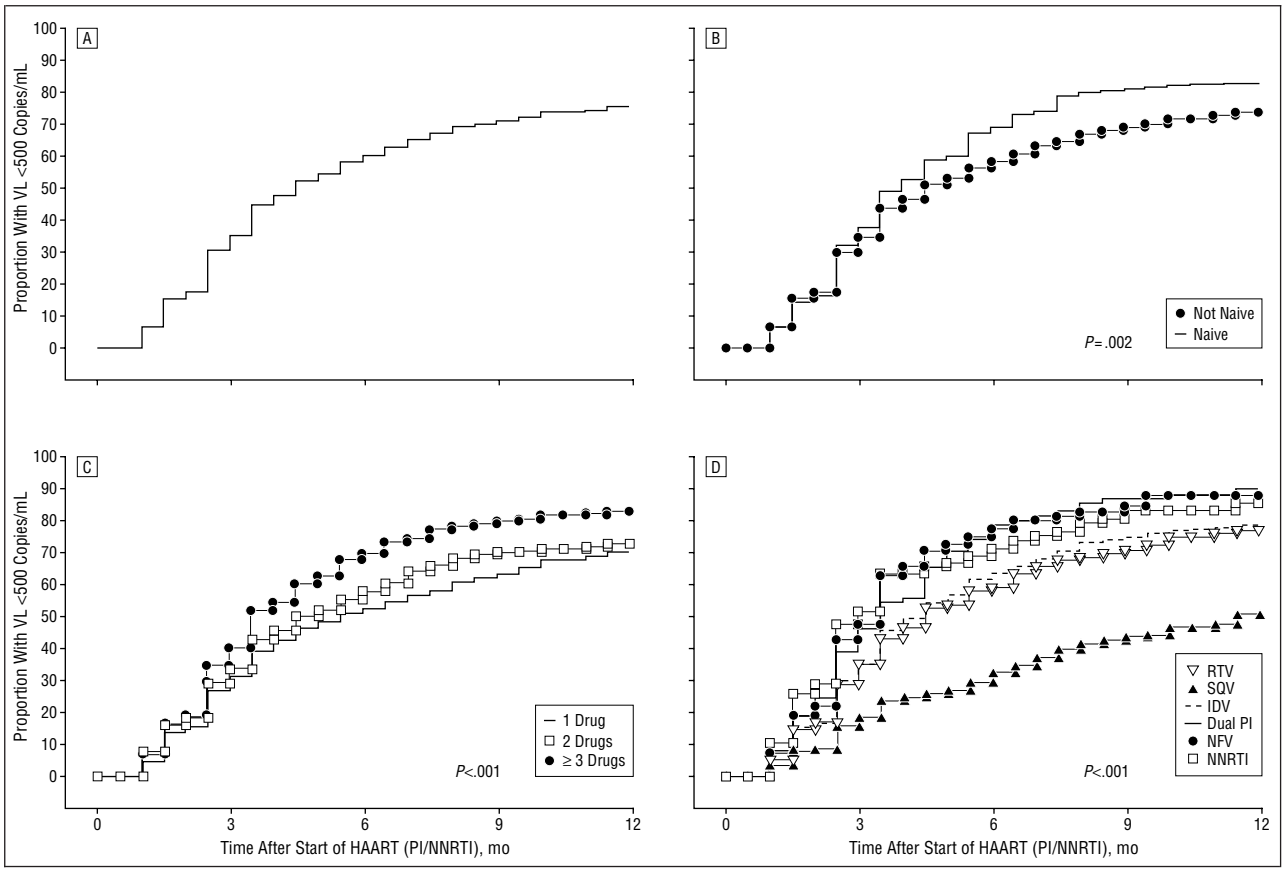

Figure 3. *Kaplan-Meier plots for the time to plasma human immunodeficiency virus 1 RNA levels below 500 copies/mL after first starting highly active antiretroviral therapy (HAART) for all patients (A); those with nucleoside retrotranscriptase inhibitor–naive vs –experienced status (B); patients starting 1, 2, and 3 or more drugs (C); and patients including particular protease inhibitors (PIs) (RTV indicates ritonavir; SQV, saquinavir; IDV, indinavir; and NFV, nelfinavir) or nonnucleoside retrotranscriptase inhibitors (NNRTIs) (D). VL indicates viral load.*

RISK OF PROGRESSION TO HIV-1 RNA LEVELS BELOW 500 Copies/mL

Significant differences in the percentage of patients achieving undetectable HIV-1 RNA levels were found between groups using various PIs ($P<.001$). Overall, plasma HIV-1 RNA levels below 500 copies/mL were attained by 89% of patients starting dual PI regimens, 83% of patients taking indinavir, 82% of patients starting NNRTI use, 81% of patients starting ritonavir therapy, 80% of those taking nelfinavir, and only 64% of patients taking saquinavir. In addition, 76% of patients starting only 1 new drug achieved undetectable HIV-1 RNA levels, and 78% of those starting 2 new drugs and 84% in whom at least 3 new drugs were added decreased HIV-1 RNA levels below 500 copies/mL. These latter differences were statistically significant ($P = .006$).

In the Kaplan-Meier analysis, 60.4% of patients had plasma HIV-1 RNA levels below 500 copies/mL 6 months after starting HAART. The median time to reach undetectable viral load levels was 4.0 months. Kaplan-Meier plots (**Figure 3**) illustrated significant differences in the risk of achieving undetectable HIV-1 RNA levels between groups of initial HAART prescription ($P<.001$), naive vs antiretroviral-experienced status ($P = .002$), and among number of new drugs started ($P<.001$). Almost 80% of patients starting a dual PI regimen showed virological success at 6 months. Seventy-five percent, 71%, 64%, and 59% of patients taking NNRTIs, nelfinavir, indinavir, and ritonavir, respectively, achieved HIV-1 RNA levels below 500 copies/mL at 6 months. Conversely, only 32% of patients who were prescribed saquinavir hard gel as a single PI reached undetectable viral load levels at 6 months of follow-up. Sixty-nine percent of treatment-naive patients but only 59% of NRTI-experienced patients achieved HIV-1 RNA levels below 500 copies/mL 6 months after initially starting HAART. Finally, 52% of patients who exclusively started taking 1 new drug at baseline achieved undetectable HIV-1 RNA levels at 6 months of follow-up. In comparison, 58% of patients who started taking 2 new drugs and 70% of those who switched 3 or more new antiretroviral drugs achieved HIV-1 RNA levels below 500 copies/mL 6 months after initially starting HAART.

Table 2 presents the results of the univariate and multivariate Cox proportional hazards models. After adjustment for confounding variables, lower baseline HIV-1 RNA levels were the stronger significant predictors of an increased hazard for virological success thereafter ($P<.001$). Initial choice of saquinavir hard gel as a single PI at the onset of HAART was a significant predictor of a decreased hazard for attaining undetectable viral load levels thereafter ($P = .001$). Indeed, it was the strongest predictor of the subsequent virological outcome after HIV-1

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Table 2. Factors Related to HIV-1 RNA Levels Less Than 500 Copies/mL*

Factor	RH† (Univariate 95% CI)	*P*	RH† (Multivariate‡ 95% CI)	*P*
Age	1.08 (1.01-1.15)	.03	1.07 (0.99-1.18)	.08
Previous AIDS diagnosis§	0.69 (0.59-0.80)	<.001	0.87 (0.72-1.06)	.17
$CD4^+$, log_2‖	1.16 (1.11-1.21)	<.001	1.09 (1.02-1.16)	.008
RNA, log_{10}‖	0.74 (0.69-0.80)	<.001	0.76 (0.69-0.84)	<.001
PI				
Ritonavir	1.00 (Reference)		1.00 (Reference)	
Saquinavir	0.57 (0.46-0.72)	<.001	0.62 (0.47-0.82)	<.001
Indinavir	1.07 (0.90-1.27)	.46	1.08 (0.88-1.33)	.44
Dual PI	1.53 (1.17-2.00)	.002	1.08 (0.75-1.54)	.64
Nelfinavir	1.49 (1.15-1.93)	.003	0.91 (0.62-1.31)	.60
NNRTI	1.51 (1.17-1.95)	.002	0.85 (0.61-1.20)	.35
Naive				
No	1.00 (Reference)		1.00 (Reference)	
Yes	1.27 (1.09-1.49)	.003	1.10 (0.86-1.41)	.44
No. of new drugs started				
1	1.00 (Reference)		1.00 (Reference)	
2	1.11 (0.95-1.29)	.20	1.08 (0.89-1.30)	.45
≥3	1.48 (1.28-1.71)	<.001	1.29 (1.03-1.61)	.02

**HIV indicates human immunodeficiency virus; CI, confidence interval; AIDS, acquired immunodeficiency syndrome; PI, protease inhibitor; NNRTI, nonnucleoside retrotranscriptase inhibitor; and HAART, highly active antiretroviral therapy.*

†Risk hazard (RH) for age is per each year older, for $CD4^+$ is per 50% higher $CD4^+$ cell count, and for HIV-1 RNA is per each log_{10} higher HIV-1 RNA level.

‡Multivariate model is stratified for center and quartile of starting HAART.

§Previous AIDS classifies patients according to their AIDS status at starting HAART.

‖$CD4^+$ and RNA were measured at date of starting HAART.

RNA levels. Patients with a higher $CD4^+$ lymphocyte count were also at increased hazard of virological success ($P = .008$). The initiation of 3 or more antiretroviral drugs ($P = .02$) to which the patient had never been previously exposed predicted an increased hazard of virological success among patients starting HAART. Multivariate Cox hazards model found that naive status was not an independent predictor of the subsequent virological response toward undetectable HIV-1 RNA levels after adjustment for all available confounders. No interaction was found between the number of new drugs started when initiating HAART and naive status. Finally, no independent predictive power could be attributed to age or sex in our multivariate analysis.

PREDICTORS OF VIROLOGICAL FAILURE IN PATIENTS WHO INITIALLY ACHIEVE HIV-1 RNA LEVELS BELOW 500 Copies/mL

One hundred twenty-nine of 1054 patients who achieved HIV-1 RNA levels below 500 copies/mL had no further follow-up and were therefore excluded from the analysis of failure. Of the remaining 925 patients, 332 (35.9%) experienced a rebound in plasma HIV-1 RNA level greater than 1000 copies/mL after initially achieving HIV-1 RNA levels below 500 copies/mL.

Kaplan-Meier analysis (**Figure 4**) showed that the risk of experiencing a rebound in HIV-1 RNA levels in patients initially achieving undetectable HIV-1 RNA levels was 24% at 6 months. Overall, the median time to virological failure was 19 months. Significant differences were found between the percentage of drug-naive and drug-experienced patients experiencing virological failure (35% and 18%, respectively, at 6 months) ($P<.001$). Risk of rebound was also significantly different for patients starting 1, 2, and 3 or more drugs at the beginning of the study (32%, 24%, and 16%, respectively, at 6 months) ($P<.001$).

Table 3 shows the results of the univariate and multivariate Cox proportional hazards models for predictors of HIV-1 RNA level rebound in previously successful patients. After adjustment for confounding variables, older patients ($P = .04$), patients starting a PI regimen other than saquinavir hard gel ($P = .04$), and those who were antiretroviral naive at starting the treatment regimen ($P = .01$) were significantly less likely to experience virological failure. Lower baseline HIV-1 RNA levels ($P = .07$) and less time to reach undetectable plasma HIV-1 RNA levels ($P = .06$) were marginally significant predictors of a decreased hazard of ensuing virological failure in patients previously achieving undetectable HIV-1 RNA levels.

COMMENT

The present study was carried out in a large, European, prospectively followed cohort of 1469 unselected HIV-positive patients. This is the first study to specifically assess predictors of virological response to HAART in such a large, unselected, heterogeneous, and multinational cohort of people infected with HIV. Because of the design of this study, its findings may be reasonably extrapolated to people living with HIV or AIDS in the European continent.

The most relevant findings were that virological success was independently predicted by lower baseline plasma HIV-1 RNA levels, higher baseline $CD4^+$ counts, initiation of 3 or more new antiretroviral drugs, and the initial choice of a HAART regimen containing a PI other than saquinavir hard gel. Also, the antiretroviral-naive status of patients independently predicted a lower risk of ensuing virological failure in initially successfully treated patients. The inclusion of saquinavir hard gel as a single PI in initial HAART approaches was a strong independent predictor for virological failure. Lower baseline HIV-1 RNA levels and less time to reach undetectable HIV-1 RNA levels below 500 copies/mL were marginally significant using multivariate analysis of risk factors for virological failure.

High levels of plasma HIV-1 RNA are strongly predictive of clinical disease progression in HIV-infected patients.[1-7] Also, reductions in HIV-1 RNA levels clearly foresee an important clinical prognostic improvement of patients.[8,22,23] The HIV-1 RNA level is consistently superior to other prognostic markers in predicting HIV infection progression in almost all patient populations evaluated to date.[1] Our results evidenced that, indeed, lower HIV-1 RNA levels at the time of first starting HAART independently predicted a higher chance of therapy in terms of achieving and maintaining undetectable HIV-1 RNA

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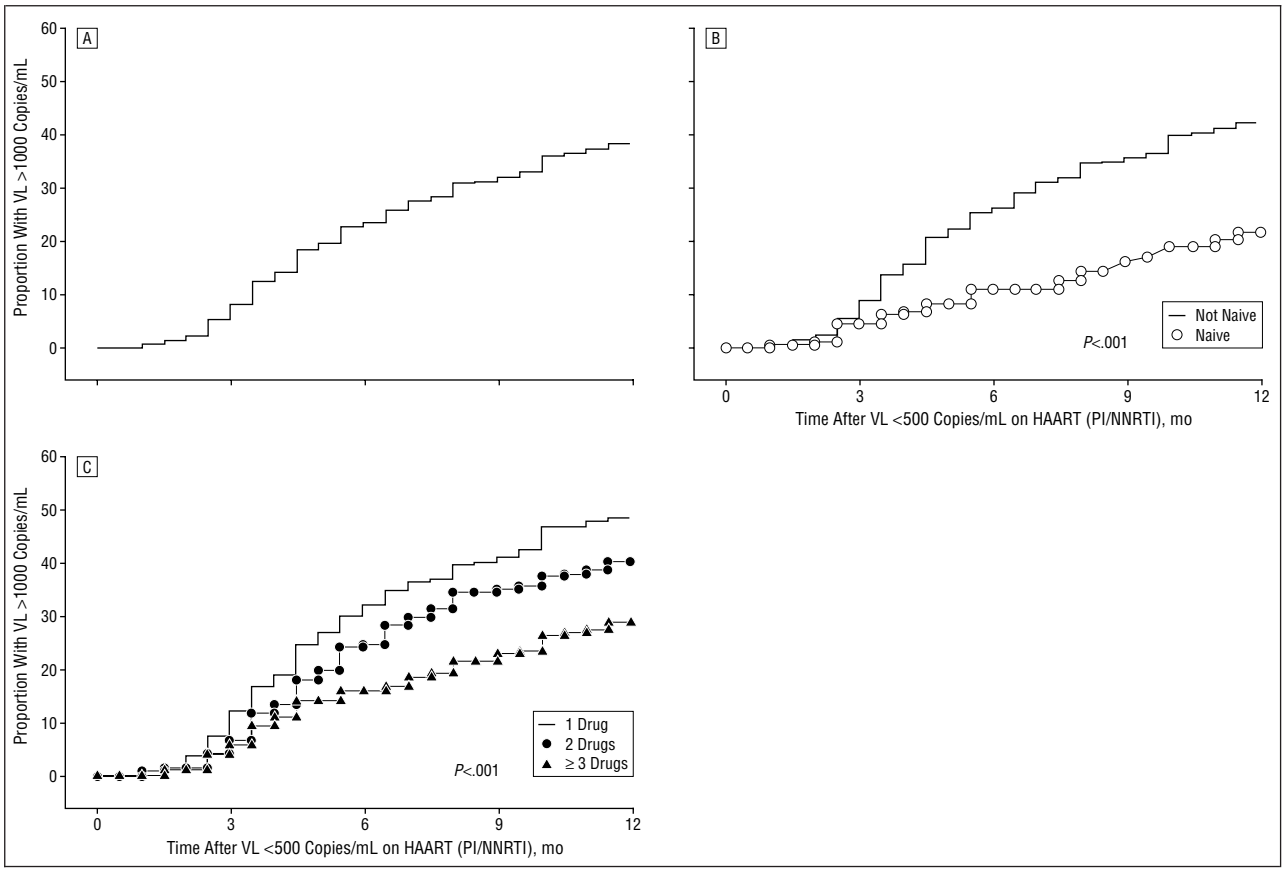

Figure 4. *Kaplan-Meier plots for the time to plasma human immunodeficiency virus 1 (HIV-1) RNA levels greater than 1000 copies/mL in patients initially achieving HIV-1 RNA levels below 500 copies/mL after first starting highly active antiretroviral therapy (HAART) for all patients (A); those with nucleoside retrotranscriptase inhibitor–naive vs –experienced status (B); and patients starting 1, 2, and 3 or more new drugs (C). VL indicates viral load.*

levels. In agreement with previously published data,[24] lower baseline HIV-1 RNA levels were the strongest predictor of an improved virological outcome.

Likewise, in accordance with results of previous studies,[24] high baseline CD4+ T-cell counts in our study independently predicted a better virological outcome of HAART after adjustment for relevant confounders. There has been an important debate concerning the predictive value of baseline CD4+ counts in terms of clinical prognosis. Considering previous studies[13,25-27] with divergent results, Lathey et al[28] argued that the prognostic value of CD4+ T-cell measurements may vary depending on the population studied and the length of the study, increasing in importance as CD4+ numbers decline. Our results help clarify that CD4+ counts play a determinant role in plasma viral responses to antiretroviral drug treatments.

The addition of at least 3 new antiretroviral drugs (2 NRTIs and a PI or an NNRTI) when first prescribing HAART implemented the virological success of therapy. In our study, patients starting at least 3 new drugs were more likely to achieve undetectable HIV-1 RNA levels than were patients starting 2 or less new drugs. This finding confirms that initial HAART regimens must be designed in their entirety, also considering the addition of at least 2 new NRTIs to achieve the best virological outcome of therapy. The simple addition of 1 PI or 1 NNRTI, even when a new NRTI is also included, seems to be clearly insufficient to maximally implement the antiviral efficacy of a starting HAART regimen. Conversely, the addition of 3 new drugs probably increases the genetic barrier of therapy, therefore permitting the best virological outcome of HAART approaches.

Furthermore, our results demonstrated that different PI-containing HAART strategies exert a different antiviral activity. Among patients first starting PIs, combinations including ritonavir plus saquinavir showed the highest antiviral potency. Yet, this modality of treatment was not an independent predictor for a particular virological outcome compared with the initial choice of nelfinavir, indinavir, or ritonavir alone. Nevertheless, combining ritonavir with saquinavir in initial PI-containing approaches has certain limitations. Because ritonavir presents a highly correlated cross-resistance pattern with indinavir and nelfinavir,[9] the eventual development of resistance to this dual PI approach might strongly constrain the efficacy of following salvage strategies containing PIs. On the other hand, it should be considered that the higher antiviral potency of this combination[29] might further suppress viral replication to the extent that the development of resistance mutations could be inhibited, hence limiting ensuing drug failure. Higher potency with the higher number of PIs combined argues for the design of alternative dual PI–containing initial HAART strategies with beneficial complementary drug resistance patterns, which may more intensely and durably sup-

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Table 3. Factors Related to HIV-1 RNA Levels Greater Than 1000 Copies/mL*

Factor	RH† (Univariate 95% CI)	P	RH† (Multivariate‡ 95% CI)	P
Age at HAART	0.87 (0.77-0.98)	.02	0.86 (0.75-0.99)	.04
Previous AIDS diagnosis at HAART§	0.99 (0.76-1.39)	.95	0.72 (0.50-1.03)	.07
$CD4^+$ at HAART, log_2‖	0.92 (0.86-0.98)	.01	0.92 (0.83-1.01)	.08
RNA at HAART, log_{10}‖	1.14 (1.00-1.30)	.05	1.18 (0.99-1.40)	.06
PI				
Saquinavir	1.00 (Reference)		1.00 (Reference)	
Other PI	0.55 (0.42-0.74)	<.001	0.66 (0.44-0.98)	.04
NNRTI	0.95 (0.56-1.62)	.86	1.33 (0.58-3.06)	.50
Naive				
No	1.00 (Reference)		1.00 (Reference)	
Yes	0.41 (0.28-0.60)	<.001	0.50 (0.29-0.87)	.01
No. of new drugs started				
1	1.00 (Reference)		1.00 (Reference)	
2	0.82 (0.64-1.06)	.13	0.86 (0.62-1.19)	.36
≥3	0.54 (0.42-0.71)	<.001	0.72 (0.49-1.07)	.11
Time to HIV-1 RNA <500¶	1.75 (1.27-2.40)	<.001	1.53 (0.99-2.38)	.06

*HIV indicates human immunodeficiency virus; CI, confidence interval; HAART, highly active antiretroviral therapy; AIDS, acquired immunodeficiency syndrome; PI, protease inhibitor; and NNRTI, nonnucleoside retrotranscriptase inhibitor.

†Risk hazard (RH) for age is per each year older, for $CD4^+$ is per 50% higher $CD4^+$ cell count, and for HIV-1 RNA is per each log_{10} higher HIV-1 RNA level.

‡Multivariate model is stratified for center and quartile of starting HAART.

§Previous AIDS classifies patients according to their AIDS status at starting HAART.

‖$CD4^+$ and RNA were measured at date of starting HAART.

¶Taken to HIV-1 RNA level <500 copies/mL (per year).

press viral replication. If the "first hit" is crucial, first-line HAART regimens including 2 PIs may achieve a faster and stronger viral suppression and therefore may account for a more durable virological response.

Contrasting with the high antiviral activity of dual PI–containing HAART combinations is the use of saquinavir as the single PI in triple-drug regimens. In our study, patients were at lower risk of achieving undetectable HIV-1 RNA levels if they included saquinavir hard gel as the only PI in HAART regimens compared with any other PI or NNRTI. Furthermore, including saquinavir in the initial design of triple-drug combinations was a strong independent predictor of the lower success of all PIs. Our results are in accordance with those of previous reports[18,30,31] and might be attributed to the limited oral biodisposibility of this drug.[32] These high rates of virological unresponsiveness advise to avoid standard doses of saquinavir hard gel capsules when other PIs are suitable. Nevertheless, previous studies[33] found that higher dosing of saquinavir resulted in a more pronounced virological effect of this drug. Also, recently approved soft-gel formulation of saquinavir might benefit from certain pharmacokinetic advantages translated in an improved antiviral activity.[34]

It was not possible to evaluate drug adherence as an independent predictor of virological success and failure in the present study. Previous studies have shown that low adherence to antiretroviral drug therapy predicted failure to HAART in NRTI-experienced patients.[30] Thus, it seems plausible to speculate that low adherence would also have been an important independent predictor of achieving and maintaining undetectable HIV-1 RNA levels in our study, as suboptimal drug levels would strongly make difficult the inhibition of HIV-1 replication. Despite our study including a relatively large percentage of intravenous drug users, who are believed to adhere worst when they are outside of drug substitution programs,[35] no differences were found in virological response depending on transmission category.

Probably, the key factor that links short-term virological response with long-term clinical improvement is the duration of plasma viral load suppression. Previous studies[36] have demonstrated that the duration of plasma HIV-1 RNA suppression is predicted by plasma HIV-1 RNA levels at the nadir. Raboud et al[15] reported that the suppression of plasma viral load below 20 copies/mL was necessary to achieve a long-term antiretroviral response. It has been recently suggested[37] that the main goal for obtaining durability of response should be to suppress HIV RNA levels to below 1 copy/mL, whenever it becomes available. Havlir et al[38] found that patients with higher rates of viral clearance were more likely to achieve and sustain viral suppression with maintenance therapy after induction antiretroviral treatment. We found that lower baseline HIV-1 RNA levels and less time to reach undetectable viral load levels were related to the durability of the virological response, with marginal statistical significance. Results of this study suggest that patients starting HAART who achieve viral suppression faster are more likely to maintain this suppression through time.

As well, patients who had been previously exposed to antiretroviral regimens were 2 times more likely to experience a viral rebound than were those who had started HAART as the first antiretroviral regimen. A plausible explanation to this finding is that antiretroviral-experienced patients are at a higher risk for the accumulation of resistant and cross-resistant mutations, which in turn decrease the genetic barrier for forthcoming drug regimens.[12] Probably, adherence issues maximize its importance in drug-experienced patients because the minimum chance given for the accumulation of further drug resistance, even by brief skips in medication intake, might be crucial to defeat the antiviral pressure of drugs and to allow virus escape. Such rationale has been revised in other studies[30,39] of virological response to treatments including adherence and genotypic resistance data.

Age was an independent predictor for virological failure in our study, with treatment less likely to fail in older patients. Similar results have been previously reported,[24] and no clear explanations are available at this moment. Older patients might be more adherent to treatments because of a better socioeconomic profile. However, pharmacokinetic or pharmacodynamic aspects cannot be discarded. Futher studies are needed to corroborate

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our findings and to eventually give plausible explanations to this phenomenon.

Although our results are reasonably clear and consistent with clinical practice and previous studies, some biases eventually affecting our results should be considered. Briefly, the variation in the quality of the HIV-1 RNA determinations, the variable frequency of HIV-1 RNA measurements, and the temporal differences in the time of starting different antiretroviral drugs within different laboratories and clinical units involved in the EuroSIDA cohorts may bias our findings to some extent. Nevertheless, these limitations should be considered somewhat inherent to the intrinsic design of any continental multicenter cohort study, which is always subjected to the variations in the local policies for the assessment of HIV infection. Further follow-up might more reliably identify factors associated with a particular virological outcome of initial HAART combinations, particularly for the factors associated with virological rebound in previously successful patients. Also, because patients were not randomized to specific treatments, there is the potential for bias in the reporting of the results of specific treatment responses. Therefore, such significant associations should be definitely clarified in the corresponding randomized controlled trials.

On the other hand, the models presented herein adjust for baseline factors because when patients start HAART, clinicians often wish to give a guide as to the likely success of the regimen, without the knowledge of how the initial response will proceed. However, we also constructed multivariate models that adjusted for changes in $CD4^+$ lymphocyte count and that accounted for the changes in therapy after initiation of HAART. The conclusions of these models (data not shown) were identical to those already presented.

It is important to adjust such models for calendar period because there are large differences across Europe in the rate and manner in which HAART was introduced.[11] There are likely to be differences in response to HAART as time progressed. Formerly, antiretroviral treatment might have been offered as monotherapy or added to an existing regimen, whereas more recently it is offered to healthier patients, rarely as monotherapy, and often with a change of all existing nucleosides. In fact, stratification by calendar period was necessary in our study because major differences were found in the drug use pattern depending on the date and mode of introduction of drugs (data not shown).

In conclusion, the best attitude to achieve undetectable viral load levels when starting HAART is to start it at the lower HIV-1 RNA levels and the higher $CD4^+$ counts, to add at least 2 new NRTIs in parallel with a PI or NNRTI, and to avoid standard doses of saquinavir hard gel capsule as a single PI. Thereafter, the lower the baseline HIV-1 RNA levels are at the onset of therapy, the lower they get, and the faster that patients achieve maximal viral suppression, the higher durability of virological response has to be expected. Finally, it has to be considered that younger and antiretroviral-experienced patients will be more likely to experience virological rebound. In these patients, the reinforcement of drug adherence is probably the best attitude to promote.

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