

Clinical Outcome of Patients with HIV-1 Infection according to Immunologic and Virologic Response after 6 Months of Highly Active Antiretroviral Therapy

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Background: The prognostic value of discordant immunologic (CD4 cell increase) and virologic (plasma HIV RNA level decrease) responses to antiretroviral treatment is not known.

Objective: To study the relation between clinical outcome of HIV-infected patients receiving highly active antiretroviral therapy (HAART) and early immunologic and virologic responses to such therapy.

Design: Prospective cohort study.

Setting: 68 hospitals in France.

Patients: 2236 protease inhibitor-naïve patients.

Intervention: Initiation of HAART with one protease inhibitor and two nucleoside analogues between July 1996 and March 1997.

Measurements: Immunologic and virologic response at 6 months. Multivariate Cox models were used to assess the relation between these responses and progression to a new AIDS-defining event or death.

Results: On the basis of 6-month immunologic and virologic responses, patients were classified into four groups: complete

response (47.5%), complete nonresponse (16.2%), immunologic response only (19.0%), and virologic response only (17.3%). After month 6 and within a median of 18 months, 69 patients died and 123 experienced a new AIDS-defining event. After adjustment, complete nonresponders and those with only a virologic response had significantly higher risks for clinical progression at 6 months (relative risk, 3.38 [95% CI, 2.28 to 5.02] and 1.98 [CI, 1.26 to 3.10], respectively) than complete responders. The difference between complete responders and those with only an immunologic response at 6 months was weaker and nonsignificant (relative risk, 1.55 [CI, 0.96 to 2.50]).

Conclusions: Immunologic response after 6 months of HAART indicates a favorable clinical outcome in HIV-infected patients regardless of virologic response. This suggests that both immunologic and virologic markers should be used in clinical practice to evaluate treatment response.

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For the Clinical Epidemiology Group of the French Hospital Database on HIV, see Appendix.

See editorial comment on pp 471-473.

Highly active antiretroviral therapy (HAART) has significantly reduced morbidity and mortality in HIV disease (1, 2). In clinical practice, plasma HIV RNA levels and CD4 cell counts are used to monitor the efficacy of therapy. The potential benefit of decreasing the viral load to the lowest possible levels is supported by the prognostic value of plasma HIV RNA levels during the natural history of HIV disease (3), the positive relationship between the nadir of the virologic response and long-term virologic response to treatment (4), and the increased risk for resistant strains of HIV in persons with uncontrolled viral replication (5). The relationship between plasma viral load and CD4 cell counts in HIV disease is complex (6–9). In the long term, the decreased risk for opportunistic infections and tumors in patients receiving HAART is related to an immunologic response to treatment, which leads to increased CD4 cell counts (10, 11) and CD4 cell function above critical thresholds (12).

Antiretroviral therapy does not totally suppress viral replication (13). Several studies have shown that CD4 cell counts may increase in some patients receiving HAART despite the persistence of detectable viremia. However, the long-term prognosis of patients exhibiting such discordant responses remains unknown (14–16). We report clinical outcomes in a large cohort of patients in France 24 months after initiation of triple therapy that contained protease inhibitors, according to virologic and immunologic response at 6 months.

Methods

Patients

The French Hospital Database on HIV (FHDH) is a national project that began in 1989. A total of 68 hospitals across France currently provide epidemiologic data on HIV infection. A trained research assistant uses standardized procedures to prospectively collect clinical, laboratory, and

treatment data from medical records by using specialized French Ministry of Health software (Dossier Médico-Économique Informatisé, version 2 [DMI2]). All participants provided informed consent for participation in the FHDH. The full database protocol has been described elsewhere (17).

For our analysis, we selected all protease inhibitor-naïve adult patients who began HAART with one protease inhibitor and two nucleoside reverse transcriptase inhibitors between July 1996 and March 1997. All selected patients had CD4 cell counts and plasma HIV RNA measurements recorded at initiation (baseline) and after 6 months of HAART. Exclusion criteria were enrollment in a trial of antiretroviral therapy, infection with HIV-2, or receipt of zidovudine or non-nucleoside reverse transcriptase inhibitors (these drugs were used only in clinical trials at the time of enrollment in this study).

Definitions of Immunologic and Virologic Responses and Clinical Outcomes

Immunologic response was defined as an increase in CD4 cell count from baseline of more than 0.05×10^9 cells/L. Virologic response was defined as a decrease in plasma HIV RNA level from baseline of more than 1 $\log_{10}$ copies/mL or a plasma HIV RNA level less than 1000 copies/mL. This value of 1000 copies/mL was chosen to overcome the heterogeneity of the assay detection limits used to quantify plasma HIV RNA during the study period in the different medical centers (19). We classified AIDS-defining events according to the 1993 revised clinical definition of the Centers for Disease Control and Prevention (18). Therefore, a CD4 cell count less than 0.2×10^9 cells/L was not considered an AIDS-defining event. In each center, trained research assistants reviewed clinical reports to ascertain death and clinical events. The clinicians who determine the occurrences of clinical progression in the medical record are aware of the patients' immunologic and virologic status.

Statistical Analysis

We examined progression to a new AIDS-defining event or death according to immunologic and virologic status after 6 months of HAART. Only deaths and new AIDS-defining events that occurred after the first 6 months of HAART were considered. Time to an event was therefore calculated from month 6 to death or to the first new AIDS-defining event. For patients with a previous AIDS

diagnosis, we considered only new AIDS-defining events and not recurrences. Univariate analyses were performed by using Kaplan–Meier survival estimates, and differences between curves were tested by using the log-rank test. Separate analyses were performed for treatment-naïve patients (those who had never received antiretroviral drugs) and treatment-experienced patients (those who had received antiretroviral drugs but not protease inhibitors).

For multivariate analysis, we used Cox proportional hazards models stratified on the protease inhibitor starting period at 3-month intervals and on previous antiretroviral therapy experience. Stratifications were introduced to account for the time effect in the choice of new therapeutic options and the imbalance between treatment-naïve and treatment-experienced patients. To select the variables in the final model, we worked backward from a complete model that included the following potential baseline confounders: sex, age, transmission group, previous AIDS status, CD4 cell count, plasma HIV RNA level, and type of protease inhibitor and nucleoside reverse transcriptase inhibitor combination. Age, CD4 cell counts, and plasma HIV RNA levels were modeled as continuous variables, using $\log_2$ transformation for CD4 counts and $\log_{10}$ transformation for HIV RNA levels. The main variable of interest—immunologic and virologic status at 6 months—was forced in the model. After several steps, the final model was adjusted for age, previous AIDS status, baseline CD4 cell count, and baseline plasma HIV RNA level.

To account for the delay in reporting deaths in the database, we used the following right-censoring strategy. Patients seen event-free in the 6 months before the date of the last database update (that is, between June and December 1998) were censored on 31 December 1998. Patients with no follow-up visit in these 6 months were considered lost to follow-up and were censored at the date of their last visit. Statistical analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Sources

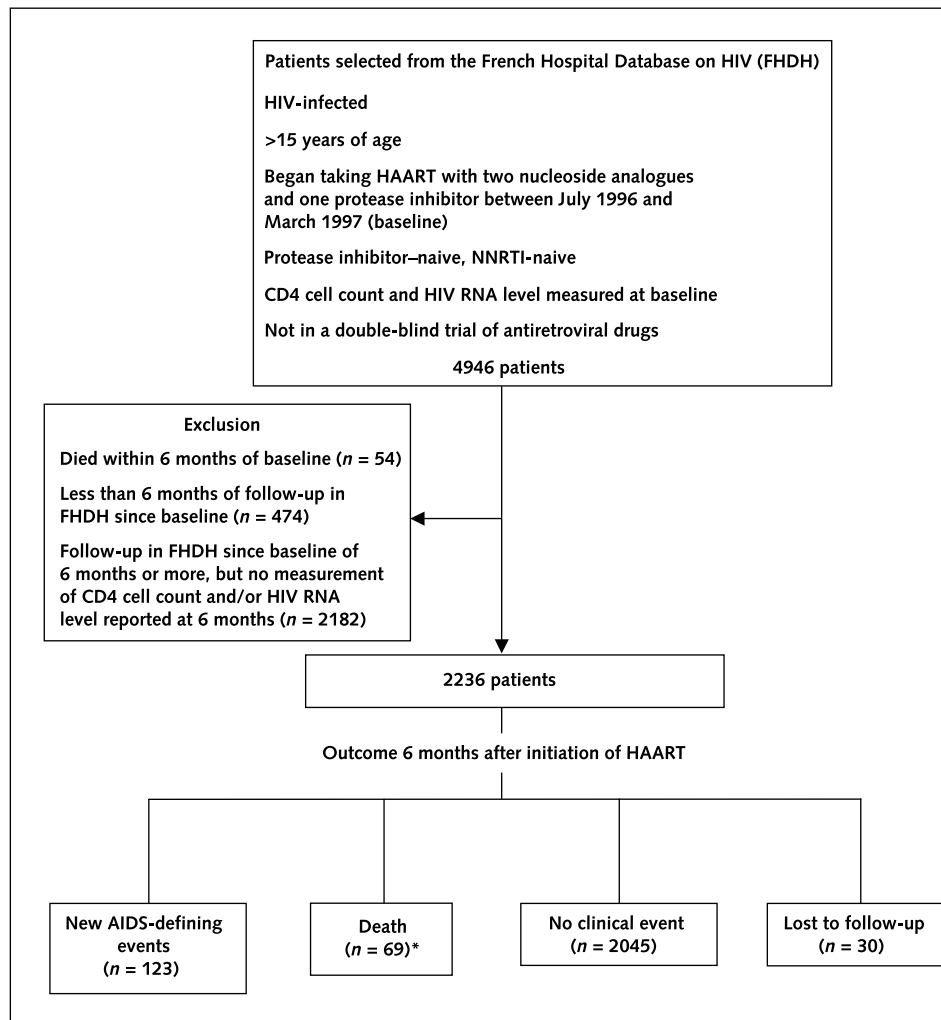
The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

Results

Patient Characteristics at Baseline

A total of 2236 protease inhibitor-naïve patients fulfilled the inclusion criteria (Figure 1). The baseline demo-

Figure 1. Patient selection.



HAART = highly active antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor. * 31 patients had a new AIDS-defining event before death.

graphic characteristics of the patient sample are shown in Table 1. Thirty percent of patients had an AIDS-defining event before enrollment. A protease inhibitor-containing triple-drug regimen was the first antiretroviral treatment prescribed in 508 treatment-naïve patients (22.7%). In the remaining 1728 treatment-experienced patients (77.3%), the median previous duration of antiretroviral treatment was 22 months (interquartile range, 10 to 41 months). The median baseline CD4 cell count was 0.15×10^9 cells/L (interquartile range, 0.065 to 0.263×10^9 cells/L), and the median plasma HIV RNA level was 35 000 copies/mL ($4.54 \log_{10}$ copies/mL [interquartile range, 3.67 to $5.13 \log_{10}$ copies/mL]). At baseline, treatment-naïve patients had

a significantly higher median CD4 cell count (0.18×10^9 cells/L [interquartile range, 0.061 to 0.348×10^9 cells/L]) and a significantly higher median plasma HIV RNA level (78 500 copies/mL [interquartile range, 15 965 to 270 000 copies/mL]) than treatment-experienced patients (0.146×10^9 cells/L [interquartile range, 0.066 to 0.243×10^9 cells/L] and 27 100 copies/mL [interquartile range, 3600 to 105 000 copies/mL], respectively).

Immunologic and Virologic Responses

After 6 months of HAART, the median increase in CD4 cell counts in the entire patient sample was 0.086×10^9 cells/L (interquartile range, 0.031 to 0.183×10^9

Table 1. Patient Characteristics according to Immunologic and Virologic Responses after 6 Months of Highly Active Antiretroviral Therapy*

Characteristic	Patients with Immunologic and Virologic Response (n = 1062)	Patients with Immunologic Response Only (n = 424)	Patients with Virologic Response Only (n = 387)	Patients with No Response (n = 363)	All Patients (n = 2236)	P Value†
Baseline						
Sex, n (%)						
Women	225 (21.2)	100 (23.6)	74 (19.1)	72 (19.8)	471 (21.1)	>0.2
Men	837 (78.8)	324 (76.4)	313 (80.9)	291 (80.2)	1765 (78.9)	
Median age, y	36.6	35.4	36.7	36.2	36.5	0.17
Transmission group, n (%)						
Homosexual	483 (45.5)	179 (42.2)	148 (38.2)	146 (40.2)	956 (42.7)	0.009
Intravenous drug user	179 (16.8)	82 (19.3)	97 (25.1)	84 (23.1)	442 (19.8)	
Heterosexual	309 (29.1)	123 (29.0)	95 (24.6)	96 (26.5)	623 (27.9)	
Other	91 (8.6)	40 (9.5)	47 (12.1)	37 (10.2)	215 (9.6)	
AIDS status, n (%)						
No AIDS	758 (71.4)	301 (71.0)	265 (68.5)	235 (64.7)	1559 (69.7)	0.13
AIDS	304 (28.6)	123 (29.0)	122 (31.5)	128 (35.3)	677 (30.3)	
Median CD4 count (interquartile range), ×10 ⁹ cells/L	0.154 (0.07–0.271)	0.14 (0.06–0.258)	0.151 (0.075–0.268)	0.141 (0.048–0.232)	0.15 (0.065–0.263)	0.03
Median plasma HIV RNA level (interquartile range), log ₁₀ copies/mL	4.67 (3.8–5.2)	4.46 (3.5–6.0)	4.39 (3.2–5.0)	4.47 (4.0–5.0)	4.54 (3.67–5.13)	0.003
Antiretroviral treatment history, n (%)						
Naive	292 (27.5)	49 (11.6)	103 (26.6)	64 (17.6)	508 (22.7)	0.001
Experienced	770 (72.5)	375 (88.4)	284 (73.4)	299 (82.4)	1728 (77.3)	
First protease inhibitor prescribed, n (%)						
Ritonavir	150 (14.1)	54 (12.7)	55 (14.2)	57 (15.7)	316 (14.1)	0.001
Saquinavir	216 (20.4)	178 (42.0)	80 (20.7)	133 (36.6)	607 (27.1)	
Indinavir	696 (65.5)	192 (45.3)	252 (65.1)	173 (47.7)	1313 (58.8)	
After 6 months of highly active antiretroviral therapy						
Increase in CD4 count from baseline (interquartile range), ×10 ⁹ cells/L	0.135 (0.09 to 0.213)	0.119 (0.079 to 0.183)	0.014 (−0.012 to 0.032)	0.006 (−0.02 to 0.03)	0.086 (0.031 to 0.183)	
Patients with CD4 count ≥ 0.200 × 10 ⁹ cells/L, n (%)	799 (75.2)	310 (73.1)	153 (39.5)	128 (35.3)	1390 (62.2)	
Decrease in plasma HIV RNA level from baseline (interquartile range), log ₁₀ copies/mL	−1.4 (−2.1 to −0.7)	−0.1 (−0.6 to 0.3)	−1.2 (−1.9 to −0.2)	0.1 (−0.4 to 0.5)	−0.8 (−1.7 to 0)	
Patients with HIV RNA levels < 1000 copies/mL, n (%)	877 (82.6)	0	311 (80.4)	0	1188 (53.1)	

* Immunologic response = an increase in CD4 cell count from baseline of at least 0.05×10^9 cells/L; virologic response = decrease in plasma HIV RNA level from baseline of at least 1 $\log_{10}$ copies/mL or an HIV RNA level that decreased below 1000 copies/mL.

† Comparison between groups, chi-square and Kruskal–Wallis tests.

cells/L) and the median change in plasma HIV RNA level was $-0.8 \log_{10}$ copies/mL (interquartile range, -1.7 to $0 \log_{10}$ copies/mL) (Table 1). The patients were classified into four groups according to immunologic and virologic responses at 6 months of treatment. One thousand sixty-two patients (47.5%) had an immunologic and virologic response (complete responders), and 363 (16.2%) did not have any response (complete nonresponders). Eight hun-

dred eleven patients (36.3%) had discordant responses. Of these, 387 (17.3%) had a virologic response but no immunologic response and 424 (19.0%) had an immunologic response but no virologic response. Table 1 shows the patients' characteristics according to plasma HIV RNA level and CD4 cell count at 6 months. Patients who were complete responders at 6 months were more often treatment-naïve at entry and were more often given indinavir or

ritonavir. Intravenous drug users were less likely to have an immunologic response to treatment. One thousand seventy-four patients (48%) changed their initial protease inhibitor regimen after a median of 8.4 months (interquartile range, 4.8 to 12.7 months). This occurred more frequently in those with no virologic response at 6 months (65%) than in those with such a response (40%).

At 12 months of treatment, CD4 cell counts and plasma HIV RNA levels were available in 1176 patients (Table 2). Compared with the remaining 1060 patients in the cohort, these patients had a slightly higher increase in CD4 cell count at 6 months (0.093×10^9 cells/L [interquartile range, 0.037 to 0.167×10^9 cells/L]) vs. 0.08×10^9 cells/L [interquartile range, 0.025 to 0.148×10^9 cells/L]) but did not otherwise differ. At 12 months, the median increase in CD4 cell count from baseline was 0.125×10^9 cells/L (interquartile range, 0.05 to 0.21×10^9 cells/L). Most patients who were complete responders at 6 months remained complete responders at 12 months (78.4%). Among patients who had only an immunologic response at 6 months, 56% had the same response at 12 months whereas 29.1% had a delayed virologic response at 12 months. One third of patients who had only a virologic response at 6 months did not change at 12 months, and 43.9% had a delayed immunologic response at 12 months. Forty-two percent of those who were complete nonresponders at 6 months remained so at 12 months.

Clinical Progression

After month 6, the median follow-up was 18 months (interquartile range, 15.2 to 20.3 months [2966 person-years]). Within this time frame, 69 patients (3.1%) died, 31 of whom had experienced an AIDS-defining event. A

total of 151 new AIDS-defining events were diagnosed in 123 patients. Thirty patients (1.3%) were lost to follow-up (Figure 1). The mortality rate was 2.3 per 100 person-years, and the incidence of new AIDS-defining events was 4.1 per 100 person-years.

Kaplan–Meier curves of progression to a new AIDS-defining event or death indicated that clinical progression differed significantly according to patients' immunologic and virologic responses at 6 months ($P = 0.001$), regardless of their previous treatment history (Figure 2). At 24 months from baseline, the rate of clinical progression gradually increased, from 4.8% (95% CI, 3.5% to 6.2%) in complete responders to 7.2% (CI, 4.6% to 9.8%) in patients with only an immunologic response to 9.5% (CI, 6.2% to 12.7%) in those with only a virologic response to 15.9% (CI, 11.9% to 19.8%) in complete nonresponders.

After adjusting for baseline characteristics, we found similar results with regard to clinical outcome. The relative risk for clinical progression was 3.38 (CI, 2.28 to 5.02) times greater for complete nonresponders than for complete responders. Patients who had a virologic response but no immunologic response at 6 months had a higher risk for progression than complete responders (relative risk, 1.98 [CI, 1.26 to 3.10]) but a lower risk than complete nonresponders (relative risk, 0.59 [CI, 0.38 to 0.91]). In contrast, patients who responded immunologically but not virologically had a weaker and nonsignificant risk for progression compared with complete responders (relative risk, 1.55 [CI, 0.96 to 2.50]).

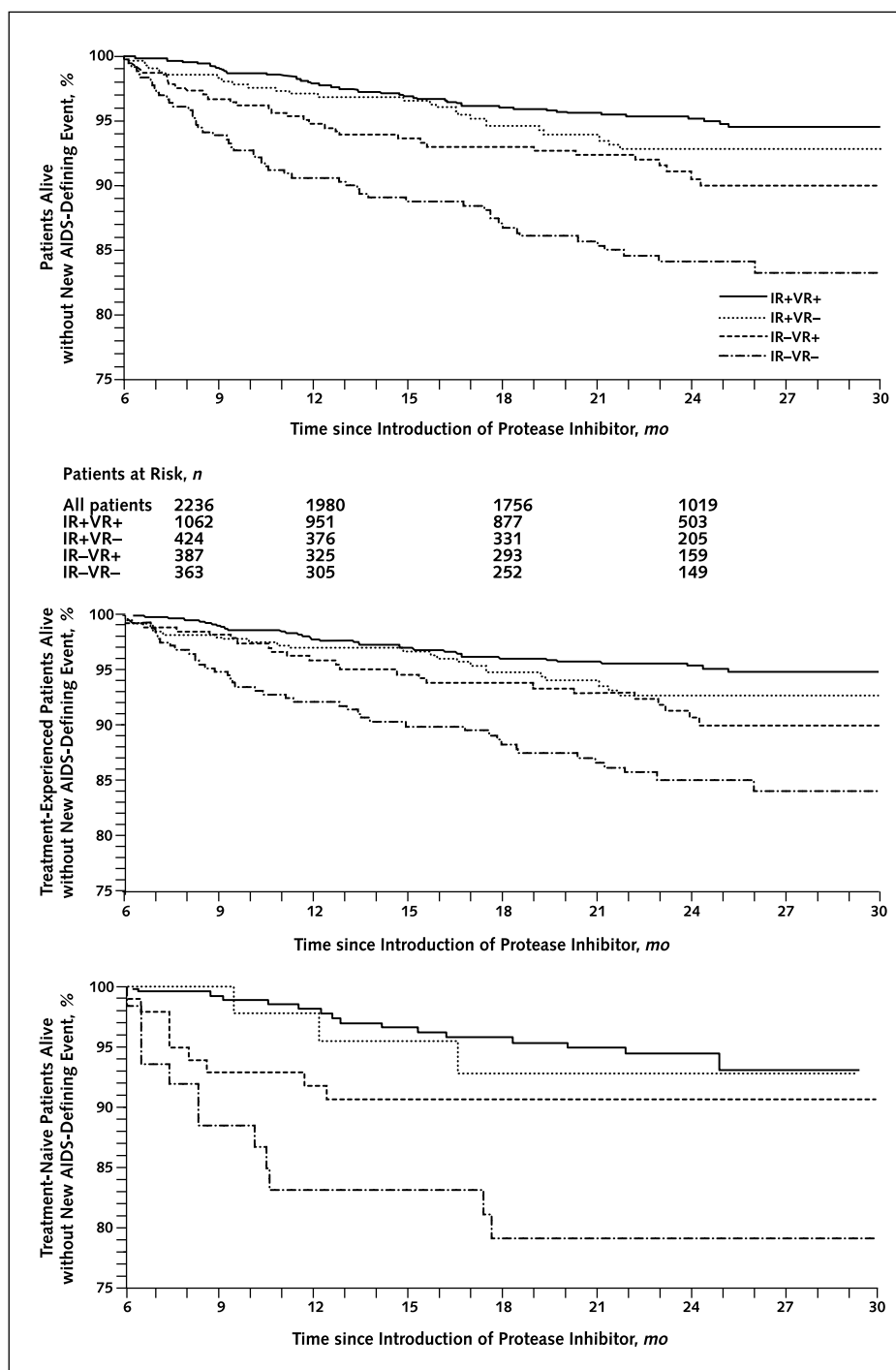
When the multivariate analysis was performed separately for treatment-naïve and treatment-experienced patients, we observed results similar to those for the entire study sample. However, among treatment-naïve patients,

Table 2. Immunologic and Virologic Responses after 12 Months of Highly Active Antiretroviral Therapy, according to Initial Responses at 6 Months*

At 6 Months	At 12 Months			
	Patients with Immunologic and Virologic Response	Patients with Immunologic Response Only	Patients with Virologic Response Only	Patients with No Response
	← % →			
Patients with immunologic and virologic response ($n = 573$)	78.4	12.4	7.3	1.9
Patients with immunologic response only ($n = 227$)	29.1	56.0	3.5	11.4
Patients with virologic response only ($n = 198$)	43.9	6.1	33.3	16.7
Patients with no response ($n = 178$)	17.4	26.4	14.1	42.1

* Analyses based on a subset of patients with biological data available at baseline, month 6, and month 12 ($n = 1176$). Immunologic response = increase in CD4 cell count from baseline of at least 0.05×10^9 cells/L; virologic response = decrease in plasma HIV RNA level from baseline of at least 1 $\log_{10}$ copies/mL or a plasma HIV RNA level that decreased below 1000 copies/mL.

Figure 2. Kaplan–Meier curves of progression to a new AIDS-defining event or death after 6 months of protease inhibitor-containing therapy, according to immunologic and virologic responses.



The top panel shows all 2236 HIV-infected study patients, the middle panel shows the 1728 treatment-experienced patients, and the bottom panel shows the 508 treatment-naïve patients. IR+VR+ = immunologic and virologic response; IR+VR- = immunologic response, no virologic response; IR-VR+ = no immunologic response, virologic response; IR-VR- = no immunologic or virologic response. Immunologic response was defined as an increase in CD4 cell count from baseline of at least 0.05×10^9 cells/L. Virologic response was defined as a decrease in plasma HIV RNA level from baseline of at least 1 log₁₀ copies/mL or an HIV RNA level that decreased to below 1000 copies/mL. $P < 0.001$ for all comparisons.

risk for progression was similar in those who had an immunologic response regardless of virologic response (relative risk, 1.06 [CI, 0.31 to 3.71]) compared with complete responders.

Discussion

Our study of a cohort of 2236 HIV-infected patients with moderately advanced immunosuppression showed a high frequency of discordant immunologic and virologic responses to HAART after 6 months. Our data indicate that the pattern of early immunologic and virologic response is predictive of clinical outcome at 24 months. Patients exhibiting an immunologic response at 6 months were at lower risk for disease progression regardless of their virologic response. Patients who exhibited only a virologic response were at intermediate risk for clinical progression, and complete nonresponders had the least favorable prognosis.

Several biases and confounding factors might have influenced the results. First, to be included in the study, patients recorded in the FHDH must have had an immunologic and virologic assessment 6 months after starting HAART. Consequently, patients who died or were lost to follow-up during the first 6 months of protease-inhibitor-containing therapy were not included. We may therefore have underestimated the risk for clinical progression. However, the rates of progression observed were consistent with those in other studies (10, 20). Second, our definition of virologic response considered both partial (that is, a decrease of viral load from baseline of $>1 \log_{10}$ copies/mL) and complete viral suppression (that is, a viral load that decreased below the accepted threshold). Compared with definitions that would have considered only complete virologic suppression, our definition may have led us to underestimate the prognostic benefit of virologic response. However, more than 80% of patients with a virologic response had viral loads below the accepted threshold (Table 1). Our study and other reports demonstrate that even partial virologic response is associated with improved clinical outcome. Therefore, use of a more stringent definition would not have altered our conclusion about the independent role of immunologic response in predicting clinical outcomes.

Third, the study sample had heterogeneous experience with previous antiretroviral therapy. Our subanalyses in treatment-naïve and treatment-experienced patients attempt to address this issue. The relationship between clinical

progression and immunologic and virologic response were only slightly different in these subgroups. Of interest, discordant responses to HAART were observed in all patients, not only those who had previously received antiretroviral drugs. Virologic failure in naïve patients may be caused by lack of adherence to therapy or by unfavorable pharmacokinetics. Treatment-experienced patients may exhibit virologic failure because of these factors or because of preexisting mutations in the reverse transcriptase gene, which confer resistance to nucleoside analogues (21–23).

Although almost 50% of patients who had only a virologic response at 6 months exhibited an immunologic response at 12 months, these patients progressed more rapidly to a new AIDS-defining event or death than complete responders. However, they were at lower risk for progression than complete nonresponders. This suggests that these patients may benefit from immune-based therapy with such agents as interleukin-2, which has been shown to improve immune function (24).

Most patients with an immunologic response but no virologic response at 6 months had similarly discordant responses at 12 months. However, they also had a low risk for clinical progression. This observation suggests that the new CD4 cells generated or redistributed from lymphoid tissues may have partially restored immune function, a hypothesis supported by a recent study showing that such patients exhibit proliferative responses to cytomegalovirus antigens (23). The favorable clinical outcomes of those who responded immunologically but not virologically confirm previous observations made in smaller study samples (14–16). However, the long-term outcomes of patients with discordant responses require further study.

Mechanisms underlying immune reconstitution associated with HAART are not yet fully understood (25). Although it has been suggested that immune recovery depends on the amplitude and duration of viral load reduction, the intensity of viral suppression needed to improve CD4 T-cell functions is still debated (12). The discordance between persistent HIV plasma viremia despite HAART and partial immune reconstitution could be explained by diminished fitness of mutant viruses (26); such defective viruses develop an altered capacity to induce immune deficiency. Other potential mechanisms include a decreased cytopathic effect of the virus, an inability of protease inhibitor-influenced mutant strains of HIV to replicate in human thymus (27), and an increased half-life of CD4 cells (28) related to decreased T-cell apoptosis (29).

Our results confirm the relation between the increase in CD4 cell counts and the improvement in clinical outcome associated with protease inhibitor-containing regimens (10, 11, 30). These data support the belief that it is safe to discontinue prophylaxis against opportunistic infections in patients whose CD4 cell count has increased above the prophylaxis threshold (31, 32). Therefore, although virologic response increases the clinical benefit associated with immunologic response, assessing and managing treatment failure solely on the virologic end point may be insufficient. As emphasized by the most recent guidelines, physicians deciding to change a patient's therapy must consider the possibility of further selection of resistance mutations with suboptimal antiretroviral treatment and the likelihood that a different regimen will control viral replication (33). Because highly resistant viral strains have been isolated from patients exhibiting paradoxical cell responses, therapeutic alternatives are sparse (14, 21). Modifications of antiretroviral regimens may be delayed until other therapeutic options emerge. Physicians should not discontinue protease inhibitor—including regimens associated with a rapid decrease in CD4 cell counts, and patients should be encouraged to adhere strictly to their current therapy even if it is only partially effective (14).

In summary, our observational study showed that although most patients exhibited both immunologic and virologic response to HAART at 6 months, discordant responses are common in clinical practice. Although many patients do not achieve complete early virologic response, clinical outcome may improve if CD4 cell count increases. Therefore, both immunologic and virologic markers should be used in assessing clinical treatment failure.

Appendix

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