

Clinical Outcome of HIV-Infected Antiretroviral-Naive Patients With Discordant Immunologic and Virologic Responses to Highly Active Antiretroviral Therapy

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Background: The prognostic significance of a response to highly active antiretroviral therapy (HAART) that is immunologically and virologically discordant is not well understood.

Methods: Four hundred four antiretroviral-naive patients initiating HAART at an urban HIV outpatient clinic in 1995 to 2004 were analyzed. The association of treatment responses at 3 to 9 months after HAART initiation with time to development of an opportunistic infection (OI) or death was determined using Cox proportional hazards modeling. Logistic regression modeling was used to examine the association between discordant responses and patient characteristics.

Results: Of 404 patients, 70.5% experienced favorable concordant responses (CD4 cell count [CD4]⁺/viral load [VL]⁺: increase in CD4 count of ≥ 50 cells/ μ L and achievement of undetectable plasma HIV RNA level), 15.8% an immunologic response only (CD4⁺/VL⁻), 8.7% a virologic response only (CD4⁻/VL⁺), and 5.0% a concordant unfavorable response (CD4⁻/VL⁻). Both types of discordant responses (CD4⁺/VL⁻ and CD4⁻/VL⁺), nonresponse (CD4⁻/VL⁻), and baseline CD4 cell count were significantly associated with earlier development of an OI or death (relative hazard [RH] = 2.81, 95% confidence interval [CI]: 1.31 to 3.97; RH = 4.83, 95% CI: 2.10 to 11.12; and RH = 0.93, 95% CI: 0.88 to 0.99, respectively). CD4⁺/VL⁻ and CD4⁻/VL⁻ were associated with nonwhite race in multivariate logistic regression models (adjusted OR = 2.83, 95% CI: 1.46 to 5.47 and adjusted OR = 6.50, 95% CI: 1.65 to 25.69, respectively).

Conclusion: Discordant immunologic and virologic responses at 3 to 9 months after HAART initiation play important roles in predicting long-term clinical outcomes in treatment-naive patients.

Key Words: clinical outcomes, discordant responses, highly active antiretroviral therapy, HIV

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Highly active antiretroviral therapy (HAART) significantly reduces morbidity and mortality in HIV disease. The likelihood of HIV disease progression among patients undergoing antiretroviral treatment (ART) can be predicted by plasma HIV RNA viral load (VL) and CD4 cell count responses 3 to 9 months after initiating HAART, independent of pretreatment values.¹ Although immunologic and virologic responses predict HIV disease progression, the relation among variable responses is still not well understood.^{2–9}

Approximately 20% to 40% of HIV-infected patients initiating HAART exhibit discordant responses (immunologic response in the absence of a virologic response or the opposite).^{4,5,7,10–13} Virologic-only responses have been associated with baseline CD4 cell counts, whereas immunologic-only responses have been associated with VL at baseline,¹⁴ and virologic-only and immunologic-only responses have been associated with infection of multiresistant viral strains.¹⁵ Studies examining discordant immunologic and virologic responses have shown significant associations with AIDS-defining events or mortality;^{4,7,8} however, different definitions of immunologic or virologic response have been used, and the results have been inconsistent.

To understand the clinical consequence of discordant immunologic and virologic responses to HAART better, we examined the associations of these responses with the risk of an opportunistic infection (OI) or death and the contribution of patient characteristics. We further evaluated patient and treatment characteristics associated with differential immunologic and virologic response combinations.

METHODS

The University of Alabama at Birmingham (UAB) Outpatient HIV Clinic (1917 Clinic) has been providing primary care to HIV-positive patients since 1988. The clinic

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began prospectively to collect information on all patients in a longitudinal, observational database in January 1992. During the study period, trained personnel extracted clinical and treatment data from medical records daily, which were entered into the database. Laboratory data were downloaded from the hospital laboratory information system directly into the database. Results of laboratory tests performed outside of UAB are entered into the database manually. The UAB database protocol was approved by the UAB Institutional Review Board for the conduct of prospective and retrospective studies.

The inclusion criteria for this study were (1) HIV-infected patients attending the 1917 clinic; (2) HAART initiation after January 1, 1995; (3) lack of ART use before treatment initiation at the clinic; (4) availability of baseline CD4 cell count and VL measurements at regimen initiation (closest value before HAART initiation); and (5) availability of at least 1 CD4 cell count and 1 plasma HIV-1 RNA measurement (VL) between 3 and 9 months after starting HAART. Patients were followed until August 31, 2004. HAART was defined as any combination of ≥ 3 antiretroviral (ARV) drugs (nucleoside reverse transcriptase inhibitor [NNRTI]-based, protease inhibitor [PI]-based, or triple-nucleoside reverse transcriptase inhibitor [NRTI]-only regimens).

Patients were categorized into 4 groups on the basis of immunologic ($CD4^+$ or $CD4^-$) and virologic (VL^+ or VL^-) responses after 3 to 9 months of HAART initiation (intent-to-treat analysis): concordant positive responders ($CD4^+/VL^+$), concordant nonresponders ($CD4^-/VL^-$), and discordant responders ($CD4^+/VL^-$ or $CD4^-/VL^+$). Immunologic response was defined as an increase of ≥ 50 cells/ μL in the CD4 count at 3 to 9 months after baseline. Virologic response was defined as achievement of an undetectable plasma HIV RNA level, with varying thresholds for VL because of different ultrasensitive assays being used over time. When multiple test results were available at 3 to 9 months of follow-up, the maximum CD4 cell count and the minimum VL measurement were used. Occurrence of an OI or death was ascertained until last contact with the patient after treatment began. Patients who did not experience death or an OI were censored at their last clinic visit date within the study period.

SAS software, version 9.1.3 (SAS Institute, Cary, NC) was used for statistical analyses. Patient characteristics were analyzed by χ^2 statistics. The Kaplan-Meier method was used to compare time to development of an OI or death between therapeutic response groups starting at 6 months after therapy initiation. Cox proportional hazards model analyses were estimated, bivariate and multivariate, to quantify the association of clinical progression, starting at 6 months after therapy initiation, with short-term immunologic and virologic response to therapy. Logistic regression by stepwise model selection was used to analyze the associations between patient, clinical, and HAART regimen characteristics and 6-month therapeutic response. Independent variables included age, race (nonwhite vs. white), gender, mode of HIV acquisition (ie, injection drug use [IDU], men who have sex with men [MSM]), baseline CD4 cell count and HIV VL, and type of HAART regimen (PI-based, NNRTI-based, or NRTI-

only). Furthermore, hepatitis B and C virus infection (determined by serology [ie, hepatitis B surface antigen (sAg) and hepatitis C antibody (Ab), respectively]) were evaluated as covariates.

RESULTS

Among 404 study patients, 50.7% were nonwhite (with 10 [2.5%] of them being non-African American) and 76.2% were male. The mean age (\pm SD) was 37.8 (\pm 9.5) years, and 42 patients (10.4%) were older than 50 years of age. Regarding mode of HIV acquisition, half (50.5%) of study patients were classified as MSM and 7.4% reported a history of IDU. At baseline, the average (\pm SD) CD4 cell count and VL were 213 cells/ μL (\pm 260) and 5.4 (\pm 5.8) \log_{10} HIV RNA copies/mL, respectively. Baseline CD4 counts were < 50 cells/ μL in 31% of patients, 50 to 199 cells/ μL in 25%, 200 to 350 cells/ μL in 22%, and > 350 cells/ μL in 22%. Six months after initiating HAART, 289 (71.5%) patients were still on their initial regimen; the remainder had changed to another regimen. More than half (58%) of the patients were initially treated with a PI-based HAART regimen, with 28 (6.9%) patients having received boosted PI-based regimens. CD4 cell counts used for categorizing responses to HAART were obtained at a median of 194 days after HAART initiation, and VL measures were obtained at a median of 144 days after HAART initiation. Of the 404 ARV-naive patients, 70.5% ($n = 285$) had concordant positive immunologic and virologic responses ($CD4^+/VL^+$), 15.8% ($n = 64$) had an immunologic response only ($CD4^+/VL^-$), 8.7% ($n = 35$) had a virologic response only ($CD4^-/VL^+$), and 5.0% ($n = 20$) had a concordant nonresponse ($CD4^-/VL^-$) 6 months after HAART initiation. During a median follow-up time of 38 months, 35 (9%) experienced an OI and 25 (6%) died (Table 1).

As a result of missing CD4 cell counts and VL measurements at baseline and/or 6 months of follow-up, 75 individuals were excluded from the analysis because they could not be categorized within one of the response groups. Excluded individuals were more likely to be nonwhite ($P = 0.003$), were less likely to be male homosexual ($P = 0.012$), were different in type of therapy received at 6 months ($P < 0.0001$), and were more likely to experience an OI or death after 6 months of therapy ($P = 0.0001$). Kaplan-Meier analyses on all 479 individuals stratified by race (white vs. nonwhite) did not demonstrate any racial differences in the development of an OI or death (data not shown), however.

Kaplan-Meier curves (Fig. 1) summarizing time to an OI or death indicated that clinical progression differed significantly according to immunologic and virologic responses 3 to 9 months after initiating HAART ($P < 0.001$). The prognosis was best for the $CD4^+/VL^+$ group, worst for the $CD4^-/VL^-$ group, and intermediate for the 2 discordant response groups. No statistical difference in prognosis was found between the immunologic response-only ($CD4^+/VL^-$) group and the virologic response-only ($CD4^-/VL^+$) group ($P = 0.424$). Statistical differences were found between $CD4^+/VL^+$ responses and the immunologic-only response ($P = 0.0006$) but not the virologic-only response ($P = 0.190$). No statistical difference was found between $CD4^-/VL^-$ responses and

TABLE 1. Characteristics of 404 Patients With HIV-1 Infection Stratified by CD4 Cell Count and VL Responses at 3 to 9 Months After Initiating HAART

	Concordant Complete Response (CD4 ⁺ /VL ⁺)	Discordant Immunologic Response Only (CD4 ⁺ /VL ⁻)	Discordant Virologic Response Only (CD4 ⁻ /VL ⁺)	Concordant Nonresponse (CD4 ⁻ /VL ⁻)
No. subjects	285	64	35	20
White (%)*	155 (54.4)	23 (35.9)	17 (48.6)	4 (20.0)
Male	214 (75.1)	49 (76.6)	29 (82.9)	16 (80.0)
History of IDU	16 (5.6)	8 (12.5)	4 (11.4)	2 (10.0)
MSM	143 (50.2)	33 (51.6)	17 (48.6)	11 (55.0)
Mean age, y (±SD)	38.1 (±9.5)	36.4 (±9.9)	39.5 (±9.7)	35.5 (±7.8)
Mean baseline HIV VL log, copies/mL (±SD)	5.4 (±5.7)	5.6 (±6.0)	5.2 (±5.5)	5.6 (±5.6)
Death†	11 (3.9)	8 (12.5)	4 (11.4)	2 (10.0)
OI/death†	30 (10.5)	16 (25.0)	6 (17.1)	8 (40.0)
Baseline CD4 count, cells/μL				
<50	84 (29.5)	21 (32.8)	11 (31.4)	10 (50.0)
50 to 199	75 (26.3)	16 (25.0)	7 (20.0)	3 (15.0)
200 to 350	65 (22.8)	12 (18.8)	7 (20.0)	3 (15.0)
>350	61 (21.4)	15 (23.4)	10 (28.6)	4 (20.0)
Type of initial HAART regimen				
PI-based	115 (40.4)	30 (46.9)	10 (28.6)	8 (40.0)
NNRTI-based	140 (49.1)	24 (37.5)	20 (57.1)	4 (20.0)
NRTI-only	27 (9.5)	9 (14.1)	4 (11.4)	8 (40.0)
Boosted PI	17 (6.0)	6 (9.4)	5 (14.29)	0 (0.0)

*Of our study population, 10 of 404 were nonwhite/nonblack (<5% of our nonwhite study population).

†Occurring at or after 6 months of HAART initiation.

the immunologic-only response ($P = 0.061$), but statistical differences were seen between CD4⁻/VL⁻ responses and the virologic-only response ($P = 0.026$). In an adjusted multivariate Cox proportional hazards analysis (Table 2), the likelihood of an OI or death was lowest in the CD4⁺/VL⁺ group

and highest in the CD4⁻/VL⁻ group. Compared with the CD4⁺/VL⁺ group, the discordant response groups had an adjusted relative hazard (RH) of 2.28 (95% confidence interval [CI]: 1.3 to 4.0) and the CD4⁻/VL⁻ group had an adjusted RH of 4.83 (95% CI: 2.1 to 11.1) for an OI or death. Regarding

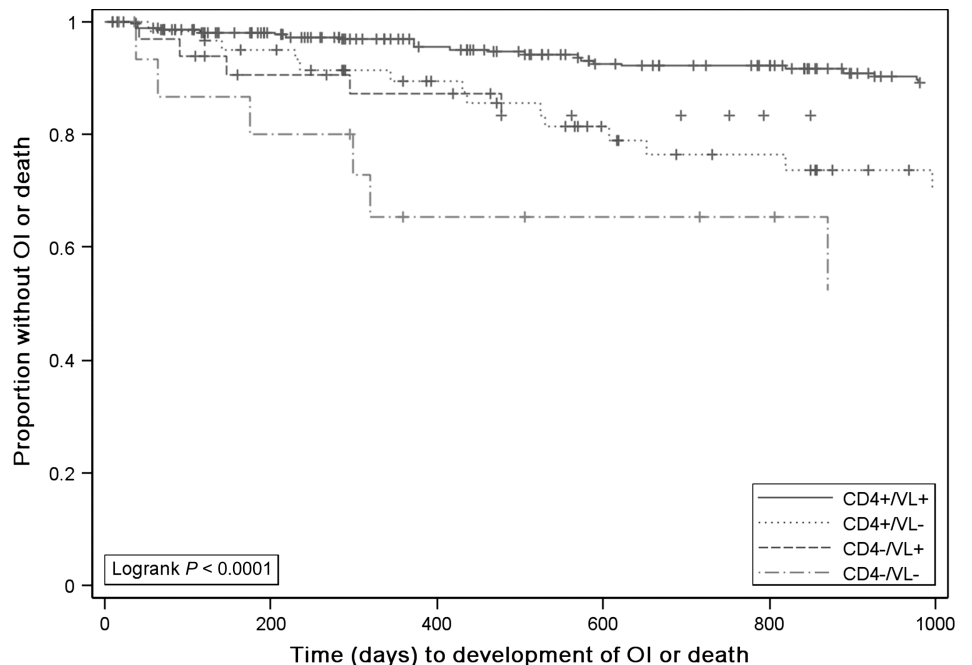


FIGURE 1. Time to death or development of an OI based on immunologic and virologic responses at 3 to 9 months after initiating HAART in 404 antiretroviral-naive patients.

TABLE 2. Predictors of Time to Development of OI/Death for 404 HIV-Positive Patients at 3 to 9 Months After Starting HAART Using Multivariate Cox Proportional Hazards Analysis

	Unadjusted Bivariate Hazard Ratio (95% CI)	Adjusted* Multivariate Hazard Ratio (95% CI)
Response to therapy after 6 mo		
CD4 ⁺ /VL ⁺	1.00 (Ref)	1.00 (Ref)
CD4 ⁺ /VL ⁻ or CD4 ⁻ /VL ⁺	2.39 (1.38 to 4.14)	2.28 (1.31 to 4.00)
CD4 ⁻ /VL ⁻	6.37 (2.91 to 13.97)	4.83 (2.10 to 11.12)
Race		
White	1.00 (Ref)	
Nonwhite	1.06 (0.64 to 1.76)	
Gender		
Female	1.00 (Ref)	1.00 (Ref)
Male	2.20 (1.05 to 4.64)	1.81 (0.86 to 3.84)
Age at HAART initiation (10 y)	1.19 (0.92 to 1.53)	1.21 (0.93 to 1.58)
History of IDU	0.93 (0.34 to 2.55)	
MSM	1.39 (0.83 to 2.33)	
Type of HAART treatment		
NRTI-only	1.00 (Ref)	
PI-based	1.50 (0.58 to 3.88)	
NNRTI-based	1.00 (0.37 to 2.72)	
Baseline CD4 count (50 cells/ μ L)	0.90 (0.85 to 0.96)	0.93 (0.88 to 0.99)

*Adjusted hazard ratio is the hazard ratio adjusted for gender, age, baseline CD4 cell count, and therapy response. Only variables that were significant at $P < 0.05$ in the bivariate analysis were considered biologically important were included in the multivariate analysis.
Ref indicates referent.

patient characteristics, being male was associated with the development of an OI or death univariately (adjusted RH = 2.20, 95% CI: 1.05 to 4.6). Baseline CD4 cell counts showed a significant inverse association with development of an OI or death (adjusted RH per 50 cells/ μ L = 0.93, 95% CI: 0.88 to 0.99; $P = 0.022$). We found no significant difference in the development of an OI or death among individuals on different initial regimen types (ie, NNRTI-based vs. PI-based and NNRTI-based vs. NRTI-only). Furthermore, the development of an OI or death was not associated with race, age, or mode of HIV acquisition when tested univariately.

Multivariate logistic regression models were used to evaluate patient, clinical, and HAART regimen characteristics associated with variable 3- to 9-month immunologic and virologic responses. Hepatitis B and C coinfection was excluded from the final multivariate models, because coinfection with either virus was not statistically associated with 6-month immunologic and virologic responses in bivariate analyses. Classification in the immunologic response-only group (CD4⁺/VL⁻) was significantly associated with nonwhite race (odds ratio [OR] = 2.83, 95% CI: 1.5 to 5.5) in comparison to the concordant positive responders (CD4⁺/VL⁺ group). Classification in the virologic response-only group (CD4⁻/VL⁺ group) was not significantly associated with any patient, treatment, or clinical characteristics in comparison to the concordant positive responders (CD4⁺/VL⁺ group). No association was observed between type of discordant response and gender, MSM, age, and type of initial HAART regimen (ie, PI-based vs. NRTI-only and NNRTI-based vs. NRTI-only). Classification in the concordant unfavorable response group (CD4⁻/VL⁻) was significantly associated

with nonwhite race (OR = 6.50, 95% CI: 1.7 to 25.7) and NRTI-only regimens (PI-based OR = 0.07, 95% CI: 0.02 to 0.30; NNRTI-based OR = 0.02, 95% CI: 0.004 to 0.13).

DISCUSSION

Our study of ART-naive patients indicated that different immunologic and virologic responses 3 to 9 months after initiating HAART were associated with long-term clinical progression, irrespective of the type of treatment used (eg, NNRTI-based vs. PI-based). In contrast to previous studies, our definition of successful virologic response after treatment initiation (<50 copies/mL) was in accordance with current HIV treatment guidelines. Interpretation of previous studies has been limited because (1) subjects were treatment-experienced, (2) the thresholds of the virologic response were more liberal, (3) the definitions of immunologic response varied,^{4,7,8} and (4) only mortality (not OI) was considered as a long-term clinical outcome.

Moore et al⁷ followed 1527 treatment-naive individuals and, as in our study, found an independent association of each type of discordant response to HAART with mortality and no difference among types of discordant responses. OIs as a risk of disease progression were not included, however, and virologic response was defined as <350 copies/mL. Other studies found significant differences between the 2 types of discordant responses in subsequent outcomes.^{4,5} A study by Piketty et al⁸ showed accelerated clinical progression after both types of discordant responses, but progression was more rapid in the CD4⁺/VL⁻ group than in the CD4⁻/VL⁺

group. Grabar et al⁴ found that CD4⁻/VL⁺ responders progressed more rapidly, however. Taken together, these studies suggest that the prognostic difference, if any, between the 2 discordant response groups is probably dependent on patient characteristics. Further study of treatment-naïve patients using standardized definitions of immunologic and virologic responses and clinical progression are needed to resolve this issue.

In our study, as in others, a lower baseline CD4 cell count had significant associations with risk of an OI or death.^{7,16} Interestingly, male gender was also univariately associated with the risk of OI development or death. Similar to previous studies, the current study did not detect an association between the type of HAART regimen (PI-based or NNRTI-based) and the risk of an OI or death.^{4,5,7,8}

Overall, most patients (70.5%) in our study experienced a favorable concordant response (CD4⁺/VL⁺) at 3 to 9 months after initiating HAART, whereas nearly a quarter of patients (24.5%) experienced discordant responses (15.8% CD4⁺/VL⁻, 8.7% CD4⁻/VL⁺) and a small proportion (5.0%) experienced a concordant unfavorable response (CD4⁻/VL⁻). In the evaluation of patient, ART, and clinical characteristics associated with each type of treatment response, only nonwhite race was independently related to an immunologic-only (CD4⁺/VL⁻) response relative to those with a concordant positive response (CD4⁺/VL⁺). Furthermore, nonwhite race was also associated with a concordant unfavorable response (CD4⁻/VL⁻) relative to a concordant favorable response (CD4⁺/VL⁺). Because >95% of our nonwhite population identified as African American, these findings are consistent with results from the AIDS Clinical Trial Group 5095 study, in which non-Hispanic black patients had a significantly shorter time to virologic failure.¹⁷ Inferior long-term clinical outcomes are well described in racial minorities relative to white patients with HIV infection^{18,19} and may, in part, be explained by a greater likelihood of short-term virologic nonresponse, as observed in this study. Further research is needed to understand better the reasons why short-term virologic failure is more common in racial minorities, including evaluation of differential adherence, toxicity, and plasma concentrations of ARV drugs relative to HIV-infected white patients.

Not surprisingly, a concordant unfavorable 3 to 9-month treatment response (CD4⁻/VL⁻) was more common in patients treated with NRTI-only regimens compared with those on PI- or NNRTI-containing regimens. These findings are consistent with clinical trial data²⁰ and are reflected in more recent HIV ART guidelines.¹

Our findings must be interpreted with respect to the limitations of this study. Because of the modest sample size, we may have had insufficient statistical power to differentiate the effects on prognosis between the 2 discordant groups. Furthermore, all cohort studies of ARV response are compromised to some degree by loss of subjects attributable to toxicity and drug intolerance as well as loss to study follow-up. The current study included only those treatment-naïve patients who remained on HAART 6 months after initiating therapy, including those who had changed regimens. Individuals stopping ART altogether and those lost to clinic follow-up

during the first 6 months after initiating therapy were not included in this analysis and could have biased our analyses.

In conclusion, among treatment-naïve patients initiating HAART, discordant responses 3 to 9 months after initiation of therapy predict long-term clinical outcomes relative to concordant favorable responses, namely, shorter time to an OI or death. Therefore, short-term increases in CD4 cell count and achievement of an undetectable plasma HIV RNA VL within 3 to 9 months of starting therapy provide important prognostic information for treatment-naïve patients initiating HAART. Future studies with larger samples are needed to clarify the differential long-term clinical outcomes among patients with discordant responses (CD4⁺/VL⁻ and CD4⁻/VL⁺) further, if significant differences indeed exist.

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