

Discordant Immunologic and Virologic Responses to Highly Active Antiretroviral Therapy Are Associated With Increased Mortality and Poor Adherence to Therapy

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Objective: To examine the independent association of discordant virologic and immunologic responses to highly active antiretroviral therapy (HAART) with mortality.

Methods: A population-based study of 1527 treatment-naive individuals initiating HAART used Cox proportional hazards modeling to determine the independent association of treatment response at 3 to 9 months with nonaccidental mortality. Logistic regression was used to examine associations with discordant responses.

Results: Viral load (VL)⁺/CD4⁻ discordant responses were seen in 235 (15.4%) of subjects, and VL⁻/CD4⁺ responses were seen in 179 (11.7%) of subjects. In adjusted Cox regression models, discordant responses were found to be independently associated with an increased risk of mortality (VL⁺/CD4⁻: relative hazard [RH] = 1.87, 95% confidence interval [CI]: 1.15 to 3.04; VL⁻/CD4⁺: RH = 2.47, 95% CI: 1.54 to 3.95). VL⁺/CD4⁻ discordance was found to be associated with increasing age, baseline HIV RNA load <100,000 copies/mL, baseline CD4 counts <50 cells/μL, the use of lamivudine (3TC)/zidovudine (ZDV), and poor adherence to therapy. VL⁻/CD4⁺ discordance was associated with younger age; injection drug use; baseline HIV RNA load >100,000 copies/mL; the use of 3TC/ZDV, didanosine (ddI)/3TC, or ddI/stavudine; and poor adherence to therapy.

Conclusion: Discordant responses are independently associated with an increased risk of mortality and are, in turn, associated with poor adherence to therapy.

Key Words: CD4 cell counts, viral load, discordant, response to therapy, adherence

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Highly active antiretroviral therapy (HAART) has been shown to improve survival dramatically among HIV-positive individuals through its ability to reduce HIV viremia to undetectable levels and to increase the number of CD4⁺ T lymphocytes in peripheral blood.^{1–3} In observational studies of patients receiving HAART, however, only 40% to 60% of patients develop significant reductions in HIV viral load (VL) and significant increases in CD4 cell counts, and between 12% and 23% have neither of these responses.^{4–7} The remaining patients see improvements in only 1 of immunologic or virologic outcome. Although it is clear that those with concordant positive responses (VL⁺/CD4⁺) have generally favorable outcomes and that those with concordant negative responses (VL⁻/CD4⁻) have much worse outcomes, the prognostic significance of discordant responses (VL⁺/CD4⁻ or VL⁻/CD4⁺) is not well understood.

Studies examining the prognostic value of discordant responses have been predominantly conducted on treatment-experienced subjects who began protease inhibitor (PI)-based HAART and have yielded inconsistent results.^{4,5,7} Immunologic responses without evidence of significant virologic suppression have been attributed to lower baseline CD4 counts,⁸ the presence of nonsyncytium-inducing viruses, viruses with multiple resistance mutations,⁹ and low levels of viral replication with viruses with reduced fitness.¹⁰ Virologic responses without concomitant immunologic responses have been attributed to coinfections,¹¹ older age, lower baseline CD4 cell count, and lower plasma VL at baseline.¹²

To clarify the significance of discordant immunologic and virologic responses in treatment-naive individuals beginning PI or nonnucleoside reverse transcriptase inhibitor (NNRTI)-based HAART, we undertook a study to examine the independent association of discordant responses with nonaccidental mortality. We then examined which baseline characteristics were associated with these responses.

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METHODS

Data Collection

Since 1992, the HIV/AIDS Drug Treatment Program (DTP) of the British Columbia Centre for Excellence in HIV/AIDS (the Centre) has distributed antiretroviral drugs at no cost to patients in the province.¹³ Physicians starting an HIV-infected individual on antiretroviral therapy complete a drug request form that compiles information on the applicant's address, past HIV-specific drug history, CD4 cell counts, plasma HIV-1 RNA, current drug requests, and enrolling physician data. At the time of the first prescription refill, participants are asked to provide informed consent for accessing medical electronic records and to complete a participant survey that elicits sociodemographic information and clinical and health status. The consent form and the participant survey are optional, and a participant's refusal to complete either does not limit his or her access to free antiretroviral therapy. The HIV/AIDS DTP has received ethical approval from the University of British Columbia Ethics Review Committee.

The Centre recommends that plasma HIV-1 RNA levels and CD4 cell counts be monitored at baseline, at 4 weeks after starting antiretroviral therapy, and every 3 months thereafter.¹⁴ All VL testing and most CD4 cell count testing in the province is conducted at St. Paul's Hospital and is uploaded daily into the DTP database. The results of CD4 cell count testing that occurs in other laboratories in British Columbia are collected through the drug request forms. Plasma HIV-1 RNA levels were determined using the Roche Amplicor Monitor assay (Roche Diagnostics, Laval, Quebec, Canada). CD4 cell counts were measured by flow cytometry, followed by fluorescent monoclonal antibody analysis (Beckman Coulter, Mississauga, Ontario, Canada).

Study Participants

Participants considered in the present study were antiretroviral naive and were first dispensed therapy containing 2 nucleosides and a PI, a ritonavir-boosted PI, or an NNRTI between August 1, 1996 and September 30, 2003. Participants must also have had at least 1 CD4 cell count and plasma HIV-1 RNA measurement available between 3 and 9 months after starting HAART, conducted within 30 days of each another. When multiple test results were available, that closest to 6 months was used.

Data Analyses

On the basis of follow-up CD4 cell count and VL measurements, participants were classified into 1 of 4 possible combinations of virologic and immunologic responses: complete responders ($VL^+/CD4^+$), complete nonresponders ($VL^-/CD4^-$), or discordant responders ($VL^+/CD4^-$ or $VL^-/CD4^+$). Immunologic response was defined as an increase in CD4 count by 50 cells/ μ L or more over the baseline level. Virologic response was defined as achieving a VL of <500 copies/mL, because detection below this level was not available before 1999.

Categoric variables were compared between the response groups using the χ^2 test, and continuous variables were

compared using the Kruskal-Wallis test. Cumulative mortality rates were estimated using Kaplan-Meier methods. Deaths occurring during the follow-up period were identified through annual record linkages carried out with the British Columbia Division of Vital Statistics. Deaths attributable to trauma, suicide, or drug overdoses were censored at the time of death and not counted as events because they were unlikely to be related to HAART effectiveness. Event-free subjects were right-censored as of September 30, 2004. Cox proportional hazards models were constructed, including response category along with other baseline factors hypothesized to be associated with mortality, with time 0 set as the later date of VL or CD4 cell count testing. A sensitivity analysis was also conducted, including accidental deaths. Adherence to therapy, defined as the amount of medication that was actually dispensed as a proportion of that needed for the first year of follow-up, was also included in these models. Logistic regression was then used to examine associations with the 2 categories of discordant responses. Separate subgroup analyses were conducted for the patients with available hepatitis C serology. All analyses were performed using SAS software version 8.0 (SAS, Cary, NC).

RESULTS

A total of 2217 antiretroviral-naive participants aged 18 years or older initiated triple combination therapy consisting of 2 nucleosides plus a PI or an NNRTI in the study period. Of these, 529 were excluded because they were missing a VL or CD4 cell measurement within the study time frame, and another 161 were excluded because available values were not taken within 30 days of each another, leaving 1527 subjects (69% of the total) for analysis. Excluded subjects were less likely to be male, to have AIDS at baseline, and to have baseline VLs >100,000 copies/mL but did not differ with respect to history of injection drug use. Excluded subjects were also slightly younger (median age = 36.8 vs. 38.9 years; $P < 0.001$), had higher baseline CD4 counts (median 250 vs. 199 cells/ μ L; $P < 0.001$).

VL measurements were conducted at a median of 182 days (6.1 months) from initiating HAART (interquartile range [IQR]: 162–203 days), and the median follow-up time from testing was 44.7 months (IQR: 20.8–67.5 days). A total of 849 participants (55.6%) exhibited a VL <500 copies/mL and an increase of 50 CD4 cells/ μ L from baseline ($VL^+/CD4^+$), and 264 (17.3%) had neither of these outcomes ($VL^-/CD4^-$) (Table 1). Virologic-only responses ($VL^+/CD4^-$) were seen in 235 subjects (15.4%), and 179 (11.7%) of subjects had only immunologic responses ($VL^-/CD4^+$). The response categories differed from each other in many baseline characteristics, which were examined in more detail in the logistic regression analysis below. A total of 172 nonaccidental deaths were identified in the study population, with 53 (6.2% crude mortality rate [CMR]) in the $VL^+/CD4^+$ group, 25 (11% CMR) in the $VL^+/CD4^-$ group, 33 (18% CMR) in the $VL^-/CD4^+$ group, and 61 (23% CMR) in the $VL^-/CD4^-$ group ($P < 0.001$).

The Kaplan-Meier survival curves for the whole group analysis stratified on the basis of response to therapy at 3 to

TABLE 1. Characteristics of 1527 HIV-Positive Individuals Classified on the Basis of VL and CD4 Cell Count Responses at 3 to 9 Months After Initiating Triple Therapy HAART

	Complete Responders (VL ⁺ /CD4 ⁺)	Virologic Response Only (VL ⁺ /CD4 ⁻)	Immunologic Response Only (VL ⁻ /CD4 ⁺)	Complete Nonresponders (VL ⁻ /CD4 ⁻)	<i>P</i>
No. subjects (%)	849 (55.6)	235 (15.4)	179 (11.7)	264 (17.3)	
Sex					
Male	751 (88.5)	203 (86.4)	146 (81.6)	203 (77)	<0.001
Female	98 (11.5)	32 (13.6)	33 (18.4)	61 (23)	
Median age (IQR range)	39.6 (33.8–46.7)	40.6 (34.5–48.5)	36.5 (31.9–45.0)	37.6 (30.8–43.6)	<0.001
History of IDU	152 (17.9)	52 (22)	59 (33)	108 (41)	<0.001
Hepatitis C positive*	192 (31.2)	65 (38)	72 (53)	146 (73.0)	<0.001
AIDS at baseline	162 (19.1)	41 (17)	24 (13)	28 (11)	0.007
Baseline HIV RNA >100,000 copies/mL	510 (60.1)	95 (40)	125 (69.8)	160 (60.6)	<0.001
Median baseline CD4 count (cells/ μ L) (IQR)	180 (80–310)	250 (130–410)	190 (60–350)	200 (90–360)	<0.001
Adherence >95%	648 (76.3)	159 (67.7)	56 (31)	29 (11)	<0.001
Nonaccidental deaths	53 (6.2)	25 (11)	33 (18)	61 (23)	<0.001

*1125 subjects with available hepatitis C serology.
IDU indicates injection drug use.

9 months are shown in Figure 1. In multivariate analyses, therapeutic response categories were found to be independently associated with an increased risk of mortality. Compared with the VL⁺/CD4⁺ group (Table 2), the VL⁺/CD4⁻ group had a relative hazard (RH) of 1.87 (95% confidence interval [CI]: 1.15 to 3.04), the VL⁻/CD4⁺ group had a RH of 2.47 (95% CI: 1.54 to 3.95), and the VL⁻/CD4⁻ group had a RH of 3.48 (95% CI: 2.26 to 5.34). Other factors that were significantly associated with mortality included increasing age (RH = 1.04 per year, 95% CI: 1.03 to 1.06), baseline CD4 counts below 50 cells/ μ L (RH = 3.89, 95% CI: 2.60 to 5.81) and between 50 and 199 cells/ μ L (RH = 2.03, 95% CI: 1.42 to 2.91), and the use of HAART regimens with lamivudine (3TC)/didanosine (ddI) (RH = 1.86, 95% CI: 1.15 to 3.00). Adherence to therapy >95% was associated with a lower risk

of mortality (RH = 0.56, 95% CI: 0.39 to 0.81). The results were largely unchanged when all-cause mortality (including the 42 accidental deaths) was modeled as the outcome, and a direct comparison between the 2 forms of discordant responses found no significant differences between them (data not shown). A subgroup analysis conducted on the 1125 subjects with available hepatitis C serology found that hepatitis C seropositivity was associated with mortality (RH = 1.96, 95% CI: 1.32 to 2.88). Other variables from the whole group model retained statistical significance (data not shown), except for VL⁻/CD4⁺ discordance, which was marginally significant (RH = 1.62, 95% CI: 0.95 to 2.77; *P* = 0.08).

In multivariate logistic regression models, VL⁺/CD4⁻ discordance was found to be associated with increasing age (adjusted odds ratio [AOR] = 1.02 per year, 95% CI: 1.00 to 1.04) and the use of 3TC/zidovudine (ZDV) (AOR = 1.45, 95% CI: 1.03 to 2.05) as the nucleoside regimen (Table 3). Baseline HIV RNA >100,000 copies/mL (AOR = 0.51, 95% CI: 0.38 to 0.69), baseline CD4 counts below 50 cells/ μ L (AOR = 0.50, 95% CI: 0.30 to 0.84), and being \geq 95% adherent to therapy (AOR = 0.70, 95% CI: 0.50 to 0.97) were found to be inversely associated with this response pattern. Immunologic-only responses (VL⁻/CD4⁺) (Table 4) were associated with a history of injection drug use (AOR = 1.52, 95% CI: 1.01 to 2.28); the use of 3TC/ZDV (AOR = 1.79, 95% CI: 1.19 to 2.69), ddI/stavudine (d4T) (AOR = 3.31, 95% CI: 1.49 to 7.38), or ddI/3TC (AOR = 2.28, 95% CI: 1.17 to 4.44); and having baseline HIV RNA >100,000 copies/mL (AOR = 1.88, 95% CI: 1.26 to 2.80). This response pattern was also inversely associated with being \geq 95% adherent to therapy (AOR = 0.15, 95% CI: 0.11 to 0.21). Hepatitis C seropositivity was not found to be associated with either form of discordance in subgroup analyses.

DISCUSSION

Our analysis has demonstrated that both forms of discordant immunologic and virologic responses to therapy as determined 6 months after HAART initiation are predictive of

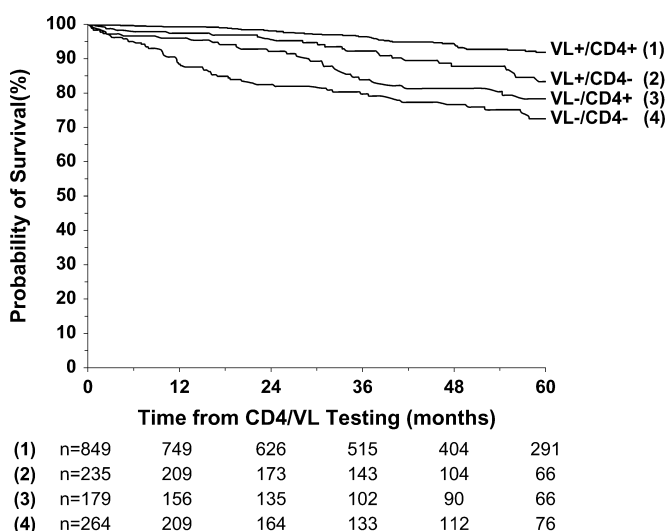


FIGURE 1. Probability of survival based on virologic and immunologic responses 3 to 9 months after initiating HAART in 1527 HIV-positive subjects.

TABLE 2. Cox Proportional Hazards Analysis of Nonaccidental Mortality for 1527 HIV-Positive Individuals Classified on the Basis of CD4 Cell Count and VL Responses at 3 to 9 Months After Starting HAART

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Response to therapy		
VL ⁺ /CD4 ⁺	1.00	1.00
VL ⁺ /CD4 ⁻	1.79 (1.11 to 2.88)	1.87 (1.15 to 3.04)
VL ⁻ /CD4 ⁺	2.92 (1.89 to 4.50)	2.47 (1.54 to 3.95)
VL ⁻ /CD4 ⁻	4.24 (2.94 to 6.13)	3.48 (2.26 to 5.34)
Male vs. female	0.76 (0.51 to 1.13)	
Age (y)	1.04 (1.02 to 1.05)	1.04 (1.03 to 1.06)
History of IDU	1.18 (0.85 to 1.63)	
AIDS at baseline	1.23 (0.84 to 1.81)	
Baseline log HIV RNA	1.39 (0.94 to 2.05)	
Baseline CD4 count (cells/μL)		
≥200	1.00	1.00
50–199	2.25 (1.58 to 3.20)	2.03 (1.42 to 2.91)
<50	3.47 (2.36 to 5.09)	3.89 (2.60 to 5.81)
Regimen containing		
Unboosted PI	1.00	
NNRTI	1.13 (0.81 to 1.58)	
Boosted PI	1.34 (0.80 to 2.27)	
NRTI combination		
3TC + d4T	1.00	1.00
3TC + ZDV	1.44 (1.02 to 2.03)	1.28 (0.91 to 1.82)
ddI + 3TC	2.60 (1.63 to 4.16)	1.86 (1.15 to 3.00)
ddI + ZDV	0.63 (0.20 to 2.01)	0.71 (0.22 to 2.27)
ddI + d4T	1.05 (0.51 to 2.17)	1.01 (0.48 to 2.11)
Other	1.30 (0.32 to 5.32)	1.44 (0.35 to 5.89)
Adherence to therapy ≥95%	0.40 (0.29 to 0.54)	0.56 (0.39 to 0.81)

IDU indicates injection drug use.

nonaccidental mortality in treatment-naïve individuals, irrespective of whether therapy was PI or NNRTI based. Previous studies had attributed this phenomenon to the use of PIs but in the absence of NNRTI data. Furthermore, we were unable to demonstrate significant differences in mortality between the 2 discordant groups, a finding supported by some previous studies but not by others. In addition, we have demonstrated the importance of adherence to therapy in determining these discordant responses, a factor that had not been examined previously.

Currently, VL is the primary criterion used for determining short-term treatment success or failure.¹⁵ Achieving virologic suppression is necessary to maximize CD4 cell count responses¹⁶ and to sustain virologic suppression.¹⁷ This analysis has also shown that immunologic responses are important determinants of later mortality on HAART, however. Although CD4 cell count increases can continue for years after HAART initiation, short-term immunologic responses seem to have significant prognostic value. Immunologic responses of 50 cells/μL have been correlated with a reduced risk for the development of opportunistic infections,¹⁸ but it is not clear whether this is a true threshold effect or reflects a continuous gradation of risk. This target may help to identify patients who are not completely adhering to therapy, however.

TABLE 3. Logistic Regression Analysis of Factors Associated With 235 VL⁺/CD4⁻ Discordant Responders Compared With 849 Concordant Responders (VL⁺/CD4⁺)

	Non-AOR (95% CI)	AOR (95% CI)
Male vs. female	0.83 (0.54 to 1.27)	
Age (y)	1.02 (1.00 to 1.03)	1.02 (1.00 to 1.04)
History of IDU	1.30 (0.91 to 1.86)	
Hepatitis C positive*	1.34 (0.94 to 1.91)	
AIDS at baseline	0.90 (0.61 to 1.31)	
Baseline HIV RNA		
>100,000 copies/mL	0.45 (0.34 to 0.61)	0.51 (0.38 to 0.69)
Baseline CD4 count (cells/μL)		
≥200	1.00	1.00
50–199	0.72 (0.53 to 1.00)	0.75 (0.54 to 1.05)
<50	0.39 (0.24 to 0.64)	0.50 (0.30 to 0.84)
Regimen containing		
Unboosted PI	1.00	
NNRTI	1.25 (0.91 to 1.71)	
Boosted PI	0.67 (0.42 to 1.04)	
NRTI regimen		
3TC and d4T	1.00	1.00
3TC and ZDV	1.58 (1.13 to 2.21)	1.45 (1.03 to 2.05)
ddI and 3TC	1.72 (1.03 to 2.87)	1.51 (0.90 to 2.56)
ddI and d4T	1.53 (0.75 to 3.12)	1.13 (0.54 to 2.35)
ddI and ZDV	1.98 (0.84 to 4.66)	1.60 (0.67 to 3.86)
Other	1.21 (0.48 to 3.06)	0.80 (0.26 to 2.47)
Adherence to therapy ≥95%	0.65 (0.48 to 0.90)	0.70 (0.50 to 0.97)

*788 subjects with available hepatitis C serology.
IDU indicates injection drug use.

Other studies on this subject have reported a range of results. Our results are similar to those reported by Piketty et al,⁷ who studied a group of 150 patients who initiated indinavir-based HAART and found an increased risk of disease progression or death in both types of discordant responders when compared with complete responders after 30 months of follow-up. These authors also found an increased risk associated with the VL⁻/CD4⁺ group over the VL⁺/CD4⁻ group, which we did not find here. Another study by Marimoutou et al⁴ found that AIDS-defining illnesses occurred in 5.6% of VL⁻/CD4⁺ responders and 2.8% of VL⁺/CD4⁻ responders compared with 0.6% of VL⁺/CD4⁺ subjects in a study of 478 patients receiving PI-based HAART, who were followed for a median of 16.8 months. The number of events was too small to examine whether the response categories were independently associated with these outcomes.

In contrast, Grabar et al⁵ found that VL⁺/CD4⁻ responders had an increased risk of disease progression or death, whereas VL⁻/CD4⁺ responders did not in 2236 patients initiating HAART. The differing results may be because 75% of patients were treatment experienced in the study by Grabar et al⁵ and all received PI-based therapy. This would be consistent with studies that have found reduced T-cell apoptosis associated with the use of PI-based therapy¹⁹; however, we did not find significant associations between discordant response and the use of PIs or NNRTIs. The results of our study are likely more generalizable to patients beginning HAART today.

TABLE 4. Logistic Regression Analysis of Factors Associated With 179 VL⁻/CD4⁺ Discordant Responders Compared With 849 Concordant Responders (VL⁺/CD4⁺)

	Non-AOR (95% CI)	AOR (95% CI)
Male vs. female	0.58 (0.38 to 0.89)	1.04 (0.63 to 1.72)
Age (y)	0.97 (0.95 to 0.99)	0.98 (0.96 to 1.00)
History of IDU	2.26 (1.58 to 3.22)	1.52 (1.01 to 2.28)
Hepatitis C positive*	2.45 (1.68 to 3.56)	NS†
AIDS at baseline	0.66 (0.41 to 1.04)	
Baseline HIV RNA		
>100,000 copies/mL	1.54 (1.09 to 2.18)	1.88 (1.26 to 2.80)
Baseline CD4 count (cells/ μ L)		
≥ 200	1.00	
50–199	0.81 (0.57 to 1.18)	
<50	1.15 (0.75 to 1.74)	
Regimen containing		
Unboosted PI	1.00	1.00
NNRTI	0.67 (0.47 to 0.95)	0.68 (0.44 to 1.05)
Boosted PI	0.45 (0.27 to 0.75)	0.62 (0.35 to 1.09)
NRTI regimen		
3TC and d4T	1.00	1.00
3TC and ZDV	2.20 (1.52 to 3.19)	1.79 (1.19 to 2.69)
ddI and 3TC	2.22 (1.27 to 3.88)	2.28 (1.17 to 4.44)
ddI and d4T	2.58 (1.27 to 5.23)	3.31 (1.49 to 7.38)
ddI and ZDV	1.91 (0.69 to 5.30)	2.32 (0.72 to 7.42)
Other	0.76 (0.17 to 3.36)	1.04 (0.22 to 4.98)
Adherence to therapy $\geq 95\%$	0.14 (0.10 to 0.20)	0.15 (0.11 to 0.22)

*753 subjects with available hepatitis C serology.

†Not significant in subgroup analysis with subjects with available hepatitis C serology.

IDU indicates injection drug use.

Adherence to therapy has previously been shown to be an important determinant of mortality in HIV-positive individuals on HAART.^{20–22} This is further supported by the Cox regression analysis presented here, whereby poor adherence was associated with mortality after adjusting treatment response groups. This association was weaker than that of previous studies, however, suggesting that poorly adherent subjects may have higher rates of mortality because they are more likely to develop incomplete immunologic and virologic responses to therapy.

Others have suggested that inherent differences in viral subtypes or fitness are important determinants of immunologic-only responses.^{9,10} Although this study did not examine these issues directly, the observation that VL⁻/CD4⁺ discordance was associated with poor adherence to therapy, high baseline VLs, injection drug use, and specific nucleotide regimens suggests that the virologic differences found in these patients may be caused by incomplete adherence or suboptimal treatment regimens and not because of primary infection with mutant viruses. This is consistent with another study from our Centre, which found that the development of resistant viral strains highly correlated to reduced adherence to therapy.²³ The viral strains that emerge with reduced adherence would be more likely to be drug resistant but would also likely have reduced fitness and therefore be less likely to inhibit CD4 cell recovery, pathways that could lead to both types of discordant responses.

The effect of nucleotide regimens may be related to bone marrow toxicities that may inhibit CD4 cell recovery or reduced virologic potencies associated with regimens other than 3TC/d4T. Further studies are required to confirm these observations before firm conclusions can be made regarding the role of nucleoside reverse transcriptase inhibitor (NRTI) regimens in these responses, however.

Our finding that VL⁺/CD4⁻ discordance is inversely associated with lower baseline CD4 cell counts contrasts with that of the EuroSIDA study, which found that lower cell counts were positively associated with discordance.¹² The differing results may be attributable to the fact that baseline CD4 cell counts were grouped a priori in 100-cell/ μ L increments in the latter study, whereas we have used strata (<50, 50–199, and >200 cells/ μ L) that have been validated empirically as having differing associations with mortality.¹³ Our results suggest that immunologic responses are larger at lower baseline CD4 cell counts, where the potential increases needed to recover immune function are greater. Immunologic responses may be less at higher CD4 cell counts, because recovery of CD4 cells may not be necessary to maintain immune competency. Both studies found that lower baseline plasma VLs were positively associated with VL⁺/CD4⁻ discordance.

This study has several limitations. First, only single VL measurements and CD4 cell counts were used to assign the treatment-response categories. If these measurements were not representative of the patient's true response to therapy, a misclassification bias could have been introduced. One would expect the misclassification in these circumstances to be more likely to underestimate the VL⁺/CD4⁺ responders, however, which would be a conservative bias. Second, the association between adherence to therapy could be attributable to reverse causation, whereby worsening adherence is attributable to more progressive disease rather than to poor adherence leading to earlier disease progression. Only adherence in the first year of therapy was used in constructing this variable, however, and the long period of follow-up in this study makes the possibility of reverse-causation much less likely. Finally, the exclusion of 31% of eligible individuals because of missing values from our database could introduce bias into our results. Excluded individuals did differ from the studied group with respect to some baseline parameters, but the effect of any such biases would likely to be small.

In conclusion, our work has demonstrated that immunologic and virologic responses are important in determining survival in patients receiving HAART. Failure to achieve treatment thresholds in either category within 3 to 9 months after initiating HAART is a significant predictor of later mortality. Adherence to therapy was found to be associated with both of the discordant treatment responses. Further research is needed to confirm these observations using other data sets of treatment-naïve individuals receiving PI- or NNRTI-based therapy and to better define therapy response targets that have clinical significance for these patients.

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