Mortality Associated With Discordant Responses to Antiretroviral Therapy in Resource-Constrained Settings

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Objectives: We assessed mortality associated with immunologic and virologic patterns of response at 6 months of highly active antiretroviral therapy (HAART) in HIV-infected individuals from resource-limited countries in Africa and South America.

Methods: Patients who initiated HAART between 1996 and 2007, aged 16 years or older, and had at least 1 measurement (HIV-1 RNA plasma viral load or CD4 cell count) at 6 months of therapy (3–9 month window) were included. Therapy response was categorized as complete, discordant (virologic only or immunologic only), and absent. Associations between 6-month response to therapy and all-cause mortality were assessed by Cox proportional hazards regression. Robust standard errors were calculated to account for intrasite correlation.

Results: A total of 7160 patients, corresponding to 15,107 person-years, were analyzed. In multivariable analysis adjusted for age at HAART initiation, baseline clinical stage and CD4 cell count, year of HAART initiation, clinic, occurrence of an AIDS-defining condition within the first 6 months of treatment, and discordant and absent responses were associated with increased risk of death.

Conclusions: Similar to reports from high-income countries, discordant immunologic and virologic responses were associated with intermediate risk of death compared with complete and no response in this large cohort of HIV-1 patients from resource-limited countries. Our results support a recommendation for wider availability of plasma viral load testing to monitor antiretroviral therapy in these settings.

Key Words: antiretroviral therapy, cohort, CD4 lymphocyte count, highly active, low-income population, mortality, treatment outcome, viral load

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INTRODUCTION

The initiation of highly active antiretroviral therapy (HAART) generally leads to a rapid reduction in plasma HIV-1 RNA levels and to an increase in peripheral $CD4^+$ cell counts.[1–3] However, some patients experience a discordant response, whereby the HIV-1 RNA plasma level is below the limit of detection but the $CD4^+$ cell count increase is blunted. Conversely, some patients exhibit a sustained $CD4^+$ cell count increase despite persistent viremia. Published data, mostly from high-income countries, have indicated that discordant responses are associated with an intermediate risk of death or clinical progression relative to complete response.[4–7]

No published study has assessed the impact of discordant responses on mortality in low-income countries. Because most HIV treatment programs rely only on clinical assessment and CD4 cell counts to monitor response to treatment, the potential association between early virological

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ART-LINC of IeDEA central coordinating team and the Collaborating centers are listed in Appendix 1.

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response and long-term survival remains largely unexplored in these settings. Additionally, limited data are available on the prognostic value of discordant responses in naive patients who start therapy with the nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimens most commonly used in developing countries.[8,9] We previously reported that the incidence of discordant responses in resource-constrained countries was similar to that observed in resource-rich settings.[10] In the present analysis, we assessed whether the risk of death was increased in patients starting HAART in resource-constrained settings who experienced discordant responses at 6 months.

METHODS

Study Population

The Antiretroviral in Lower Income Countries collaboration of the International Databases to Evaluate AIDS (ART-LINC of IeDEA) is a large collaborative network of HIV/AIDS treatment programmes in low-income and middle-income countries in Africa, South America and Asia.[11,12] The collaboration was established in 2003 to characterize the prognosis of HIV-infected patients treated with HAART in resource-limited settings; to compare the experience between different settings, delivery modes, and types of monitoring; and to compare outcomes with those observed in industrialized nations. The data collected at participating sites are regularly transferred to data management and statistical teams at the University of Bern, Switzerland, and the University of Bordeaux, France, where data are cleaned and merged. The present analysis includes all data available up to June 29, 2007. All previously drug-naive participants who initiated HAART between 1996 and 2007 were aged 16 years or older at treatment initiation and had a known date of therapy initiation, a documented baseline CD4, and at least 1 measurement [CD4 cell count or plasma viral load (PVL)] or sufficient follow-up time (6 months after HAART initiation) were eligible for analysis. Sites that did not routinely measure HIV PVL or had >80% of PVL measurements missing at 6 months of treatment were excluded from the analysis. At all sites, local ethics committees or institutional review boards approved the study.

The following variables were assessed: age at therapy initiation (years); gender; clinic; stage of disease at HAART initiation, classified as less [Centers for Disease Control and Prevention (CDC) stages A or B, World Health Organization (WHO) stages I or II] or more advanced (CDC stage C, WHO stages III or IV); incidence of an opportunistic infection during the first 6 months of treatment; and baseline (−6 months to +1 week) CD4 cell count (cells/μL). The baseline date was the date of antiretroviral therapy initiation. Ascertainment of opportunistic conditions was made by the local medical staff. All reported conditions that met CDC stage C or WHO stage IV criteria were considered to be AIDS-defining events. The exposure of interest was 6-month response to therapy (3–9 month window), categorized according to virological (HIV PVL < 500 copies/mL) and immunological (increase of at least 50 CD4 cells/μL) responses, considered jointly as complete (VR+IR+), virologic only (VR+IR−), immunologic only (VR−IR+), and absent (VR−IR−). First-line HAART regimens were categorized as NNRTI-based [1 NNRTI plus 2 nucleoside reverse transcriptase inhibitors (NRTI)]; protease inhibitor (PI)–based (2 NRTIs plus 1 ritonavir-boosted or unboosted PI); or other (including triple NRTI regimens and any other regimen containing a minimum of 3 drugs).

Outcomes

The endpoint was all cause mortality documented after the 6 (3–9) month measurement of response to therapy. Time was calculated from the 6-month measurement and ended at the earliest of the date of death or last follow-up visit. A patient was considered lost to follow-up if the last visit was recorded during the first year after starting HAART and the patient had at least 1 year of additional potential follow-up before the closing date of the database. This definition was chosen for the sake of comparability with other studies and was previously employed in a previous publication by this group.[12] The closing date was defined for each cohort as the date of the most recent follow-up recorded in the database. Death was ascertained by local medical staff.

Statistical Analysis

Between-group comparisons were made by using the χ^2 test for categorical variables and the Kruskall–Wallis test for continuous variables. Kaplan–Meier curves were used to show survival from 6-month response to HAART to death, and log-rank tests were used to test the hypothesis of equality between survival functions. Associations between independent variables and mortality were assessed using Cox proportional hazards regression with complete responders serving as the reference group. Wald tests were used to test for differences between the 2 types of immunologic and virologic discordant responses, using linear contrasts of the coefficients. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Huber–White robust standard errors were calculated to account for intrasite correlation. The proportional hazards assumption was assessed graphically by plotting scaled Schoenfeld residuals against survival time for each factor separately, and by log–log survival plots for categories of immunologic and virologic response, adjusted for other covariates.

Missing information on 6-month PVL or CD4 cell counts was imputed for those who had only one of these measurements, based on mortality status, loss to follow-up status, clinic, baseline CD4 cell count, sex, age, type of HAART regimen, and year of HAART initiation. The ice command in Stata was used to multiply impute missing values.[13] In these imputations, values of the missing data were randomly sampled from their predicted distributions conditional on covariates and survival time. Analyses were run on each of 10 datasets that included the imputed values and the results combined with Rubin rules.[14] Analyses were performed using Stata version 9.0 (Stata Corp, College Station, TX).

RESULTS

Of 37,263 records in the ART-LINC database, a total of 17,785 antiretroviral (ARV)-naive patients aged 16 years or older from 18 clinics, with at least 1 laboratory measurement at

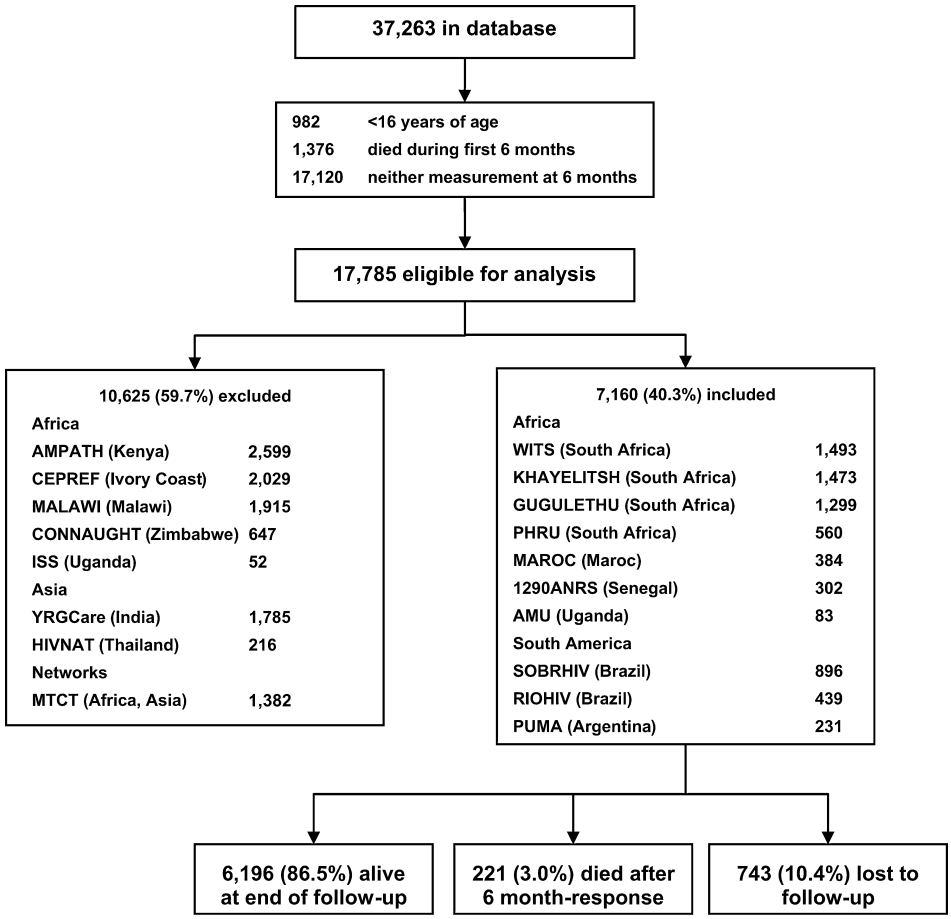

FIGURE 1. Patients' disposition and main outcomes.

6 months were potentially eligible for this analysis. Data from 8 clinics (5 from Africa, 2 from Asia, and 1 Africa–Asia network) on 10,625 patients (59.7%) were excluded due to high levels of missing laboratory measurements at 6 months (Fig. 1). Excluded and included patients were similar with regard to age (median 34 vs. 35 years, respectively, $P = 0.86$); sex (60.7% vs. 62.1% female, respectively, $P = 0.08$); and survival rates (1.49 vs. 1.48 per 100 person-years; $P = 0.85$). However, excluded patients were more likely to start treatment on a nonstandard regimen (9.1 % vs. 3.7%, respectively; $P < 0.001$) and less likely to start on a PI-based regimen (1.9% vs. 15.7%, respectively; $P < 0.001$) than NNRTI-based regimens; had a higher baseline CD4 cell count (median 130 vs. 100 cells/μL; $P < 0.001$), a shorter follow-up (median 1.34 vs. 1.48 years; $P < 0.001$); and were less likely to be lost to follow-up (5.7% vs. 10.4%; $P < 0.001$).

Of the 7160 patients included in the analysis, 4347 were female (60.7%), with a median age of 34 years [interquartile range (IQR) 30–41] and a median baseline CD4 cell count of 100 (IQR 42–173) cells per microliter. Most patients (82.2%) were at an advanced stage of disease and were prescribed a NNRTI-based regimen as first-line therapy (80.6%). Of the 7160 patients, 5663 (79.1%) had both PVL and CD4 cell count measured at 6 months of therapy, and 1497 (20.9%) had either CD4 cell count (1181) or PVL (316). The rate of missing response was similar in Africa and South America (21.1 and 20.2%, respectively). Data on 6-month measurements were imputed for these patients, and the following results are based on imputed data.

At 6 (3–9) months, 4974 patients (69.5%) showed complete response; 1260 (17.6%) had virologic-only response; 540 (7.5%) had immunologic-only response; and 386 (5.4%) showed no response. Baseline CD4 cell count was lowest for immunologic-only responders, followed by complete responders, nonresponders, and virologic-only responders ($P < 0.001$) (Table 1).

The median follow-up time was 1.01 year (IQR 0.54–1.72; Table 1) and varied significantly across clinics (data not shown). The 2 Brazilian clinics had the longest follow-up times, with medians of 4.02 (IQR 1.13–6.21); and 4.23 years (IQR 1.82–6.43). The overall rate of loss-to-follow-up was 10.4% and was highest among virologic nonresponders (Table 1).

Among those who had a 6-month measurement, a total of 221 deaths were reported during 15,107 person-years, corresponding to a mortality rate of 1.46 (95% CI 1.28 to 1.67) per 100 person-years. Mortality rates varied by clinic and were generally higher in the African clinics (1.83 per 100 person-years; 95% CI 1.57 to 2.14) than in the South American clinics (0.96 per 100 person-years; 95% CI 0.75 to 1.23).

The mortality rate was highest among nonresponders, followed by immunologic-only, virologic-only, and complete responders [3.72 (95% CI 2.77 to 4.99), 1.88 (95% CI

TABLE 1. Patient Baseline Characteristics and Outcomes According to Immunologic and Virologic Responses at 6 Months of Therapy

Variable	Total, N = 7160	VR+IR+, N = 4974	VR+IR−, N = 1260	VR−IR+, N = 540	VR−IR−, N = 386
Baseline characteristics					
Female gender n (%)	4347 (60.7)	3147 (63.3)	724 (57.5)	288 (53.3)	188 (48.7)
Age (IQR), yrs*	34 (30–41)	34 (30–41)	36 (31–43)	33 (29–39)	34 (30–40)
Baseline CD4 count cells/μL (IQR)*	100 (42–173)	93 (40–162)	141 (73–217)	76 (27–148)	117 (43–200)
Clinical stage n (%)					
Less advanced	753 (10.5)	532 (10.7)	164 (13.0)	30 (5.6)	27 (7.0)
Advanced	5886 (82.2)	4095 (82.3)	1012 (80.3)	462 (85.5)	317 (82.1)
Unknown	521 (7.3)	347 (7.0)	84 (6.7)	48 (8.9)	42 (10.9)
Regimen type n (%)					
NNRTI based	5769 (80.6)	4212 (84.7)	1038 (82.4)	309 (57.2)	210 (54.4)
PI based	1125 (15.7)	607 (12.2)	164 (13.0)	200 (37.0)	154 (39.9)
Other†	266 (3.7)	155 (3.1)	58 (4.6)	31 (5.7)	22 (5.7)
Geographic region					
Africa	5595 (78.1)	3929 (70.2)	962 (17.2)	435 (7.7)	268 (4.8)
South America	1566 (21.9)	892 (57.0)	257 (16.4)	233 (14.9)	184 (11.7)
Outcomes					
Follow-up time in years, (IQR)*	1.01 (0.54–1.72)	0.99 (0.53–1.59)	0.97 (0.47–1.57)	1.37 (0.76–1.37)	1.23 (0.62–3.94)
Mortality rate per 100 person-years (95% CI)	1.46 (1.28 to 1.67)	1.03 (0.85 to 1.25)	1.83 (1.36 to 2.45)	1.88 (1.32 to 2.68)	3.72 (2.77 to 4.99)
Loss to follow-up, n (%)	743 (10.4)	422 (8.5)	129 (10.2)	116 (21.5)	76 (19.7)

*Median (IQR).
†Any other nonstandard combination of 3 or more drugs.
VR+IR+, complete response; VR+IR−, virologic-only response; VR−IR+, immunologic-only response; VR−IR−, nonresponse.

1.32 – 2.68), 1.83 (95% CI 1.36 – 2.45), and 1.03 (95% CI 0.85 –1.25), respectively; Table 1]. The log–rank test for equality of survival functions showed significant differences between these groups ($P < 0.001$), with the complete responders having the best survival and the nonresponders having the worst survival (Fig. 2).

In multivariable analysis adjusted for age, clinical stage and CD4 cell count at HAART initiation, occurrence of an AIDS-defining condition during the first 6 months of therapy, clinic, and year of HAART initiation, discordant immunologic and virologic responses and nonresponses were associated with an increased risk of death (Table 2). Compared with complete responders, virologic-only responders had a HR of 1.90 (95% CI 1.38 to 2.63), immunologic-only responders had a HR of 2.00 (95% CI 1.30 to 3.30), and nonresponders had a HR of 5.48 (95% CI 2.87 to 10.46). The two of discordant responses were not significantly different from each other (Wald test $P = 0.46$). A higher baseline CD4 cell count was independently associated with improved survival (HR = 0.81 for an increase in 100 cells per microliter; 95% CI 0.68 to 0.96). Having an AIDS-defining condition during the initial 6 months of therapy was associated with a HR of 1.89 (95% CI 1.18 to 3.02). Plots of scaled Schoenfeld residuals for each variable included in the final model did not show violation of the proportional hazards assumption.

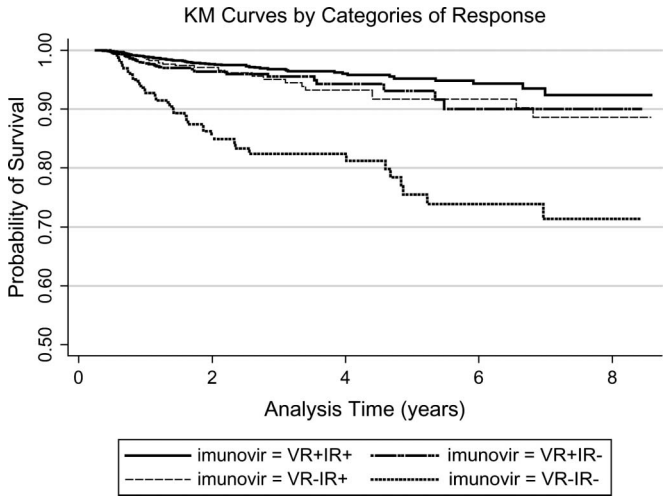

FIGURE 2. Kaplan–Meier curves of probability of survival according to categories of immunologic and virologic responses at 6 months in 7160 patients in ART-LINC of leDEA Collaboration.

The Cox model fitted to the complete case data is shown in Table 3. Although the HRs are qualitatively similar to the corresponding estimates in Table 2, several estimates were no longer statistically significant in the smaller sample, that is, immunologic-only response, baseline CD4 cell count, AIDS-defining event, and other HAART regimen, whereas the HR for age above 50 became statistically significant in the smaller sample.

In a subanalysis including only patients taking either NNRTI-based or PI-based regimens (n = 6882), there was a significant interaction between type of regimen and response (likelihood ratio χ^2 P value = 0.006). Among nonresponders, the hazard of death was increased if the initial regimen was NNRTI based.

TABLE 2. Unadjusted and Adjusted Cox Proportional Hazards and 95% Confidence Intervals of All-Cause Mortality for 7160 Patients*

Variable	Unadjusted HR	*P*	Adjusted HR	*P*
6-month response				
Complete (ref)	1.00	—	1.00	—
Virologic only	1.85 (1.35 to 2.52)	<0.001	2.11 (1.55 to 2.87)	<0.001
Immunologic only	1.76 (1.09 to 2.86)	0.002	1.88 (1.16 to 3.04)	0.002
Absent	4.68 (2.57 to 8.53)	<0.001	5.73 (3.30 to 9.95)	<0.001
Baseline CD4 cell count (100cells increase/μL)	0.79 (0.68 to 0.91)	0.002	0.81 (0.68 to 0.98)	0.039
Age in years				
16–29 (ref)	1.00	—	1.00	
30–39	1.00 (0.72 to 1.39)	0.989	1.04 (0.69 to 1.52)	0.847
40–49	1.12 (0.93 to 1.36)	0.226	1.18 (0.88 to 1.57)	0.262
50+	1.43 (0.93 to 2.20)	0.103	1.58 (0.95 to 2.64)	0.078
Clinical stage				
Less advanced (ref)	1.00	—	—	—
Advanced	1.06 (0.58 to 1.94)	0.838	—	—
Unknown	1.10 (0.56 to 2.15)	0.773	—	—
AIDS-defining event	1.66 (1.07 to 2.56)	0.022	1.88 (1.17 to 3.02)	0.009
HAART regimen				
NNRTI based (ref)	1.00	—	1.00	
PI based	1.31 (0.91 to 1.89)	0.147	1.50 (0.70 to 3.18)	0.292
Other	0.58 (0.36 to 0.94)	0.026	0.45 (0.25 to 0.80)	0.007

*Adjusted for year of therapy initiation and clinic as fixed effects.

Sensitivity Analyses

We assessed the extent to which different loss to follow-up rates may have affected our results by excluding from the multivariable model clinics with loss to follow-up rates greater than 15%. The HRs for the 3 responses remained similar to those in the full model (HR for VR+IR− 1.68, 95% CI 1.08 to 2.62; HR for VR−IR+ 1.71, 95% CI 0.69 to 4.24; and HR for VR−IR− 7.61, 95% CI 5.69 to 10.17). Exclusion of the

TABLE 3. Unadjusted and Adjusted Cox Proportional Hazards and 95% CIs of All-Cause Mortality for 4944 Patients With Complete Data*

Variable	Unadjusted HR	*P*	Adjusted HR	*P*
6-Month response				
Complete (ref)	1.00	—	1.00	—
Virologic only	1.46 (1.05 to 2.04)	0.024	1.50 (1.08 to 2.09)	0.015
Immunologic only	1.51 (0.78 to 2.92)	0.218	1.53 (0.90 to 2.58)	0.111
Absent	4.56 (2.01 to 10.36)	<0.001	5.43 (2.20 to 13.42)	<0.001
Baseline CD4 cell count (100 cells increase/μL)	0.85 (0.76 to 0.95)	0.007	0.90 (0.71 to 1.13)	0.373
Age in years				
16–29 (ref)	1.00	—	1.00	
30–39	0.99 (0.64 to 1.55)	0.990	1.06 (0.65 to 1.72)	0.820
40–49	1.18 (0.94 to 1.48)	0.154	1.24 (0.85 to 1.82)	0.266
50+	1.58 (1.02 to 2.48)	0.041	2.00 (1.22 to 3.28)	0.006
Clinical stage				
Less advanced (ref)	1.00	—	—	—
Advanced	1.04 (0.58 to 1.85)	0.891	—	—
Unknown	1.04 (0.55 to 1.98)	0.900	—	—
AIDS-defining event			1.45 (0.91 to 2.30)	0.115
HAART Regimen				
NNRTI based (ref)	1.00	—	1.00	—
PI based	1.21 (0.87 to 1.67)	0.243	1.57 (0.65 to 3.75)	0.311
Other	0.71 (0.48 to 1.05)	0.094	0.51 (0.22 to 1.20)	0.123

*Adjusted for year of therapy initiation and clinic as fixed effects.

Brazilian clinics also did not substantially change the estimated HRs, suggesting no bias due to different lengths of follow-up in our analysis (HR for VR+IR− 1.75, 95% CI 1.22 to 2.51; HR for VR−IR+ 1.35, 95% CI 0.50 to 3.63; and HR for VR−IR− 7.84, 95% CI 6.11 – 10.05). The HRs of discordant responses were also similar in African (HR for VR+IR− 1.79, 95% CI 1.18 to 2.40; HR for VR−IR+ 1.35, 95% CI 0.50 to 3.67; and HR for VR−IR− 7.92, 95% CI 6.16 to 10.17) and South American regions (HR for VR+IR− 1.91, 95% CI 0.71 to 5.16; HR for VR−IR+ 1.54, 95% CI 1.16 to 2.05; and HR for VR−IR− 4.07, 95% CI 2.23 to 7.44). Overall, the results of these sensitivity analyses showed consistency of HRs for discordant responses.

DISCUSSION

We report on survival associated with immunologic and virologic discordant responses at 6 months after HAART initiation in a large collaboration of cohorts from lower income countries. Our analysis shows that both types of discordant responses are associated with increased risk of death relative to complete responders, which is in agreement with previous reports from developed countries.[4–6,15]

Understanding the relationship between early responses to HAART and mortality has critical implications for guiding treatment modifications, particularly for those patients who show discordant responses, because partial response to therapy has been associated with increased risk of disease progression and death in several studies. In a study conducted in France, virologic-only responders and nonresponders had a higher probability of clinical progression, whereas immunologic-only responders and complete responders had similar risks.[16] In contrast, in other studies, immunologic-only response was also associated with a higher risk of clinical progression. In a cohort of ARV-experienced patients with advanced HIV disease starting PI-based HAART that was followed for over 30 months, discordant responders at 12 months experienced significantly more AIDS-defining events than complete responders, with immunologic-only responders having a slightly higher probability of being event-free compared with virologic-only responders.[4] In another study, involving over 2100 ARV-experienced and naive patients followed for a median of 44 months, immunologic-only responders and virologic-only responders had significantly lower risk of clinical progression than nonresponders but had a 2.3-fold and 1.9-fold greater risks of death or of experiencing a new AIDS-defining event than complete responders, respectively.[5] Similar findings were recently reported by Tan et al[15] among 404 patients from an urban clinic in the United States.

Few studies have assessed the prognostic value of discordant responses in previously naive patients and in recipients of NNRTI-based regimens. Our results are similar to those reported by Moore et al,[6] who assessed the independent association of discordant responses with mortality in 2217 ARV-naive individuals initiating HAART in British Columbia. These authors also reported that discordant responses were associated with increased risk of death when compared with complete responders. Likewise, in a study involving previously HAART-naive injection drug users, although discordant responders experienced increased mortality in comparison to complete responders, progression rates did not differ whether early response was immunologic only or virologic only.[17] Another study of 850 virologically suppressed patients showed that poor CD4 cell recovery was associated with higher risk of death or an AIDS-defining event and that consequences of poor response were greater at lower baseline CD4 values.[18]

We found a significant interaction between use of NNRTI-based regimen and nonresponse, suggesting that a poor response to this class of drug has more deleterious effect on long-term survival than a PI-based regimen. Although our findings should be interpreted with caution due to inherent limitations of this type of analysis, in particular, selection-by-indication bias, data suggesting that failure of PI-based regimens is associated with less rapid progression than NNRTI regimens are accumulating.[19,20] One concern that arises from the wide use of NNRTI-based regimens is that qualitative differences in immunologic-only response could exist between PI and NNRTI recipients due to different genetic barriers to resistance and potential intrinsic properties of individual drugs or classes of drugs.[21,22] A study of 1138 previously HAART-naive HIV-infected individuals from British Columbia showed that patients who developed resistance to NNRTI had a risk 3.02 times higher of progressing to death than those who had no resistance.[23] In a study assessing the impact of time from virologic failure to treatment switch, Petersen et al[24] showed that delayed modification after failure of a NNRTI-based regimen was associated with increased risk of immunologic failure and mortality. Further studies are thus needed to clarify the prognostic importance of different patterns of immunologic and virologic response in recipients of PI and non-PI regimens.

Our study has several limitations. First, data on adherence were not available. Several studies have shown the independent association between poor adherence and increased mortality.[6,25,26] Second, other possible confounders could not be assessed in our study. For example, studies on the pathogenesis of immunologic-only response have suggested possible roles of factors associated with viral subtype,[27,28] phenotype,[29] and/or fitness,[22] and T-cell activation,[30,31] and host-related determinants such as genetic polymorphisms.[32] Poor CD4 cell recovery has been associated with regimens containing didanosine plus tenofovir[33] and polymorphisms of interleukin-6 and central major histocompatibility complex genes.[34] Third, the definition of immunologic response used in the present and in other studies (an increase in CD4 cell count of at least 50 cells) may be subject to a regression toward the mean effect, by which those with the highest baseline values would be less likely to respond than those with low baseline values.[35] Fourth, the exclusion of nearly 60% of patients due to lack of information on the 6-month response could have introduced a bias into our results. Most ART-LINC participating sites do not perform routine PVL for treatment monitoring; therefore, the analysis was limited to a sample that may not be representative of countries where ARV programs have been rolled out. Although excluded and included patients were similar in baseline characteristics and survival rates, the relatively short follow-up time precludes further extrapolations as to whether such selection might affect long-term outcomes. Therefore, our results may not be applicable to patients from

lower income countries, which do not have a 6-month laboratory assessment. Finally, we also noticed a generally higher rate of loss to follow-up among nonresponders. That these patients also were more likely to die indicates a potential ascertainment bias that could have led to underestimating the hazard for this group.

In conclusion, we found that in developing countries, both types of immunologic and virologic discordant responses were associated with higher mortality rates when compared with complete responses. No published study has assessed the impact of discordant responses on mortality in low-income countries, where most patients initiate HAART with NNRTI-based regimens. Most studies published so far have been conducted in developed countries and have included patients mostly using PI-based regimens. Our results suggest that, as in resource-rich settings, both immunologic and virologic assessments are important for predicting mortality in patients receiving HAART in resource-constrained countries and provide a strong argument for recommending the wider availability of PVL testing to monitor antiretroviral therapy in these settings.

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APPENDIX 1: THE ANTIRETROVIRAL THERAPY IN LOW INCOME COUNTRIES (ART-LINC) COLLABORATION OF THE INTERNATIONAL EPIDEMIOLOGIC DATABASES TO EVALUATE AIDS (IEDEA)

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