

Proinflammatory Cytokine Changes in Clinically Stable, Virologically Suppressed, HIV-Infected Patients Switching From Protease Inhibitors to Abacavir

To the Editor:

Excess cardiovascular risk has been observed in HIV-infected patients,¹ driven by traditional risk factors such as smoking, hypertension, diabetes, and aging, although therapy-induced hyperlipidemia and HIV-induced proinflammatory state and immune activation seem to play a role.²⁻⁴

A recent report from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study, one of the largest cohorts evaluating cardiovascular risk in HIV-infected patients, assessed the associations between nucleoside analogues and myocardial infarction. Contrary to the hypothesis expecting a role for thymidine analogues because of their negative effects on plasma lipids, insulin sensitivity, and limb fat loss, DAD investigators unexpectedly found that the recent use of didanosine and abacavir increased the risk of myocardial infarction by 50% and 90%, respectively.⁵ These findings were even more surprising as abacavir has a neutral lipid profile, does not interfere with insulin sensitivity, is not associated with limb fat loss in naive patients, and even promotes a fat increase in patients with lipoatrophy switching to abacavir from thymidine analogues.^{6,7} Although the DAD investigators adjusted the effect of abacavir as much as possible, the possibility of bias cannot definitively be ruled out. However, if abacavir really plays a role in promoting cardiovascular disease, other mechanisms apart from lipid changes,

insulin sensitivity, and body fat alterations would have to be involved.

Several studies have shown that changes in inflammatory cytokines such as adiponectin and tumor necrosis factor (TNF)-alpha may be related to increased cardiovascular risk in the general population.⁸⁻¹⁰ More recently, this association has been suggested in HIV-infected patients, mainly those with uncontrolled viral replication before initiating or after discontinuing antiretroviral therapy.¹⁻³

The Nevirapine, Efavirenz and Abacavir (NEFA) trial assessed the relative merits of abacavir, efavirenz, or nevirapine as substitutes for the protease inhibitor (PI) component in stable virologically suppressed patients treated with a first-generation, unboosted PI and willing to simplify their regimen.¹¹ In an intensive metabolic substudy of NEFA,¹² we found favorable lipid changes in patients switching to any of the 3 options, namely a decrease in total cholesterol in the abacavir group, an increase in HDL cholesterol, and a decrease in the ratio of total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol (TC:HDL) in the nonnucleoside reverse transcriptase inhibitor (NNRTI) groups.¹²

In addition, adiponectin and soluble tumor necrosis factor alpha receptor type 2 (sTNFR2) were assessed in baseline and 96-week serum samples adequately stored at -80°C for further laboratory analysis, contemplated in the initial design before the substudy. Plasma adiponectin was determined by radioimmunoassay (Linco Research, St. Charles, MO) with a detection threshold of 1 ng/mL and plasma sTNFR2 by a solid-phase enzyme immunoassay with amplified reactivity (Biosource Europe, Fleurus, Belgium) and a detection threshold of 0.1 ng/mL. In samples from 54 of 90 patients included in the metabolic substudy who continued with the assigned drug up to the end of follow-up (18 abacavir, 19 nevirapine, and 17 efavirenz), an increase in adiponectin levels and a decrease in sTNFR2 were observed in the overall population 96 weeks after the PI switch.¹²

We now present an analysis of the changes observed in these adipokines according to the antiretroviral regimen

received in the NEFA metabolic substudy.

Groups were comparable for baseline characteristics, including age {abacavir 38 years [IQR (interquartile range) 34-47], efavirenz 37 (35-45), and nevirapine 41 (37-46)}, proportion of men (abacavir 79%, efavirenz 84%, and nevirapine 83%), risk groups (drug users: abacavir 34%, efavirenz 41%, and nevirapine 41%; homosexuals: abacavir 21%, efavirenz 25%, and nevirapine 17%; heterosexuals: abacavir 38%, efavirenz 25%, and nevirapine 41%), AIDS (abacavir 34%, efavirenz 50%, and nevirapine 45%), and CD4 count [abacavir 456 cells/ μL (IQR 308-728); efavirenz 549 (274-674), nevirapine 338 (249-552)], with the exception of stavudine use (abacavir 82.8%, efavirenz 62.1%, nevirapine 87.5%; $P = 0.043$). Although a trend to an increase in adiponectin levels was observed in patients switched to nevirapine [median (IQR) 5.5 (4.2-9.8) to 8.4 (4.9-10.7) $\mu\text{g}/\text{mL}$; $P = 0.1$] and there were no changes in the efavirenz arm [4.4 (3.4-7.8) to 4.1 (2.8-7.8) $\mu\text{g}/\text{mL}$; $P = 0.3$], a significant decrease in adiponectin was seen in abacavir patients [8.7 (2.9-16.1) to 5.2 (2.6-7.7) $\mu\text{g}/\text{mL}$; $P < 0.05$] (Fig. 1A). Changes in adiponectin levels differed between the NNRTI and abacavir groups ($P < 0.001$). Conversely, a reduction in sTNFR2 was observed in the NNRTI arms, which was significant in the nevirapine group [6.8 (5.1-8.4) to 5.7 (4.2-7.5) ng/mL; $P < 0.05$] and efavirenz group [6.9 (5.6-7.9) to 6.5 (5.4-7.5) ng/mL; $P = 0.3$], whereas a nonsignificant increase was found in abacavir patients [5.2 (5.0-9.8) to 6.7 (5.3-8.9) ng/mL; $P = 0.6$] (Fig. 1B).

After adjusting for several variables, including sex, age, Δ triglyceride, Δ TC/HDL, CD4, viral load, stavudine use, and lipodystrophy, in a multivariate linear regression model, abacavir remained significantly associated with a decrease in adiponectin levels ($\beta = -6.001$, $P = 0.004$) and a trend to an increase in sTNFR2 ($\beta = 1.267$, $P = 0.146$).

Adiponectin is an adipokine with metabolic and anti-inflammatory effects. Hypoadiponectinemia is a significant predictor of endothelial dysfunction in peripheral vasculature and coronary

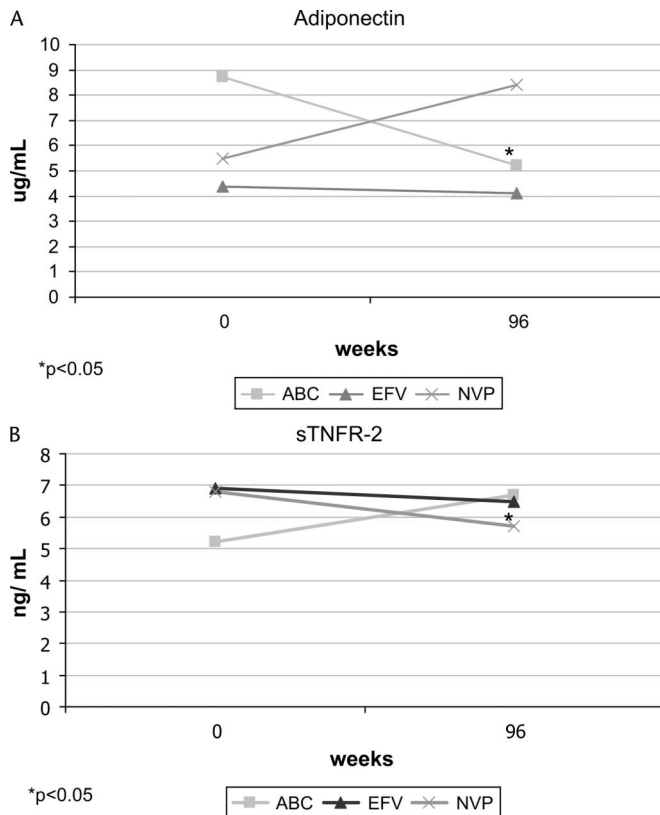


FIGURE 1. Changes in adiponectin (A) and sTNFR2 (B) plasma levels according to treatment arm. ABC, abacavir; EFV, efavirenz; NVP, nevirapine.

arteries, independently of the insulin resistance index, body mass index, and dyslipidemia.^{8,9} The vasculoprotective effects of adiponectin seem to derive from a direct action on the vascular system by increasing endothelial nitric oxide production and inhibiting the atherosclerotic process.^{13,14} The sTNFR2 is related to the metabolic action of TNF-alpha in insulin resistance states and inflammation and has an important role in the atherosclerosis process.¹⁰ In humans, TNF-alpha promotes endothelial dysfunction by impairing endothelium-dependent vasodilation; plasma levels of this factor are elevated in patients at increased risk for recurrent coronary events.^{10,15} Thus, a pattern of decreased adiponectin levels together with increased sTNFR2, such as that observed in our abacavir patients, may favor an increase in cardiovascular risk. Of note, nevirapine, which is one of the most lipid-friendly antiretroviral drugs,¹² was also associated with the best “adipokine profile” in this study.

In summary, we observed proinflammatory cytokine changes in

virologically suppressed HIV-infected patients switching from PIs to abacavir. These findings are in keeping with those of the DAD study and suggest a proinflammatory role for abacavir in otherwise clinically stable and virologically suppressed patients. Nonetheless, our data were obtained from a relatively small group of patients and therefore should be interpreted with caution and confirmed in future studies.

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The Relationship Between Prolonged Antiretroviral Therapy and Cryptogenic Liver Disease

To the Editor:

Chronic liver disease causes substantial morbidity and mortality in HIV-positive patients, with chronic hepatitis B virus (HBV), hepatitis C virus (HCV) infection, alcohol consumption, and drug-related toxicity being commonly cited.¹⁻³ In addition, some individuals with elevated liver enzymes without an obvious underlying etiology may still develop complications such as portal hypertension.⁴ In the context of HIV, this “cryptogenic” liver disease has previously been reported in association with prolonged didanosine exposure.⁴ We thus undertook a study to assess the association between prolonged antiretroviral therapy (ART) and cryptogenic liver disease (CLD).

We defined CLD as persistently elevated hepatic transaminase levels in the absence of replicative HBV or HCV infection or other common causes of chronic liver disease.⁴ The normal level of alanine aminotransferase (ALT) was ≤ 37 IU. We identified 90 patients from a cohort of 4500 HIV-positive patients attending the Chelsea and Westminster Hospital who underwent a liver biopsy between January 2004 and July 2007. We retrospectively reviewed the case notes including full ART history and laboratory results of these patients to exclude other causes of chronic liver disease including autoimmune hepatitis, Wilson disease, alpha-1 antitrypsin deficiency, and syphilis.

Each of the cases, which fulfilled our definition of CLD, were then matched for age, sex, race, duration of HIV diagnosis, and CD4 count with a control. Variables were compared using a Kruskal-Wallis test to assess for any association between ART and the development of CLD.

Of the 90 patients who had a liver biopsy during this 41-month period, 13 constituted our definition of CLD. All of these had persistently elevated ALT for greater than 6 months. There was no history of excessive alcohol use

except for 1 patient who abstained from alcohol consumption for more than 1 year before liver biopsy. Syphilis serology and liver autoantibodies (antinuclear antibody [ANA], liver-kidney microsomal autoantibodies of type 1 [LKM-1]) were negative in all patients. Normal levels of alpha-1 antitrypsin, copper/ceruloplasmin, ferritin, and transferrin saturation excluded metabolic causes of liver disease. All patients had a negative HBV surface antigen and HCV antibody, and in addition, HBV DNA and HCV RNA levels (lower limit of detection was 500 copies/mL and 3200 copies/mL, respectively) were confirmed by polymerase chain reaction in most patients to exclude occult HBV and HCV infection.

Of the 13 patients with CLD, the mean age measured 45 years (range 39–65 years), and 10 were males (77%). The median CD4 count at biopsy was 187 cells per cubic millimeter [interquartile range (IQR) 190]. All patients had an undetectable HIV viral load at biopsy, except for 1 with a viral load of 356 copies per milliliter. All had normal ALT before commencing ART, and all were triple antiretroviral class experienced. The biopsy findings showed portal fibrosis in 9 (69%), cholangiopathy in 2 (15%), sclerosing cholangitis in 1 (7.7%), and Ishak stage 5 cirrhosis in 1 (7.7%). Biopsies of 2 patients with mild portal fibrosis were also suggestive of nodular regenerative hyperplasia (NRH).

The median duration of exposure with ART in CLD patients were as follows: nucleoside reverse transcriptase inhibitors as follows: (1) 10 patients on didanosine, 62 months (IQR 44.75), (2) 6 individuals receiving tenofovir, 47.5 months (IQR 10), (3) 8 on zidovudine, 43 months (IQR 60.5), (4) 8 on lamivudine, 29 months (IQR 33.25), (5) 6 on stavudine, 35.5 months (IQR 23.5), (6) 4 on abacavir, 11 months (IQR 23.25), and (7) 4 on emtricitabine, 3 months (IQR 7.5) and nonnucleoside reverse transcriptase inhibitors as follows: (1) 6 on efavirenz, 59 months (IQR 23.5) and (2) 5 on nevirapine, 39 months (IQR 26). The protease inhibitors received were as follows: (1) 2 individuals on nelfinavir, 52 months (IQR 1), (2) 6 on ritonavir (all on boosted dose), 18.5 months (IQR 7.75), (3) 3 on fosamprenavir, 13 months (IQR 10), (4) 5 on atazanavir, 14 months (IQR 13), (5) 3 on lopinavir, 8 months (IQR

9.5), (6) 4 on saquinavir, 8.5 months (IQR 8.25), and (7) 1 on indinavir, 5 months (Table 1).

Three patients (23%) developed portal vein thrombosis, 4 (31%) developed episodes of hepatic decompensation with ascites, and 2 (15%) developed portal hypertension. One patient subsequently died of hemorrhage from esophageal varices complicating their CLD. The case-control analysis revealed no significant association between ART and the development of CLD. In particular, there was no link with didanosine ($P = 0.096$) although this was most frequently used and for the longest duration.

In the general population, rates of CLD are below 0.01%⁴ with a prevalence of 5%–30% amongst cirrhotic patients.⁵ Estimates within the HIV-positive population are limited, with a prevalence of 17 of 3200 (0.5%) in 1 case-control study.⁴ In our cohort, only 13 of 90 liver biopsies performed from a cohort of 4500 HIV-positive patients during a 31-month period were compatible with a diagnosis of CLD. An undetectable HIV viral load in 12 of 13 indicates that HIV itself is unlikely to be the cause of hepatic dysfunction. All had normal ALT before commencing ART, suggesting that ART may be responsible for hepatic inflammation. Although didanosine was used most frequently and for the longest duration, in the case-control analysis, there was no correlation between specific antiretroviral drugs and CLD. This contradicts a previous case-control study, in which the only independent predictor of the developing CLD was long-term didanosine exposure.⁴ Furthermore, in another study of 27 HIV-positive patients with CLD receiving didanosine who discontinued this drug, clinical and laboratory improvement occurred in 13 patients (48%) after 12 months.⁶ Mitochondrial damage associated with didanosine may be the underlying mechanism for the development of CLD,⁴ however, the lack of correlation with other nucleoside analogues known to cause mitochondrial toxicity does not support this hypothesis.

Two of our patients had evidence of NRH, a condition in which there are small, diffuse, regenerative nodules in the absence of significant fibrosis.⁷ A review of 8 HIV-positive patients with CLD and NRH on biopsy revealed that

TABLE 1. Demographics, Antiretroviral Usage, and Liver Biopsy Histological Findings of 13 Subjects With CLD

Number	Sex	Age (yrs)	Race	CD4 at Time of Biopsy (cells/mm ³)	Time From HIV Diagnosis to Biopsy (mo)	Biopsy Result	Antiretroviral Regimen (Duration of Treatment in Months)
1	M	65	White	187	83	Portal fibrosis	AZT (26)
2	M	40	White	342	161	Mild portal fibrosis, mild NRH	AZT (20), ddI (59), d4T (70), 3TC (30), NVP (11), ATAZ (5), RTV (8), SQV (3), NFV (51), IND (5)
3	M	50	White	105	167	Portal and perisinusoidal fibrosis, NRH	AZT (104), ddI (102), 3TC (96), NVP (72), EFV (8)
4	F	42	Black African	140	78	HIV-associated sclerosing cholangitis	AZT (60), ddI (65), ABC (2), 3TC (8), ATAZ (14), RTV (14), NFV (53)
5	F	39	Black African	57	156	Mild portal fibrosis	AZT (144), ddI (120), ABC (5), FOS (3)
6	M	44	White	156	82	Cholangiopathy	AZT (1), 3TC (22), EFV (4)
7	M	46	White	293	152	Developing cirrhosis	ddI (34), 3TC (48), d4T (36), TFV (47), FTC (3), EFV (83)
8	M	46	White	392	121	Portal and perisinusoidal fibrosis	ddI (92), d4T (61), TFV (34), FTC (3), EFV (97)
9	M	44	White	321	58	Marked fibrosis amounting to developing cirrhosis	ddI (44), ABC (59), TFV (48), FTC (3), ATAZ (20), RTV (22)
10	M	41	White	327	83	Chronic hepatitis and cholangiopathy	AZT (72), 3TC (80), NVP (39), EFV (81)
11	M	42	White	702	190	Mild fibrosis	ddI (82), d4T (35), TFV (56), 3TC (23), FTC (33), NVP (35), ATAZ (18), LPV (23), RTV (23), SQV (15), FOS (23)
12	F	41	White	109	80	Moderate portal fibrosis	AZT (18), ddI (44), d4T (30), ABC (17), TFV (40), 3TC (28), EFV (37), ATAZ (4), LPV (8), RTV (22), SQV (5), FOS (13)
13	M	45	White	137	79	Portal fibrosis	ddI (47), d4T (8), TFV (53), NVP (61), LPV (4), RTV (15), SQV (12)

3TC, lamivudine; ABC, Abacavir; ATAZ, atazanavir; AZT, Zidovudine; ddI, didanosine; d4T, stavudine; EFV, efavirenz; FOS, fosamprenavir; IND-indinavir; LPV-lopinavir; NFV-nelfinavir; NVP, nevirapine; RTV, ritonavir (all at boosted dosage); SQV, saquinavir; TFV, tenofovir.

all were receiving didanosine.⁸ The authors speculate that NRH may be due to a combination of HIV, ART with didanosine, and also a prothrombotic state leading to intrahepatic thrombosis and NRH.⁸ Two further case reports of patients who had been on either nevirapine and didanosine⁹ or didanosine followed by nevirapine¹⁰ and a case series of 6 patients, with 5 on didanosine,¹¹ have presented similar findings and suggest that either HIV or ART are associated with NRH. Both of our patients with NRH were white and had been on didanosine for a duration of 59 months and 102 months, respectively; in addition, both also had treatment experience with nevirapine.

Patient numbers here were small, though similar to other studies, and indicative of how uncommon this diagnosis seems to be. Despite this, we have demonstrated that there does not seem to be an association between antiretroviral use and the development of CLD. Inaccuracies and observer bias may have occurred due to the retrospective collection of some data. In addition, we did not

perform a thrombophilia screen on the patients with a histological diagnosis of NRH and thus could not confirm the presence of a prothrombotic state as indicated by the previous literature.^{8,11}

With greater experience of long-term ART and the availability of new drugs in existing and novel classes, ART-related toxicity is of increasing concern. Although acute liver failure is clearly documented with some drugs such as nevirapine⁴ and coinfection with HCV and concomitant ART may lead to a progression in fibrosis,¹² there has been limited assessment of the long-term consequences of ART on the liver. In conclusion, our study does not confirm an association between the development of CLD and the prolonged use of antiretroviral drugs.

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Discordant Immunologic and Virologic Responses to Antiretroviral Therapy and Associated Mortality in a Large Treatment Program in Rwanda

To the Editors:

We read with interest the study by Tan et al¹ showing that discordant

immunologic and virologic responses at 3–9 months after starting highly active antiretroviral treatment play important roles in predicting long-term clinical outcomes (incidence of opportunistic disease and death) in treatment-naïve patients. Although the prevalence and risk factors for discordant responses in low-income countries are thought to be similar to those in high-income countries,² the prognostic significance of discordant responses has not been assessed in the former, where there is clearly a different burden of opportunistic disease. The patient population too is different in low-income settings where it is predominantly female, individuals often present with advanced disease, and patients starting treatment are mostly treatment naïve and generally start antiretroviral therapy (ART) with a first-line ART regimen containing a nonnucleoside reverse transcriptase inhibitor. For this reason, we evaluated the association between discordant immunologic and virologic responses and short-term mortality in a relatively large ART cohort in Rwanda between October 2003 and July 2007.

Médecins Sans Frontières has been supporting an ART program in 2 urban government health centers in Kigali, Rwanda, since 2003, with currently over 3000 patients started on treatment and with high patient retention (94% by 1 year).^{3,4} Patients were started on ART according to World Health Organization eligibility criteria. Approximately 90% of this cohort was started on generic fixed-dose combination regimens containing stavudine, lamivudine, and nevirapine. Viral load (VL) measurements were performed routinely after 1 year of treatment. Virologic success (VL⁺) was defined as a VL <40 copies per milliliter. Immunologic success (CD4⁺) was defined as an increase in CD4 count >50 cells per microliter from baseline. Virologic and immunologic responses were categorized as concordant or discordant and subgrouped as follows: concordant responses were either concordant positive responders (VL⁺/CD4⁺) or concordant nonresponders (VL⁻/CD4⁻); discordant responders were differentiated into patients displaying a virologic-only (VL⁺/CD4⁻) or an immunologic-only (VL⁻/CD4⁺) response on ART. The all-cause mortality rate, starting from the

time of VL measurement, was calculated per response category. Kaplan-Meier estimates were used to compare survival between groups. The association of response category with risk of mortality was assessed using a Cox proportional hazards model.

A total of 1251 ART-naïve adults were started on treatment during the study period, of whom, 289 had incomplete CD4 data and were excluded. Of the 962 patients who were included in the analysis, VL testing was done at a median period of 1.3 years after starting ART. The median baseline CD4 count was 149 cells per microliter, and most patients were in World Health Organization clinical stage II or III at baseline (Table 1). In total, 627 (65.2%) were concordant responders, and 46 (4.8%) were concordant nonresponders. Discordant responses were seen in 289 patients (30.0%), with 172 (17.8%) virologic-only responses (VL⁺/CD4⁻) and 117 (12.2%) immunologic-only responses (VL⁻/CD4⁺). The median follow-up period after VL determination was 13 months (interquartile range 6–15 months). Over more than 903 patient-years of follow-up, only 11 deaths were observed, reflecting (besides the relatively short follow-up period) the fact that these patients had been on ART for more than a year and hence had passed the more pronounced early mortality phase during the first few months of ART. Still, a difference in mortality rate between response categories was observed, ranging from 5.0 of 1000 patient-years for concordant responders to 54.2 of 1000 patient-years for concordant nonresponders. Discordant responses had a mortality rate of 28.8 of 1000 patient-years for virological-only responses and 11.4 of 1000 patient-years for immunological-only responders. Kaplan-Meier estimates summarizing the time to death by response category also showed significant differences between the categories (log-rank test: $P = 0.004$), with an estimated 1-year mortality (after response category determination) ranging from 0.4% for concordant responders, 3.4% for discordant responders, and 5.8% for concordant nonresponders. Relative to the concordant positive responders, a significant difference in prognosis was seen for concordant nonresponders ($P < 0.001$) and for discordant responders

TABLE 1. Cox Proportional Hazard Analysis of All-Cause Mortality by Immunologic and Virologic Response Categories*

	Deaths n (%)†	HR‡	P	Adjusted HR‡	P
Response to ART					
Concordant responders	3/627 (0.48)	1	—	1	—
Discordant responders	6/289 (2.08)	4.7 (1.2 to 18.9)	0.03	4.7 (1.2 to 19.2)	0.03
Concordant nonresponders	2/46 (4.35)	11.5 (1.9 to 69.1)	0.007	8.5 (1.3 to 54.1)	0.02
Age					
≤35 years	3/423 (0.7)	1	—	1	—
>35 years	8/539 (1.48)	1.9 (0.7 to 5.2)	0.22	2.0 (0.5 to 8.2)	0.35
Sex					
Male	4/263 (1.52)	1	—	1	—
Female	7/699 (1.00)	0.5 (0.2 to 1.5)	0.26	1.1 (0.9 to 3.1)	0.88
Baseline WHO clinical stage					
I/II	3/278 (1.08)	1	—	1	—
III/IV	8/684 (1.17)	0.9 (0.3 to 3.2)	0.84	0.8 (0.2 to 3.2)	0.79
Baseline CD4 count					
≤50 cells/μL	3/129 (2.33)	1	—	1	—
>50 cells/μL	8/833 (0.96)	0.45 (0.1 to 1.8)	0.83	0.3 (0.1 to 1.2)	0.10
Baseline body weight					
≤50 kg	2/228 (0.88)	1	—	1	—
>50 kg	9/700 (1.29)	1.2 (0.3 to 5.3)	0.81	1.2 (0.3 to 6.0)	0.78
Adherence§					
>95%	4/653 (0.61)	1	—	1	—
≤95%	7/309 (2.27)	3.8 (1.3 to 10.7)	0.01	4.1 (1.2 to 14.2)	0.03

HR, hazard ratio; WHO, World Health Organization.

*The different immunologic and virologic response categories and other baseline factors reported to be associated with mortality while on ART within low-income countries were included in the model. Cox regression excluding 34 patients with missing weight data.

†Values are expressed as n of deaths/total N; the percentage of patients who died is given in parentheses.

‡HR; 95% confidence interval in parentheses.

§Based on pharmacy refills as a measure of adherence to therapy

($P = 0.005$). No significant difference between both discordant response categories was found ($P = 0.373$). In multivariate analysis, both a discordant (hazard ratio 4.7; $P = 0.03$) and a concordant nonresponse (hazard ratio 8.5; $P = 0.02$) remained associated with increased mortality (Table 1). In a separate analysis, a threshold of 1000 copies per milliliter was used, to exclude viral “blips,” which essentially provided similar results (data not shown).

Given the constrained resources, for health facilities in resource-limited settings that are faced with high patient burdens and shortages of staff (both in terms of numbers and capacity), it would be useful to focus more specialized medical attention toward those most at risk. Our data are in line with those of Tan et al¹ and suggest that patients with discordant responses represent a population at risk. The fact that a significant difference with concordant responders was observed within a relatively short period suggests that the risk is likely to be substantial. There are a number of unanswered questions. Is there a relation between the level of drug adherence over

time and the discordant response category? Do subclinical or undiagnosed opportunistic infections particularly tuberculosis play a role in the incidence or outcomes of discordant responses? In this regard, the observed association between the occurrence of tuberculosis while on ART and virologic-only responses might be of interest (data not shown). In these resource-limited settings, does nutrition, helminth infection,⁵ or other inflammatory conditions interfere with immune recovery on ART or does a poor immune response reflect irreversible damage due to advanced HIV disease? Would patients with immunologic-only responses benefit from earlier switches to protease inhibitor therapy?⁶ Finally, would isoniazid preventive therapy or other adjunctive treatments reduce the incidence and/or associated mortality of discordant responses? The answers to these questions merit further research.

There are a number of limitations to this analysis. First, it is an observational study performed retrospectively on existing data, and as such residual confounding cannot be excluded. More detailed data on adherence, clinical

events, laboratory results, and baseline and repeat VL measurements might have been informative but were not available due to resource limitations. The strengths of this study are that the data come from a routine setting and are thus likely to reflect the operational reality on the ground; patients lost to follow-up were traced by community support groups, and deaths were reliably ascertained; and finally, in contrast to the study of Tan et al,¹ where the response category was determined at 3–9 months after ART initiation, this was done after at least 1 year on treatment in our cohort. The latter probably better reflects what is achievable in most resource-constrained settings, with limited access to VL tests. Anyhow, our data provide another strong argument for wider availability of VL tests in these settings.

In conclusion, discordant responders and concordant nonresponders are a population at risk in low-income countries meriting targeted medical attention. Better understanding of the mechanisms underlying discordant responses would allow the design of management strategies to reduce associated mortality in low-income countries. With currently more than 3 million patients on highly active antiretroviral treatment in low-income countries, of whom, approximately 1 in 3 (30%) might be discordant responders who are at relatively high risk of death even while on ART, this issue is of high relevance to clinical management and public health.

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