Grade 4 Events Are as Important as AIDS Events in the Era of HAART

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Objective: To estimate incidence and predictors of serious or life-threatening events that are not AIDS defining, AIDS events, and death among patients treated with highly active antiretroviral therapy (HAART) in the setting of 5 large multicenter randomized treatment trials conducted in the United States.

Methods: Data were analyzed from 2947 patients enrolled from December 1996 through December 2001. All patients were to receive antiretrovirals throughout follow-up. Data collection was uniform for all main outcome measures: serious or life-threatening (grade 4) events, AIDS, and death.

Results: During follow-up, 675 patients experienced a grade 4 event (11.4 per 100 person-years); 332 developed an AIDS event (5.6 per 100 person-years); and 272 died (4.6 per 100 person-years). The most common grade 4 events were liver related (148 patients, 2.6 per 100 person-years). Cardiovascular events were associated with the greatest risk of death (hazard ratio = 8.64; 95% CI: 5.1 to 14.5). The first grade 4 event and the first AIDS event were associated with similar risks of death, 5.68 and 6.95, respectively.

Conclusions: Grade 4 events are as important as AIDS events in the era of HAART. To adequately evaluate the impact of HAART on morbidity, comorbidities and other key factors must be carefully assessed.

Key Words: morbidity, mortality, HAART, AIDS, comorbidities

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The introduction of highly active antiretroviral therapy (HAART) and an improved understanding of HIV-1 viral dynamics led to a dramatic decline in US AIDS-related morbidity and mortality beginning in 1996.[1–4] This dramatic decline, together with the hope that HIV could be eradicated,[5] led clinicians and HIV treatment guideline committees to adopt an aggressive strategy in treating HIV,[6] focusing primarily on the benefits of HAART: "hit early, hit hard."[7] However, as current antiretroviral therapy is unable to eradicate HIV,[8] and is associated with increased toxicities, HIV treatment guideline committees have recently adopted a less aggressive set of guidelines for treating HIV.[9,10]

All 4 classes of antiretrovirals (ARVs) and all 19 Food and Drug Administration–approved ARVs have been directly or indirectly associated with life-threatening events and death.[9,11–13] However, the cause of many serious or life-threatening events is multifactorial and clear attribution to the use of HAART, specific ARV drugs, HIV infection, or other factors is frequently not possible. Potential risk factors for the development of life-threatening clinical events among HIV-infected individuals on HAART include HIV virus–host interactions,[14–17] stage of HIV disease,[18–20] ARV drugs,[9,11–13] genetic predisposition,[21–25] age,[26] comorbid conditions,[27–35] coinfections (e.g., hepatitis B or hepatitis C),[36–44] concomitant medications,[43,45–49] nutritional status,[50–55] recreational drugs and alcohol,[56–58] other social behaviors and practices,[53,59–62] and physician experience.[63,64]

The short-term toxicities and benefits of HAART have been well described in the setting of clinical trials; however, data quantifying morbidity in the era of HAART are limited. We therefore estimated the incidence and determinants of serious or life-threatening events that are not AIDS defining, AIDS events, and death among patients treated with HAART in the setting of 5 large multicenter randomized treatment trials conducted in the United States.

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Appropriate informed consent was obtained for all participants and clinical research was conducted in accordance with the guidelines for human experimentation of the US Department of Health and Human Services.

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METHODS

Study Population

The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) is a National Institutes of Health–funded clinical trials group that conducts research through a national network of community-based clinical sites. The trials were conducted in 18 community-based units located in 16 cities throughout the United States: Chicago, IL; San Francisco, CA; Detroit, MI; New York, NY; Portland, OR; Houston, TX; Atlanta, GA; New Haven, CT; Newark, NJ; Camden, NJ; Philadelphia, PA; Washington, DC; Albuquerque, NM; New Orleans, LA; Denver, CO; and Richmond, VA. Each unit provides HIV primary care but differs in its configuration, varying from geographically limited, hospital clinic–based units to geographically widespread units with a variety of hospital-based, private practice, community health care, and health maintenance organization providers.

Patients participating in 1 of 5 CPCRA clinical trials formed the cohort for this investigation.[65–69] These trials were chosen because they used a common system for collection of adverse events and AIDS events, and in all studies patients were to receive antiretroviral therapy (ART) throughout follow-up. Two studies were comparisons of initial HAART regimens (NvR: CPCRA 042 and FIRST: CPCRA 058)[65,66]; one study evaluated the effect of stopping prophylaxis for MAC (Mycobacterium Avium Complex) (CR-MAC-CPCRA 048)[67]; one study evaluated the effect of interleukin-2 (IL-2) on viral load and CD4 cell count (IL-2: CPCRA 059)[68]; and another study (MDR: CPCRA 064) is evaluating the effect of a 4-month interruption of ART on clinical progression.[69] For the latter 2 studies, only patients enrolled in the control groups (i.e., the group without IL-2 in CPCRA 059 and the group assigned to receive continuous ART in CPCRA 064) were used in these analyses.

Data Collection

At the time of enrollment, a medical history was obtained, and demographic data and risk behaviors were recorded. $CD4^+$ T-lymphocyte ($CD4^+$) cell count measurements were performed by the laboratory normally used by the patient's health care provider. In 3 of the studies, serology for hepatitis B (hepatitis B surface antigen) and hepatitis C (hepatitis C antibody) infection was analzyed. During follow-up, for each of the 5 trials, deaths, AIDS events,[70] and non–AIDS-defining events considered severe or life threatening (i.e., meeting grade 4 severity status) were reported using standardized forms and procedures.

With regard to AIDS events, all possible AIDS events were reviewed by an endpoints review committee to determine whether the criteria for the event were met. Those events that met criteria as probable or definite clinical AIDS events were included in these analyses. For these analyses, AIDS events were defined as clinical events that have been associated with advanced HIV-related immunodeficiency that meet the 1993 revised Centers for Disease Control AIDS surveillance definition with 2 exceptions: a $CD4^+$ cell count of <200 was not counted as an AIDS event, and recurrent bacterial pneumonia was not counted as an AIDS event. The rationale for this definition has been described previously.[70]

For these analyses, grade 4 events are defined as non–AIDS-related events considered severe or life threatening (i.e., meeting grade 4 severity status). Grade 4 events included laboratory abnormalities, clinical signs and symptoms, diseases, and clinical syndromes. In the case of grade 4 laboratory abnormalities, specific criteria for grade 4 severity is specified in a toxicity manual devised by the Division of AIDS, National Institutes of Allergy and Infectious Diseases, National Institutes of Health. For many clinical conditions, specific criteria for defining grade 4 severity are stated in the manual. In some cases clinical judgment was used to determine the severity grade. In such cases, the following guideline was given to characterize a grade 4 event: "extreme limitation in activity—significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care possible." For the sake of this analysis, we have presented the most common grade 4 events and have grouped them accordingly: cardiovascular events were grouped to include cardiac or vascular events (i.e., cardiac arrest, myocardial infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, unstable angina, congestive heart failure, and splenic infarct); kidney-related events were grouped to include kidney failure, grade 4 elevation in serum creatinine (>6× upper level of normal [ULN]), and HIV-related nephropathy; hemorrhage events were grouped to include gastrointestinal bleeding, bleeding (at an unspecified location), nose bleeding, and hematuria (gross); liver-related events were grouped to include grade 4 transaminase elevations (>10× ULN), grade 4 elevations of bilirubin (>5× ULN), clinical hepatitis, fulminant hepatitis, liver failure, toxic hepatitis, cirrhosis, fatty liver, hepatic encephalopathy, and liver disorder/disease; pancreatitis events were grouped by grade 4 elevation of amylase (>5× ULN), grade 4 elevation of lipase (>5× ULN), and clinical pancreatitis; thrombocytopenia events included grade 4 diminution of platelets (<20,000/mm^3) and idiopathic thrombocytopenic purpura; psychiatric events included suicide attempt, suicidal ideation, hallucinations, depression, anxiety/panic attack, delirium, psychosis, paranoia, bipolar disorder, and manic hyperactivity/agitation; grade 4 anemia is defined as diminution of hemoglobin < 6.5 g/dL ; and grade 4 neutropenia is defined as absolute neutrophil count < 500 /mm^3.

Importantly, according to protocol, any event considered to be grade 4 in severity was to be reported irrespective of the relationship to the treatments under investigation and irrespective of any other medications taken concomitantly. Grade 4 events were to be reported even if study treatments had been

temporarily discontinued. All grade 4 events were reported, not just the first to occur. At minimum, patients were to be seen every 4 months during follow-up. Grade 4 events were centrally reviewed by a nurse who coded the event according to a coding system based on the 9th revision of the International Classification of Diseases.[71]

We performed a subset analysis with regard to liver events, attempting to see whether chronic viral hepatitis coinfection impacted on grade 4 liver events, grade 4 events overall, AIDS events, and death. In the serology analysis, we limited our analysis to the 3 studies that collected hepatitis serology at baseline: CPCRA 058, CPCRA 059, and CPCRA 064. In these 3 studies, serology for hepatitis B (hepatitis B surface antigen) and hepatitis C (hepatitis C antibody) infection was performed at baseline. This analysis reflects 1628 patients from these 3 studies with baseline serologies that were treated with ART. The serology data were collected uniformly in these 3 studies, although the assay methodology varied by site and over time. We do not attempt to compare this subset to the overall group. To facilitate the analysis of the impact of chronic viral hepatitis coinfection on the incidence of grade 4 events, mortality, and AIDS, in the serology cohort, we considered hepatitis B and hepatitis C together.

Statistical Analysis

Incidence rates per 100 person-years are cited, as well as cumulative event probabilities based on Kaplan-Meier estimates. Proportional hazards regression was used to study predictors of grade 4 events and to estimate the risk of death associated with different types of grade 4 events. Hazard ratios (HRs) obtained from the regression model were adjusted for the following covariates assessed at the time of enrollment: age, gender, race, injection drug use, body mass index, CD4 cell count, prior AIDS, and use of prior ART. Regression analyses were also stratified by protocol (5 strata). Two-sided *P* values and 95% CIs are cited. To determine the risk of death associated with grade 4 and AIDS-defining events, the development of the event was considered a time-dependent covariate in the regression analysis. These analyses were adjusted for the same set of baseline covariates as mentioned previously. The closing date used for time-to-event analyses was July 2000 for 2 of the studies (CPCRA 048 and CPCRA 059),[67,68] December 31, 2001 for 1 study (CPCRA 042),[65] and February 28, 2002 for the 2 ongoing studies (CPCRA 058 and CPCRA 064).[66,69] All analyses ignored treatment interruptions during follow-up. In that respect the analyses carried out here are analogous to an intent-to-treat analysis for a clinical trial.

RESULTS

Between December 1996 and December 2001, 2947 patients with a diagnosis of HIV infection were enrolled into 1 of 5 CPCRA clinical trials defining the cohort for this analysis. Patient's clinical status ranged from relatively early HIV disease to advanced HIV disease (Table 1). Fifty-three percent of patients were ARV naive, and 47% were treatment experienced at the time of enrollment. Average age was 39.3 years; 83% were male and 17% were female; 41.5% were white, 44.8% were African American, and 13.7% were Latino. Approximately 16% of patients reported a history of injection drug use, and 55% reported homosexual activity as an HIV risk factor. $CD4^+$ cell count averaged 211 cells/mm^3 (interquartile range: 38–322 cells/mm^3), and 40.0% had a prior clinical AIDS diagnosis.

All patients in this cohort were prescribed ART following enrollment. At 12 months of follow-up, 1951/2120 (92%) were prescribed ART with 1475/2120 (70%) on protease inhibitor–based regimens, 421/2120 (20%) on nonnucleoside reverse transcription inhibitor–based regimens (no protease inhibitor), and 55/2120 (3%) solely on nucleoside reverse transcription inhibitors. Thus, at 12 months, 169/2120 (8%) had either temporarily or permanently discontinued ART.

Median follow-up was 20.7 months (interquartile range: 13.3–32.3 months), a total of 5940 person-years. During follow-up, 675 patients experienced a grade 4 event (11.4 per 100 person-years); 332 developed an AIDS event (5.6 per 100 person-years); and 272 died (4.6 per 100 person-years). Cumulative event curves are shown in Figure 1. The cumulative percentage of patients with a grade 4 event after 12, 24, and 36 months are, respectively, 15.6%, 23.7%, and 30.8%. Corresponding percentages for AIDS are, respectively, 7.3%, 10.8%, and 16.5% and corresponding percentages for death are, respectively, 3.9%, 7.9%, and 13.1%.

The most common grade 4 events were: liver related (148 patients; rate = 2.6 per 100 person-years); neutropenia (89; 1.5/100 person-year); anemia (64; 1.1/100 person-year);

TABLE 1. Baseline Characteristics of 2947 Patients in Cohort

Age (ys)	39.3 ± 8.8
$CD4^+$ cell count (cells/mm^3)	210.6 ± 215.5
Body mass index (kg/m^2)	24.4 ± 4.8
Gender	
Male (%)	83.0
Female (%)	17.0
Race	
White (%)	41.5
African American (%)	44.8
Latino (%)	13.7
Risk Factors	
Prior intravenous drug use (%)	15.9
Homosexual	55.0
Prior AIDS (%)	40.0
AR naïve (%)	53.0
AR experienced (%)	47.0

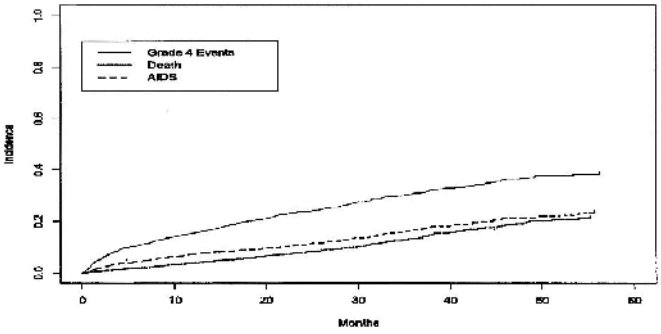

FIGURE 1. Cumulative incidence of grade 4 events, AIDS events, and death.

cardiovascular (51; 0.89/100 person-year); pancreatitis (50; 0.85/100 person-year); psychiatric (44; 0.75/100 person-year); kidney-related (34; 0.58/100 person-year); thrombocytopenia (32; 0.54/100 person-year); and hemorrhage (25; 0.42/100 person-year) (Fig. 2).

Incidence of Clinical Events by Baseline CD4$^+$ Cell Count

The numbers of patients and rates per 100 person-years of risk for AIDS, grade 4 events, and death are summarized in Table 2. The rates of each type of event increased with lower CD4$^+$ cell count levels. The slope of this relationship was much steeper for AIDS and death than for grade 4 events. As a consequence, among patients with higher CD4$^+$ cell counts, the great majority of events occurring were grade 4 events.

Baseline Predictors of Grade 4 Events Using a Multivariate Model

Based on multivariate analysis of predictors of any grade 4 event and specific grade 4 events, younger patients (for every decade in years, HR = 0.83, $P = 0.0001$) and patients who were ARV naive (HR = 0.59, $P = 0.001$) had a lower risk of grade 4 events; patients with a history of injection drug use (HR = 1.41, $P = 0.0006$), lower baseline CD4$^+$ cell count (for every 100 cells, HR = 1.06, $P = 0.04$), and a prior diagnosis of AIDS (HR = 1.22, $P = 0.03$) had an increased risk of grade 4 events. Female gender was significantly associated only with grade 4 neutropenia (HR = 1.76, $P = 0.03$), while African American race was associated with neutropenia (HR = 3.78, $P = 0.0001$), anemia (HR = 2.46, $P = 0.008$), and kidney-related events (HR = 22.41, $P = 0.0025$). Latino race was associated with neutropenia (HR = 2.75, $P = 0.01$). Higher body mass index at entry was associated with significantly less neutropenia (for 1 kg/m^2 HR = 0.93, $P = 0.01$) and less anemia (HR = 0.90, $P = 0.003$).

Risk of Death Associated With Grade 4 Events and AIDS

Of the 272 deaths, 117 experienced an AIDS event during follow-up prior to death and 153 experienced a grade 4 event prior to death. One hundred fifty-nine patients (69 of whom died later) experienced both a grade 4 and an AIDS event. Table 3 gives the risk of death associated with each of these categories of grade 4 events, the first grade 4 event that occurred, and the first AIDS event that occurred. Cardiovascular events were associated with the greatest risk of death (HR = 7.08; 95% CI: 4.2–12.1). The first grade 4 event and the first AIDS event were associated with similar risks of death: 5.68 and 6.95, respectively.

Hepatitis Serology Subset

Baseline results of serologic testing for hepatitis B and C were available for 1628 patients. Seroprevalence in this subset was as follows: 6.4% for hepatitis B infection (positive hepatitis B surface antigen); 17.9% for hepatitis C infection (positive hepatitis C antibody); 0.7% for both hepatitis B and hepatitis C; and 24.3% for hepatitis B and/or C. Among the 1628 patients with baseline hepatitis serology information, the rate of grade 4 adverse events was 11.2 per 100 person-years for those not coinfected, 14.9 for those coinfected with hepatitis B, 16.7 for those coinfected with hepatitis C, and 16.4 for those coinfected with hepatitis B and/or hepatitis C.

Coinfection with hepatitis B was strongly associated with an increased risk for developing a grade 4 liver event, with a HR = 5.97 (95% CI: 3.05–11.71; $P = 0.0001$). Similarly, coinfection with hepatitis C was strongly associated with an increased risk for developing a grade 4 liver-related event with a HR = 2.74 (95% CI: 1.29–5.84; $P = 0.009$). Hence, coinfection with hepatitis B or hepatitis C yielded a HR = 4.15 (95% CI: 2.26–7.60; $P = 0.0001$). After adjustment for other covariates, coinfection with hepatitis B or hepatitis C was not significantly associated with developing any grade 4 event, HR = 1.27 (95% CI: 0.92–1.74; $P = 0.15$), mortality, HR = 1.19 (95% CI: 0.61–2.32; $P = 0.60$), or AIDS (HR = 1.20; 95% CI: 0.70–2.05; $P = 0.51$) (Table 4).

DISCUSSION

This is one of the first analyses to quantify the rate of serious or life-threatening events, AIDS events, and death in a large cohort of patients treated with HAART. Our principal

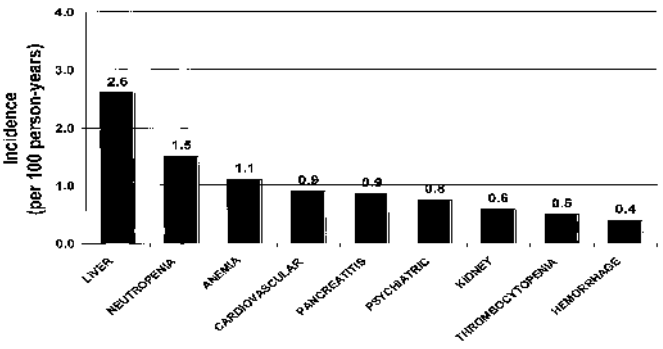

FIGURE 2. Most common grade 4 events.

TABLE 2. Rate of AIDS, Grade 4 Events, and Death by Baseline $CD4^+$ Cell Count

Baseline $CD4^+$ Cell Count (cells/mm^3)	AIDS		Grade 4		Death	
	No. Patients With Event	Rate*	No. Patients With Event	Rate*	No. Patients With Event	Rate*
<200	298	7.5	471	11.8	241	6.1
200–399	25	2.2	130	11.6	23	2.0
≥400	6	0.8	71	8.9	6	0.8

*Per 100 person-years.

finding is that the rate of grade 4 events is greater than the rate of AIDS events, and that the risk of death associated with these grade 4 events was very high for many events. Thus, the incidence of AIDS events fails to capture most of the morbidity experienced by patients with HIV infection prescribed HAART. Furthermore, among patients with higher $CD4^+$ cell count, those for whom the benefits of therapy are most uncertain, nearly all of the morbidity was due to grade 4 events. For patients with lower $CD4^+$ cell counts, the rates of both grade 4 and AIDS events were higher. Nonetheless, it is reassuring that these rates are much lower than rates seen in a similar cohort that received dual nucleosides.[72] Thus, although more effective ART is associated with decreased morbidity from both grade 4 and AIDS events, significant morbidity remains.

We believe these findings have 2 immediate implications. First, the usual procedure used in clinical trials of collecting adverse event data only while patients are taking study therapy and not collecting adverse event data after patients discontinue study treatment may need to be reevaluated. It is entirely possible that treatments may cause toxicities (e.g., liver damage or acceleration of atherosclerosis) that may not be apparent while the patient is taking the therapy and may only be manifest many months or years later. A rigorous intention-to-treat analysis for adverse event data as was employed here could provide important data with respect to establishing the toxicity profile of different regimens. Also, longer-term follow-up is necessary as many adverse events are not likely to emerge in the limited follow-up carried out for treatment trials for licensure.[73] As has been recently pointed out by others, complete and rigorous safety data collection and reporting in trials[74,75] would be exceedingly helpful. Perhaps trials could incorporate review committees of medical experts to classify serious events uniformly.

TABLE 3. Risk of Death Associated With Grade 4 Events and AIDS*

Event	Hazard Ratio	95% CI	*P* value
Cardiovascular	7.08	4.15–12.05	0.0001
Kidney related	4.60	2.45–8.66	0.0001
Hemorrhage	4.41	1.97–9.89	0.0003
Liver related	3.49	2.38–5.12	0.0001
Pancreatitis	3.40	1.82–6.33	0.0001
Thrombocytopenia	2.66	1.37–5.15	0.004
Psychiatric	1.91	0.79–4.63	0.15
Anemia	1.76	0.998–3.09	0.051
Neutropenia	1.02	0.61–1.72	0.93
Other adverse event	3.64	2.70–4.91	0.0001
Any grade 4 event	5.68	4.33–7.44	0.0001
AIDS	6.95	5.26–9.18	0.0001

*Development of the event was considered a time-dependent co-variate in this regression analysis. This analysis was adjusted for age, gender, race, injecting drug use, baseline $CD4^+$ cell count, prior AIDS, body mass index, and use of ARVs prior to enrollment.

A second implication of these findings is that there is a need to carefully assess comorbid conditions, socioeconomic status, recreational drug and alcohol use, and concomitant medications at baseline and throughout follow-up. If therapy could be optimized to reduce the incidence of these serious or life-threatening events by even a modest amount, the impact on morbidity and mortality would be great. For example, patients at increased risk for cardiovascular events might benefit from being placed on a protease inhibitor–sparing HAART regimen.[76–78] Similarly, patients with a history of severe depression may be better off with an efavirenz-sparing HAART regimen.[79,80]

The findings for patients coinfected with hepatitis B and/or C emphasize the importance of evaluating comorbidities. Patients coinfected with hepatitis B and/or C have higher incidence rates of grade 4 liver events. In multivariate analyses for these patients who were all prescribed HAART, hepatitis B and/or C coinfection was the only significant predictor of grade 4 liver events, the most common grade 4 event seen in this cohort. It is possible that the risks and benefits of HAART therapy on morbidity and mortality are different among patients with these coinfections.

Likewise, our finding that African American race was associated with an increased risk of renal events illustrates the

TABLE 4. Association of Hepatitis B and/or Hepatitis C Coinfection With Clinical Events

Event	No. Patients With Events	Unadjusted Hazard Ratio	95% CI	*P* Value	Adjusted Hazard Ratio*	95% CI	*P* Value
Liver	52	3.00	1.75–5.11	0.0001	4.15	2.26–7.60	0.0001
Grade 4	274	1.52	1.19–1.96	0.001	1.27	0.92–1.74	0.15
AIDS	97	1.29	0.84–1.98	0.24	1.20	0.70–2.05	0.51
Death	66	1.85	1.14–3.01	0.01	1.19	0.61–2.32	0.60

*Hazard ratio (coinfected with B or C vs. not coinfected) adjusted for age, gender, race, injecting drug use, baseline $CD4^+$ cell count, prior AIDS, body mass index, and use of ARVs prior to enrollment.

difficulty in attribution of adverse events to HAART outside of the context of a randomized trial. It is well established that blacks have a higher risk of renal failure than whites in the US population.[81] Whether HAART exacerbates this risk is uncertain. If it does, and we know that some specific drugs have been associated with acute renal changes (e.g., adefovir),[82] then this would be an important consideration for risk stratification for starting or maintaining ART.

Our study had several limitations. Grade 4 event classifications were crudely grouped for the purpose of this analysis and were composed of laboratory and/or clinical events. Grade 4 events were not reviewed and classified with the same rigor as AIDS events (e.g., a central review committee of medical experts was not used to classify grade 4 events). Some potentially important predictors were not adjusted for in the multivariate analysis (e.g., history of grade 4 event prior to enrollment, socioeconomic status, recreational drug and alcohol use, co-morbid conditions besides hepatitis B or C infection, and concomitant use of other medications). Finally, this observational analysis cannot clearly establish an association of specific grade 4 events with ART, in general, or with specific treatments. Some patients continued the same regimen throughout follow-up, whereas others stopped or started new regimens during follow-up.

In summary, morbidity and mortality for patients with HIV infection have been substantially reduced with HAART. However, morbidity remains high in the era of HAART. Better evidence is needed to determine how much of this morbidity is directly due to HAART. To adequately assess the impact of HAART on morbidity, we need to obtain more comprehensive data with regard to comorbid conditions, socioeconomic status, recreational drug and alcohol use, and concomitant medications at baseline and throughout follow-up.

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