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Non-AIDS-defining events among HIV-1-infected adults receiving combination antiretroviral therapy in resource-replete versus resource-limited urban setting

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Abstract

Objective—To compare incidence and distribution of non-AIDS-defining events (NADEs) among HIV-1-infected adults receiving combination antiretroviral therapy (cART) in urban sub-Saharan African versus United States settings.

Design—Retrospective cohort analysis of clinical trial and observational data.

Methods—Compared crude and standardized (to US cohort by age and sex) NADE rates from two urban adult HIV-infected cART-initiating populations: a clinical trial cohort in Gaborone, Botswana (Botswana) and an observational cohort in Nashville, Tennessee (USA).

Results—Crude NADE incidence rates were similar: 10.0 [95% confidence interval 6.3–15.9] per 1000 person-years in Botswana versus 12.4 [8.4–18.4] per 1000 person-years in the United States. However, after standardizing to an older, predominantly male US population, the overall NADE incidence rates were higher in Botswana [18.7 (8.3–33.1) per 1000 person-years]. Standardized rates differed most for cardiovascular events (8.4 versus 5.0 per 1000 person-years) and non-AIDS-defining malignancies (8.0 versus 0.5 per 1000 person-years) – both higher in Botswana. Conversely, hepatic NADE rates were higher in the United States (4.0 versus 0.0 per 1000 person-years), whereas renal NADE rates [3.0 per 1000 person-years (United States) versus 2.4 per 1000 person-years (Botswana)] were comparable.

Conclusion—Crude NADE incidence rates were similar between cART-treated patients in a US observational cohort and a sub-Saharan African clinical trial. However, when standardized to the US cohort, overall NADE rates were higher in Botswana. NADEs appear to be a significant problem in our sub-Saharan African setting, and the monitoring, prevention, and treatment of NADEs should be a critical component of care in resource-limited settings.

Keywords

combination antiretroviral therapy; HIV/AIDS; non-AIDS-defining events; urban sub-Saharan Africa; urban United States

Background

The widespread availability of combination antiretroviral therapy (cART) in the developed world has resulted in significant reductions in HIV-associated morbidity and mortality over the past two decades [1]. Effective therapies have promoted immunologic recovery, but adverse metabolic complications and negative health outcomes now commonly classified as non-AIDS-defining events (NADEs) have emerged as a major health concern among long-term cART-treated adults [2–5].

NADEs are typically classified as cardiovascular, renal, hepatic-related disorders, or non-AIDS-defining malignancies, and the causes are likely multifactorial and potentially related to demographics (e.g., older age as cART-treated adults are surviving longer), lifestyle (e.g., smoking as well as alcohol use/abuse), persistent HIV-1 viral replication (e.g. prolonged immunosuppression and/or immune or coagulation pathway activation), the presence of certain co-morbid medical conditions (e.g. chronic hepatitis B and/or C infection), and long-term cART-related complications (e.g. dyslipidemia, central adiposity, insulin resistance/diabetes mellitus, and/or arterial hypertension), among other factors [6–15].

The US and western European data from the International Network for Strategic Initiative in Global HIV Trial (INSIGHT), Strategies for Management of Antiretroviral Therapy (SMART), and Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) study groups [16] have also shown that among HIV-infected persons with high CD4⁺ cell counts, serious NADEs occur more frequently and are associated with a greater mortality risk compared to AIDS-defining events (ADEs). ADEs and NADEs occurred in 286 and 435 study participants, respectively, with 47 (16%) and 115 (26%) subsequent deaths [16]. The 6-month cumulative mortality was 4.7% [95% confidence interval (CI) 2.8–8.0] after experiencing an ADE compared to 13.4% (10.5–17.0) after experiencing a serious NADE. Among patients experiencing a NADE who subsequently died ($n = 115$), 87 (76%) of these deaths were attributed to NADE causes, with non-AIDS-associated malignancy, cardiovascular disease, and hepatic-related causes being the most common [16].

In contrast to the United States and Europe, few studies have evaluated NADEs in sub-Saharan Africa, where the majority of cART-treated adults presently reside. In this study, we report NADE rates from two different urban adult HIV-1-infected populations: a randomized clinical trial of population in Gaborone, Botswana (Botswana) versus an observational cohort in Nashville, Tennessee, USA (USA).

Methods

Study populations

We retrospectively evaluated HIV-1-infected adults receiving cART in two geographically distinct populations from Gaborone, Botswana and Nashville, Tennessee, USA (Table 1).

The Botswana cohort included patients enrolled in the completed Adult Antiretroviral Treatment and Drug Resistance (*Tshepo*) study between 1 December 2002 and 31 December 2007 [17]. *Tshepo* was an open-label, randomized, 3×2×2 factorial design study conducted at Princess Marina Hospital in Gaborone, Botswana evaluating the efficacy,

tolerability, and incidence of drug resistance mutations among six different first-line cART regimens: zidovudine, lamivudine, and nevirapine (ZDV/3TC/NVP); zidovudine, lamivudine, and efavirenz (ZDV/3TC/EFV); zidovudine, didanosine, and nevirapine (ZDV/ddI/NVP); zidovudine, didanosine, and efavirenz (ZDV/ddI/EFV); stavudine, lamivudine, and nevirapine (d4T/3TC/NVP); and stavudine, lamivudine, and efavirenz (d4T/3TC/EFV). Study participants were followed for 3 years with monthly scheduled study visits (5 years of total follow-up time as study enrollment occurred over a 2-year period). Study participants qualified for cART based on existing Botswana national antiretroviral treatment guidelines [18,19], namely, an AIDS-defining illness and/or CD4⁺ cell count of 200 cells/ μ l or less; or CD4⁺ cell count between 201 and 350 cells/ μ l and a corresponding plasma HIV-1 RNA level greater than 55 000 copies/ml, which was consistent with consensus United States adult treatment guidelines at the time the study was designed. Additional inclusion criteria were hemoglobin value greater than 8.0 g/dl; absolute neutrophil count greater than $1.0 \times 10^3/\mu$ l; aminotransferase levels less than five times the upper limit of normal (ULN); and, for women of child-bearing potential, a willingness to maintain active contraception throughout the duration of the study and a negative urine pregnancy test within 14 days of study enrollment. Exclusion criteria included a poor Karnofsky performance score (40 or below); an AIDS-defining malignancy other than mucocutaneous Kaposi's sarcoma; grade 2 (moderate) or higher peripheral neuropathy; major psychiatric illness; and for women, active breastfeeding or less than 6 months postpartum. During the study period, boosted protease inhibitor-containing regimens were available for all participants with confirmed virologic failure, toxicities, or concomitant medical conditions that required a switch from a non-nucleoside reverse transcriptase inhibitor (NNRTI) to a protease inhibitor.

The Nashville cohort included patients seen at the Comprehensive Care Center (CCC), a nonprofit, urban, community HIV clinic affiliated with an academic medical center, between 1 January 2003 and 31 December 2007.

Patients were seen on a routine schedule at the CCC (e.g., every 3–6 months depending on disease status), and clinic visits included a standard history and physical assessment, a detailed review of current medications and dosages and counseling as appropriate, and routine measurement of CD4⁺ cell counts, plasma HIV-1 RNA levels, and age-appropriate health screening. Of note, all patients in the Botswana cohort did undergo routine lipid chemistry monitoring with fasting lipid profiles being performed on all patients with abnormalities on nonfasting cholesterol [total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol] and triglyceride determinations. Study participants found to have elevated lipid values (grade 3 or higher) using the Division of AIDS chemistry grading scales, were treated with lipid-lowering agents (i.e., pravastatin, niacin, and/or gemfibrozil). Subspecialty care, including nutrition support and psychiatry, was available on-site.

Non-AIDS-defining event determination

Included NADEs were noted as grade 3 or higher clinical diagnoses using established Division of AIDS (DAIDS) tables for Grading Severity of Adult Adverse Experiences (Botswana) [20,21] or as established diagnoses utilizing International Statistical Classification of Diseases, version 9 coding (ICD-9) in the electronic medical record (USA). These were cerebrovascular accident (stroke), cerebral/ subarachnoid hemorrhage, myocardial infarction, coronary artery disease, congestive heart failure, end-stage renal disease, renal failure, cirrhosis of liver, esophageal varices, hepatic failure, hepatic coma, hepatic encephalopathy, intestinal adenocarcinoma/lymphoma, penile carcinoma, small cell carcinoma, malignant melanoma, hepatocellular carcinoma, squamous cell carcinoma, and squamous cell carcinoma of the anus.

In Botswana, all NADE onset and resolution dates were confirmed by study data management staff and were reviewed by coordinating study physicians as needed. Death information was obtained from serious adverse event logs, with additional information being obtained from study staff as needed. An autopsy was obtained for one of the on-study deaths, but otherwise all cause of death information was obtained utilizing verbal autopsy forms.

For the Nashville cohort, when NADE dates were not present in the electronic medical record, paper medical records were reviewed and the appropriate onset date was determined. Clinical data were entered into an electronic medical record by medical providers at the time of the patient encounter or by clinic personnel. Laboratory data and all cART use (including dates) were validated by systematic chart review, and follow-up began at the time of cART initiation. All events were reviewed and confirmed by study investigators. Information on death was obtained from a registry maintained by the clinic and by searching the national Social Security Death Index [22].

Statistical methods

Categorical variables were compared between groups using χ^2 tests, whereas continuous variables were compared using Wilcoxon rank-sum tests. Incidence CIs were computed using Poisson regression, except for the incidence of hepatic events, which were computed for both cohorts using Wilson CIs because of the lack of events in the Botswana cohort. Botswana NADE rates were standardized to the age and sex distribution of the US cART-treated population by fitting Poisson regression models to the US data with age as a continuous variable. We tested for an interaction between age and sex and for a nonlinear relationship between age and the log rate of NADEs. No interactions or nonlinear relationships were identified. Regression parameters were used to obtain predicted NADEs from the Botswana data. Analyses were conducted using SAS statistical software (version 9.2; SAS Institute, Cary, North Carolina, USA) and R statistical software (version 2.9.0, www.r-project.org). Analysis scripts are available at (<http://biostat.mc.vanderbilt.edu/ArchivedAnalyses>).

Ethical approvals

Ethical review board approval was obtained from the Ministry of Health, Botswana (Health Research Development Committee), the Harvard School of Public Health (Human Subjects Committee), and the Vanderbilt University Institutional Review Board.

Results

Baseline characteristics of cohort participants are given in Table 2. Patients in the Botswana cohort ($n=650$) were younger, more likely women, and had lower CD4⁺ cell counts at cART initiation than those in the US cohort ($n=1129$).

Overall, there were 18 (2.8%) and 25 (2.2%) NADEs in the Botswana and US cohorts, respectively, representing 1794 (median: 3.0, interquartile range: 3.0–3.0) and 2013 (median: 1.5, interquartile range: 0.6–2.9) person-years of follow-up. Of the 18 NADEs in the Botswana cohort, nine were cardiovascular, four were renal, five were malignancies, and none were hepatic in etiology. Of the 25 NADEs in the US cohort, 10 were cardiovascular, six were renal, one was a malignancy, and eight were of liver (Table 3).

Overall crude NADE incidence rates were similar in our urban cohorts of adult cART-treated patients in Botswana and the United States, namely, 10.0 (95% CI 6.3–15.9) per 1000 person-years in Botswana versus 12.4 (8.4–18.4) per 1000 person-years in the United States. Crude rates of cardiovascular and renal NADEs were similar between the two

settings: 5.0 (2.6–9.6) per 1000 person-years (Botswana) versus 5.0 (2.7–9.2) per 1000 person-years (USA), and 2.2 (0.8–5.9) per 1000 person-years (Botswana) versus 3.0 (1.3–6.6) per 1000 person-years (USA), respectively. Crude rates of hepatic NADEs differed between the two settings, with no events in Botswana compared to 4.0 (95% CI 2.0–7.8) per 1000 person-years in the USA. Crude rates of non-AIDS-defining malignancies were higher in Botswana compared to the USA: 2.8 (1.2–6.7) per 1000 person-years versus 0.5 (0.1–3.5) per 1000 person-years, respectively.

When standardized to the US population, however, non-AIDS-defining event rates were higher in Botswana when compared to the US cART-treated population. There were 18.7 (95% CI 8.3–33.1) NADE events per 1000 person-years in Botswana versus 12.4 (8.4–18.4) events per 1000 person-years in the USA. The largest discrepancies were for cardiovascular [8.4 (2.4–18.4) versus 5.0 (2.7–9.2) events per 1000 person-years] and non-AIDS-defining malignancies [8.0 (1.3–20.8) versus 0.5 (0.1–3.5) events per 1000 person-years], which were substantially higher in Botswana. Conversely, renal NADE rates remained comparable in both settings [3.0 (1.3–6.6) per 1000 person-years (USA) versus 2.4 (0.0–7.2) per 1000 person-years (Botswana)]. The differences between the crude and standardized rates were due to the older age and predominantly male sex of the US cohort, both of which were associated with an increased risk of NADE in Botswana (Table 1 of online Appendix, <http://links.lww.com/QAD/A145>).

In Botswana, the majority of the non-AIDS-defining malignancies were Hodgkin's lymphomas, with the other being a penile carcinoma. Among persons with NADEs, 44 versus 88% were men in Botswana and the USA, respectively. Among those with NADEs, the median time from cART initiation to NADE was 1.34 years (0.56–2.65 years) in Botswana versus 1.52 years (0.52–1.94 years) in the USA. In terms of the contribution of NADEs to overall mortality by setting, 11 of the 37 (29.7%) of total deaths in the Botswana cohort were attributable to NADE, compared to three of the 69 (4.4%) deaths in the US (Nashville, Tennessee) setting. All of the three US NADE deaths were attributed to hepatic disease (100%), whereas in Botswana, they were attributed primarily to cardiovascular (72.7%) as well as non-AIDS malignancy (27.3%)-related causes.

Discussion

Crude incidence rates for non-AIDS defining events –both overall and for cardiovascular and renal events –were similar between urban cohorts of adult cART-treated patients in the USA and Botswana. Crude incidence rates for hepatic events tended to be higher in the US cohort, whereas rates of non-AIDS malignancies were higher in the Botswana clinical trial cohort. However, when standardized based on the age and sex distribution of the US cohort, we found that the rates of NADE were approximately 50% higher in Botswana, with especially elevated rates of cardiovascular events and malignancies.

Our crude rates of NADE are similar to those in a recent report from Belloso *et al.* [23], that found an NADE incidence rate of 8.4 per 1000 person-years in a multicenter Latin American cohort ($n=6007$). In their cohort, the most common NADEs were hepatic disease ($n=54$), followed by cardiovascular disease ($n=40$), and non-AIDS defining malignancies ($n=35$).

The standardized rates of overall NADEs, cardiovascular disease, and non-AIDS-defining malignancy were increased in Botswana compared to the USA as the population experiencing events was younger and more likely women in Botswana. In the US cohort, similar events occurred more frequently among patients with traditional risk factors for these diseases, specifically male sex and older age (Table 2 online appendix, <http://links.lww.com/QAD/A145>).

Cardiovascular events were the most common non-AIDS-defining events in both settings. The frequency of cardiac events may be associated with antiretroviral use or alternatively, the chronic inflammatory state that exists despite virologic suppression [6–15]. Antiretroviral regimens differed according to treatment site in the present study. Very few participants in Botswana received abacavir and/or protease inhibitor-based cART, largely due to financial considerations. In addition, cART-treated persons in Botswana differed considerably in sociodemographic characteristics and traditional cardiovascular disease risk profiles (younger age, predominantly women) compared to their US counterparts. Cardiovascular disease-associated deaths will increasingly contribute to non-AIDS-defining mortality in both settings, especially in areas of Botswana with greater consumption of ‘western’ diets that contain higher caloric and fat content. It will be important to monitor rates of cardiovascular events in resource-limited settings as large cART-treated cohorts of adults and children survive longer.

HIV-associated nephropathy (HIVAN) is a distinct phenotype and is the most recognized and deleterious renal disease in HIV-infected persons [24–29]. Rates of renal NADEs were similar in our two urban cART-treated populations, with slightly higher rates being recorded in the US setting. These findings were unexpected given recent genetic association (*MYH9* and *ApoLI*) studies showing that HIVAN emerges almost exclusively in persons of African descent, with HIV-infected individuals of African descent estimated to have a 20-fold greater risk for developing HIVAN compared to non-African descent individuals. Reasons for lower than expected renal NADEs being identified among Botswana-treated adults remain to be elucidated, but may be related to younger age, lower rates of comorbid medical conditions, or less frequent co-administration of potentially nephrotoxic medications. A study from Zambia found that renal insufficiency was prevalent (33.5%) at the time of cART initiation and was associated with increased mortality risk, although only a small proportion of patients (3.1%) had evidence of severe renal insufficiency (i.e., <30 ml/min), with the majority (73.5%) of patients having mild renal impairment, which was defined as having a creatinine clearance between 60 and 89 ml/min using the Cockcroft–Gault formula [30]. Another possibility includes ascertainment bias, but this is unlikely as all clinical trial participants in Botswana were systematically screened for organ system toxicities and had consistently scheduled (more intensive during the first 1 year of follow-up) comprehensive chemistries, which included blood urea and creatinine measurements.

Increased rates of liver-related deaths, especially those due to hepatocellular carcinoma among persons co-infected with HIV and hepatitis B or C virus, continue to be reported from North American and European multi-center cohorts [31–33]. Preliminary data from sub-Saharan Africa, however, have shown significantly lower rates of hepatitis C co-infection rates among HIV-infected adults [34–36], with prevalence rates in the 0–4.8% range, which may explain the lack of liver-related NADEs and associated mortality observed in Botswana. Chronic hepatitis B is the leading cause of hepatocellular carcinoma globally and as regional data have shown hepatitis B co-infection rates in the 10% range, one would have expected some liver-related NADEs in Botswana. Clearly, longer-term follow-up is needed. In addition, all cART-treated adults in Botswana were placed on at least one antiretroviral medication (i.e., lamuvidine) with intrinsic hepatitis B activity, with some receiving two (i.e., tenofovir and lamuvidine or emtricitabine), which certainly may have contributed to nonexistent hepatic events in this at-risk setting.

It is unlikely that the absence of observed hepatic events is related to inferior diagnostic capacity in Botswana, as the trial patients received frequent liver function test monitoring [e.g. serum glutamic oxaloacetic transaminase/aspartate transaminase (SGOT/AST), serum glutamic pyruvic transaminase/alanine transaminase (SGPT/ALT), alkaline phosphatase, total bilirubin, and lactate dehydrogenase (LDH)], and ultrasound and computed

tomography (CT) imaging was utilized as warranted. In addition, we performed routine hepatitis B serology on all patients and hepatitis A and C serology if clinically indicated.

Higher rates of non-AIDS-defining malignancies were also seen in Botswana. The cause of this disparity is unclear, but it may be related to lower CD4⁺ lymphocyte counts at cART initiation. A meta-analysis of studies among HIV-infected individuals conducted in the USA found increased rates of malignancies linked to infectious causes (e.g., Epstein-Barr virus, human herpes virus 8, hepatitis viruses B and C, *Helicobacter pylori*, and human papilloma virus) and higher rates of renal, lung, trachea, and bronchus cancers, but no difference was observed in breast, prostate, or common epithelial cancers (e.g., colon) [37]. Our data suggest that Hodgkin's lymphomas may be a significant cause of non-AIDS-defining malignancy mortality in the region, and as diagnostic capacity improves, it will be important to establish cancer registries to better describe oncologic disease patterns.

Of course, there are numerous challenges and limitations to comparing incidence rates from an observational cohort in the USA with a randomized clinical trial population in Botswana. These include, but are not limited to, differences in visit schedules, laboratory and clinical monitoring, cART regimens (higher rates of tenofovir and protease inhibitor-containing cART in the USA), diagnostic capacity (limited in Botswana, without on-site MRI or cardiac catheterization capacity), collection of death information (verbal autopsies in Botswana, whereas death registry reviews and clinician assessment in USA), circulating viruses, and patient characteristics (both measured and unmeasured). There were also differences between the cohorts in the definitions of virological failure, which may have led to more cART-treated adults in Botswana remaining at low-moderate levels of viremia (during the bulk of the trial in Botswana, failure was defined as two confirmed plasma HIV-1 RNA levels of greater than 5 000 copies/ ml [17–19,38–41]). In contrast, a substantially lower proportion of cART-treated adults in our urban US setting (57.6 versus 85.3%) met our criteria for virologic 'success', namely, the proportion of persons having greater than 80% of their plasma HIV-1 RNA levels less than 400 copies/ml on or after 4 months of cART. Additional analyses are planned to look more in-depth at the potential significance of such differences. Lastly, although we standardized rates of NADEs based on age and sex, we admit there are numerous other differences between the cohort populations and attempting to control for all potential confounders is futile.

Recognizing these limitations, we observed similar to higher rates of NADEs in a clinical trial cohort in Botswana compared to a routine care cohort in the USA. This is important, because rates of NADEs have not been well characterized in sub-Saharan Africa, and these rates appear to be at least as high in this setting as those in a developed country setting. It is important to design larger studies in sub-Saharan Africa to better characterize incidence rates and elucidate potential differences in the profile and frequency of NADEs. As increasing numbers of 'at-risk' adults develop NADEs, a parallel expansion of clinical training curricula to encompass preventive healthcare will be necessary, and interventional studies evaluating the potential pharmacologic role of anti-inflammatory agents such as angiotensin receptor blockers and/or statins should also be considered. The scale-up of cART in resource-limited settings represents a major accomplishment of global health efforts, but addressing the sequelae of chronic HIV infection and its treatment remains a challenge to local health systems and implementing partners.

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J.R.K. assisted the first author on study development, analysis, and article preparation.

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Table 1

Characteristics of combination antiretroviral therapy programs according to site: Urban sub-Saharan Africa (Adult ARV Treatment and Drug Resistance [*Tshepo*] study, Gaborone, Botswana) and Urban United States (Comprehensive Care Center, Nashville, Tennessee).

Program aspect	Gaborone, Botswana <i>n</i> =650	Nashville, Tennessee, USA <i>n</i> =1129
First-line cART regimens	ZDV/ddI/NVP (16.6%) ^a ZDV/ddI/EFV (16.6%) ^a ZDV/3TC/NVP (16.8%) ZDV/3TC/EFV (16.8%) d4T/3TC/NVP (16.6%) d4T/3TC/EFV (16.6%)	TDF/FTC/EFV (16.7%) ZDV/3TC/EFV (14.3%) TDF/FTC/ATV/r (7.9%) ZDV/3TC/NFV (6.1%) ZDV/3TC/LOP/r (4.5%) ZDV/3TC/NVP (3.4%) ZDV/3TC/ABC (2.4%) ZDV/3TC/EFV (2.0%) d4T/3TC/NFV (1.8%) d4T/3TC/EFV (1.8%) Other combinations (39.2%)
ARV initiation criteria (CD4 ⁺ cell count-based)	2 CD4 ⁺ cell strata: CD4 ⁺ <200 and CD4 ⁺ between 201 and 350 and plasma HIV-1 RNA level of > 55 000 copies/ml	CD4 ⁺ <350 based on national clinical guidelines
Person-years of follow-up	1794 Median =3.0, IQR =(3.0–3.0)	2013 Median =1.5, IQR =(0.6–2.9)
Mortality rate	37 total deaths (mortality rate =20.6 per 1000 person-years)	69 total deaths (mortality rate =34.3 per 1000 person-years)
Virologic success rates ^b	85.3% (539 of 632 evaluable individuals)	57.6% (547 of 950 evaluable individuals)
How NADEs captured	ACTG definitions and laboratory values	ICD-9 codes and laboratory values
Cohort inclusion/exclusion criteria	Study determined inclusion/exclusion criteria Inclusion: (nonpregnant and/or postpartum, Hgb value >8.0; SGOT/SGPT values <5× ULN, Karnofsky performance score > or equal to 50) Exclusion: (presence of an AIDS-defining malignancy other than mucocutaneous Kaposi's sarcoma)	None
Follow-up (visit schedule/intensity)	Scheduled monthly visits (CD4 ⁺ and VL every 2 months)	Variable (on average q 3 monthly visits)

3TC, lamivudine; ABC, abacavir; ACTG, Adult Clinical Trials Group; ARV, antiretroviral; ATV/r, atazanavir/ritonavir; cART, combination antiretroviral therapy; d4T, stavudine; ddI, didanosine; DSMB, Data Safety and Monitoring Board; EFV, efavirenz; FTC, emtricitabine; Hgb, hemoglobin (in g/dl); ICD-9, International Statistical Classification of Diseases, version 9 classification; LOP/r, lopinavir/ritonavir; NADE, non-AIDS-defining event; NFV, nelfinavir; NVP, nevirapine; SGOT (AST), serum glutamic-oxaloacetic transaminase (OR aspartate transaminase); SGPT (ALT), serum glutamic pyruvic transaminase (OR alanine aminotransferase); ULN, upper limit of normal; VL, plasma viral load (HIV-1 RNA level in copies/ml); ZDV, zidovudine.

^a All participants were switched to ZDV/3TC/NVP or ZDV/3TC/EFV effective June 2006 based on DSMB findings of inferiority in primary endpoint.

^b Virologic success rates (virologic 'success' defined as proportion of evaluable participants having 80% or more of their plasma HIV-1 RNA levels < 400 copies/ml on/after 4 months of cART).

Table 2

Patient demographics at time of combination antiretroviral therapy initiation according to site.

	Gaborone, Botswana <i>n</i> =650	Nashville, Tennessee <i>n</i> =1129	<i>P</i> value
Female sex	451 (69.4%)	289 (25.6%)	<0.001
Race/ethnicity	650 (100%) African (Tswana)	627 (55.5%) Caucasian 392 (34.7%) African–American 72 (6.4%) Hispanic 38 (3.4%) Other	<0.001
Age (in years) (median, IQR)	33.3 (28.9–38.7)	40.1 (33.6–46.2)	<0.001
BMI (median, IQR)	21.3 (19.2–24.3)	24.5 (21.9–28.2)	<0.001
CD4 ⁺ cell count (median, IQR)	199 (136–252)	243 (110–408)	<0.001

IQR, interquartile range.

Table 3
Crude versus standardized Non-AIDS-defining event rates according to site (overall and by type).

	Botswana			US (Nashville)		
	N	Crude	Standardized	N	Incidence per 1000 person-years (95% CI)	P value* (comparing standardized rates)
NADE	18	10.0 (6.3–15.9)	18.7 (8.3–33.1)	25	12.4 (8.4–18.4)	0.20
Cardiovascular	9	5.0 (2.6–9.6)	8.4 (2.4–18.4)	10	5.0 (2.7–9.2)	0.20
Renal	4	2.2 (0.8–5.9)	2.4 (0.0–7.2)	6	3.0 (1.3–6.6)	0.92
Hepatic	0	0.0 (0.0–2.1)	0.0 (0–0)	8	4.0 (2.0–7.8)	N/A
Malignancy	5	2.8 (1.2–6.7)	8.0 (1.3–20.8)	1	0.5 (0.1–3.5)	0.015
Years to event; median (IQR)	1.3 (0.6–2.7)			1.5 (0.5–1.9)		
BMI at time of event; median (IQR)	26.6 (19.1–31.9)			24.0 (22.0–28.0)		
CD4 ⁺ cell count at time of event; median (IQR)	274 (159–506)			224 (134–364)		
NADE mortality	12/18 (67%)			3/25 (12%)		

CI, confidence interval; IQR, interquartile range; N/A, not available; NADE, non-AIDS-defining event; PY, person-years.

* P values test the null hypothesis that the relative risk of NADE after adjusting for age and sex is the same in the Botswana and US cohorts. A P value could not be computed for hepatic NADE because there were no events in Botswana.