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Antiretroviral therapy using zidovudine, lamivudine, and efavirenz in South Africa: tolerability and clinical events

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Abstract

Objective—To describe the safety and tolerability of zidovudine, lamivudine, and efavirenz in a low-income setting.

Design—We conducted a prospective cohort study in a workplace HAART programme in South Africa, which uses a first-line regimen of efavirenz, zidovudine, and lamivudine and provides routine clinical and laboratory monitoring 6-monthly pre-HAART and at 2, 6, 12, 24, 36, 48 weeks during HAART.

Methods—We assessed the incidence of specified clinical and laboratory events (AIDS Clinical Trials Group grade 3 or higher) and associated regimen changes, hospitalizations, and deaths one year before HAART initiation and one year on-HAART using person-year analysis.

Results—Between November 2002 and October 2005, 853 subjects (98% male, median age 40 years, and median CD4 cell count at HAART initiation 186 cells/μl) met enrollment criteria. The incidence of events on-HAART was higher than pre-HAART for neutropenia and nausea/vomiting. Dizziness was common early after HAART initiation (not evaluated pre-HAART). Of those with neutropenia, 88% had no apparent clinical consequences. The incidence of anemia, hepatotoxicity, peripheral neuropathy, and rash was similar or higher pre-HAART than on-HAART. Mean hemoglobin rose during the time on-HAART and was higher at 24 and 48 weeks than at baseline ($P < 0.001$).

Discussion—This regimen was well tolerated with a short-term increase in neutropenia, nausea, and probably neurocerebellar events. Most significantly, in contrast to reports from high-income countries, we observed a long-term improvement in the hemoglobin concentration.

Introduction

Safety and tolerability are concerns when selecting a HAART regimen. Agent affordability is an additional criterion in low-income countries. In 2002, the World Health Organization

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(WHO) recommended a first-line HAART regimen including either stavudine or zidovudine, lamivudine, and either nevirapine or efavirenz [1]. Stavudine is associated with peripheral neuropathy, lipodystrophy, and lactic acidosis, whereas zidovudine is associated with severe anemia, neutropenia, and lipodystrophy [2]. In resource-limited settings, monitoring for zidovudine-induced anemia places added demands on limited laboratory services, and many programmes selected stavudine rather than zidovudine as part of the standard first-line regimen.

Despite the efficacy of stavudine-containing regimens, evidence of morbidity and mortality from stavudine-associated lactic acidosis, peripheral neuropathy, and lipoatrophy has accumulated from low-income country HAART programmes [3–7]. Accordingly, the WHO published guidelines in 2006 that favor the use of zidovudine or tenofovir plus lamivudine and either efavirenz or nevirapine. Stavudine was changed to a secondary option [8].

Little has been published focusing on the safety and tolerability of a regimen of zidovudine, lamivudine, and efavirenz in an African HAART programmes. The objective of this study was to define the adverse event profile, tolerability, and time of occurrence of toxicities for a regimen of zidovudine, lamivudine, and efavirenz, and to describe the frequency of these events before HAART initiation in a cohort of South African patients.

Methods

Subjects

Patients included in this study were enrolled in a single company workplace HIV programme in South Africa, started HAART between November 2002 and October 2005, and were followed up to November 2006. The programme has been described in detail elsewhere [9]. HAART eligibility was based on modified WHO criteria: CD4 lymphocyte count less than 250 cells/μl, WHO stage 3 and CD4 lymphocyte count less than 350 cells/μl, or WHO stage 4. First-line HAART was zidovudine, lamivudine, and efavirenz. Until November 2004, a substitution of stavudine for zidovudine was recommended for most subjects with hemoglobin less than 8 g/dl; after November 2004 the recommendation was changed to less than 10 g/dl. An absolute neutrophil count less than 750 cells/μl was also an indication for substituting stavudine for zidovudine. Cotrimoxazole was provided to patients with CD4 cell counts below 200 cells/μl. Isoniazid was provided for 6 months to individuals with no previous history or evidence of active tuberculosis. Once on HAART, patients had routine follow-up visits with clinical and laboratory monitoring at 2 and 6 weeks and every 3 months.

Subjects were included for analysis if they received HAART containing zidovudine, lamivudine, and efavirenz, received laboratory evaluation during the first 6 weeks, and initiated HAART at least 12 months before the end of the observation period. Pre-HAART was defined as one year before HAART and up to, but not including, a ‘baseline’ evaluation. The baseline evaluation was the last evaluation before HAART initiation. On-HAART was defined as time receiving HAART up to 378 days after HAART initiation.

Ascertainment of adverse events

Data for adverse events came from structured visit forms and results from routine and acute laboratory testing, including hemograms, liver enzymes, serum HIV RNA, and CD4 lymphocyte counts obtained from all outpatient and inpatient visits. Company personnel records were used for death records. A special adverse event reporting form was used for subjects receiving HAART. Before HAART initiation, laboratory tests were obtained at baseline, every 6 months for hemoglobin and CD4 cell count, and otherwise as clinically

indicated. On-HAART evaluations were performed at 2 and 6 weeks, every 3 months, and when clinically indicated.

Selection of adverse events and definitions

We analysed adverse events commonly associated with zidovudine (anemia, neutropenia, nausea or vomiting, and lipodystrophy) and efavirenz (hepatotoxicity, neurocerebellar disturbance, and rash). In addition, although no subjects in our study received stavudine, to compare better with other HAART programmes, we included adverse events commonly associated with stavudine (lactic acidosis and peripheral neuropathy). Peripheral neuropathy was assessed by patient self-report of 'numbness or tingling in the feet' or physical examination evidence of decreased sensation to light touch in the extremities or diminished Achilles deep tendon reflexes. Neurocerebellar symptoms were based on patient self-report of dizziness, ataxia, insomnia, bizarre dreams, or hallucinations. Rash included patient self-report or physical examination finding of WHO stage 2 skin conditions including, but not limited to, drug reactions, seborrheic dermatitis, angular cheilitis, and onychomycosis and excluding Kaposi's sarcoma, prurigo nodularis, and herpes zoster. Laboratory events were graded based on AIDS Clinical Trials Group (ACTG) or modified ACTG grading scales (Table 1) pre-HAART and on-HAART [10,11]. Clinical events were clinical events graded by the provider only on-HAART.

Any regimen change with reason coded as adverse effect or any hospital admission occurring within 14 days of an event was classified as potentially related to the event. Any death within 30 days of an event was classified as potentially related to the event; the cause of death was identified by chart review.

Analysis

For each adverse event, we calculated the incidence rate of first event during the pre-HAART and on-HAART periods using time to first event. When calculating pre-HAART event rates we only included subjects for whom laboratory or visit data before the HAART baseline visit were available (90% of subjects contributed to pre-HAART event rates). Pre-HAART person-years at risk were calculated from the first clinical evaluation or one year before HAART initiation, if the subject had clinical evaluations for more than one year before HAART, until an event or the baseline visit. Person-years at risk on-HAART were calculated from the time of HAART initiation to the earliest of the following: time of event, change or discontinuation of HAART regimen, date of last clinical or laboratory encounter in the database, or one year of follow-up on-HAART. The impact of cotrimoxazole prophylaxis on events was assessed on-HAART using survival time analysis. As a result of limitations in start and stop dates of cotrimoxazole use before HAART initiation we did not assess the impact of cotrimoxazole prophylaxis pre-HAART. The number of subjects receiving isoniazid preventive therapy during the study period was insufficient for analysis (pre-HAART 12; on-HAART 44).

The 12 months on-HAART was further subdivided into time intervals reflecting the timing of laboratory visits: weeks 2, 6, 12, 24, 36, and 48. For each of these time intervals we calculated the period prevalence of each event with the number evaluated during that period as the denominator. If multiple clinical or laboratory investigations were obtained during a period, we used the highest grade reached (e.g. minimum hemoglobin, maximum alanine aminotransferase).

Differences in hemoglobin between baseline and 24 and 48 week follow-up were compared using a paired *t*-test. A two-sample *t*-test was used to compare hemoglobin at baseline for those who developed grade 3 or 4 anemia, and hemoglobin change from baseline to 24 and

48 weeks in subjects with and without suppression of HIV RNA (< 400 copies/ml) at each time.

Statistical analysis was completed using Intercooled Stata software version 9.2 (Stata Corp., College Station, Texas, USA). All hypothesis tests were two-sided.

Ethical approval for this study was obtained from the Research Ethics Committee of the Anglo-Gold Health Service and the Research Ethics Board of the London School for Hygiene and Tropical Medicine, and the Internal Review Board at Johns Hopkins University School of Medicine.

Results

During the enrolment period, 938 subjects were started on HAART, 853 met the inclusion criteria. Of those excluded, 35 had no laboratory evaluations within 6 weeks of HAART initiation, 48 were on alternative HAART regimens, and two did not consent to participation. The proportion of deaths among those excluded because of no laboratory evaluations within the first 6 weeks was similar to included subjects [two deaths (5.7%) and 34 deaths (4.0%), respectively]. Of the 853 subjects, the median age was 40 years [interquartile range (IQR) 36–45] and 98% were men (Table 2). The median time of enrollment on-HAART was for the complete observation period (378 days, IQR 188–378). The median pre-HAART assessment time (848 subjects) was 350 days (IQR 154–371).

Adverse events

Of the 853 subjects, 92 (11%) developed grade 3 or 4 laboratory and 18 (2.1%) developed grade 3 or 4 clinical events on-HAART (Table 3). Twenty subjects (2.3%) had a regimen change or termination of treatment because of a laboratory or clinical event: six for liver enzyme elevations; five for neurocerebellar toxicity; four for anemia; four for neutropenia; and one for severe emesis. One of the 34 deaths and 21 of 223 hospital admissions were temporally associated with a grade 3 or 4 event. During the first year of HAART, the rate of laboratory and clinical assessments was 7.0 per person-years compared with 3.0 per person-years during the pre-HAART observation period; both pre and on-HAART frequencies were in keeping with the number of visits specified in the programme protocol. Pre-HAART 52 subjects (6.1%) developed grade 3 or 4 laboratory events.

Laboratory adverse events

Eleven subjects had low hemoglobin at baseline (range 7.4–9.9 g/dl) and, although not eligible to receive zidovudine per treatment guidelines, were placed on zidovudine at the discretion of the provider and were included in this study. Pre-HAART, 13 subjects [incidence 2.1 per 100 person-years; 95% confidence interval (CI) 1.2–3.6] developed grade 3 or 4 anemia. On-HAART 17 subjects (incidence 2.8 per 100 person-years; 95% CI 1.7–4.4) developed grade 3 or 4 anemia. Two subjects had repeat episodes of grade 3 or 4 anemia on-HAART. None of the subjects who had an episode of grade 3 or 4 anemia pre-HAART also had an episode on-HAART. Mean baseline hemoglobin was, however, lower for those with, compared to those without, grade 3 or 4 anemia during follow-up (11.4 g/dl; 95% CI 10.8–12.1 versus 12.8 g/dl; 95% CI 12.7–12.9; two-sample *t*-test; $P = 0.001$). Cotrimoxazole was not associated with grade 3 or 4 anemia ($P = 0.25$).

After HAART initiation, the proportion of subjects with grade 3 or 4 anemia peaked at week 6 and then declined. The median hemoglobin also declined until week 6 before increasing (Figs 1 and 2). Compared with the baseline value, hemoglobin at 24 weeks increased by 0.28 g/dl (95% CI 0.14–0.41; paired *t*-test; $P < 0.001$) and at 48 weeks by 0.60 g/dl (95% CI 0.43–0.77; paired *t*-test; $P < 0.001$). To assess the impact of control of HIV on hemoglobin,

we compared hemoglobin among subjects with and without the suppression of HIV RNA. The hemoglobin increase was higher among subjects with the suppression of HIV RNA, although not statistically significant. Among 335 subjects with 24-week HIV-RNA testing, the difference in mean change from baseline to 24 and 48 weeks between those with HIV-RNA suppression and those without was 0.18 and 0.16 g/dl (24 weeks: 95% CI –0.26–0.62; two-sample *t*-test; $P = 0.42$; 48 weeks: 95% CI –0.43–0.75; two-sample *t*-test; $P = 0.6$).

Five patients were hospitalized (the specific reason for hospitalization was unknown), six patients had a change of regimen, and none died within 14 days of grade 3 or 4 anemia during the first 12 months of HAART.

At baseline before HAART initiation, five subjects with an absolute neutrophil count less than 750 cells/μl (range 500–700) were placed on zidovudine containing HAART at the discretion of the clinic provider. Pre-HAART, 15 subjects (incidence 2.8 per 100 person-years; 95% CI 1.7–4.6) developed grade 3 or 4 neutropenia. On-HAART, 50 subjects (incidence 8.4 per 100 person-years; 95% CI 6.4–11.2) developed grade 3 or 4 neutropenia; 10 subjects had multiple episodes leading to a total of 63 total episodes of grade 3 or 4 neutropenia. Cotrimoxazole was significantly associated with grade 3 or 4 neutropenia on-HAART [hazard ratio (HR) 2.3; $P = 0.035$].

We evaluated both hospitalization and episodes of community-acquired pneumonia to assess whether major infection appeared to be increased among subjects with grade 3–4 neutropenia. Six admissions (representing 12% of all individuals with neutropenia) occurred within 14 days of neutropenia. One subject was diagnosed with pneumonia within 14 days of neutropenia out of 19 subjects diagnosed with community-acquired bacterial pneumonia on-HAART. One subject died within 14 days of neutropenia with extrapulmonary tuberculosis and advanced HIV disease. Three subjects had a change in regimen associated with neutropenia.

Pre-HAART 28 subjects (incidence 6.6 per 100 person-years; 95% CI 4.6–9.5) developed grade 3 or 4 elevations in liver enzymes. On-HAART, 34 subjects (incidence 5.8 per 100 person-years; 95% CI 4.2–8.1) developed grade 3 or 4 hepatotoxicity, two of whom had repeat episodes (37 total episodes of hepatotoxicity). Detailed analysis of factors associated with hepatotoxicity in this cohort has previously been presented [12]. On-HAART, five subjects had a regimen change and 10 had a hospital admission temporally associated with hepatotoxicity.

Clinical adverse events

Rash was common pre-HAART and on-HAART. Pre-HAART, 227 subjects (62 episodes per 100 person-years; 95% CI 54.4–70.6) reported or had a rash on physical examination [excluding Kaposi's sarcoma (17 subjects), prurigo nodularis (26 subjects), and herpes zoster (14 subjects)]. On-HAART, rashes affected 228 subjects (29%; 48 episodes per 100 person-years; 95% CI 42–55) [excluding Kaposi's sarcoma (13 subjects), prurigo nodularis (16 subjects), and herpes zoster (5 subjects)]. Further differentiation of rashes, including drug hypersensitivity reactions, was not possible. The concomitant use of cotrimoxazole increased the incidence of rash on-HAART (HR 1.5; $P = 0.002$).

Possible peripheral neuropathy cases were identified by subject self-report, physical examination, and adverse event reporting. Both pre-HAART and on-HAART, 20% of subjects self-reported numbness or tingling in the feet. Because of the high frequency and non-specific nature of this symptom, further analysis was limited to physical examination and adverse event reporting forms. Pre-HAART 61 subjects (incidence 8.2 per 100 person-years; 95% CI 6.3–10.4) were identified with possible peripheral neuropathy by examination

or adverse event reporting, compared with 62 on HAART (incidence 11 per 100 person-years; 95% CI 8.5–14). Forty-seven of the 62 subjects with possible peripheral neuropathy on-HAART also had peripheral neuropathy pre-HAART, suggesting an etiology other than antiretroviral toxic neuropathy (e.g. HIV-related distal sensory neuropathy). By week 12, the proportion of subjects with suspected peripheral neuropathy had declined to a level similar to baseline (Fig. 2). No subjects changed or stopped HAART because of peripheral neuropathy.

Ten subjects self-reported body shape change pre-HAART compared with eight on-HAART. Body shape change was reported from 15 days to 365 days after starting HAART. No cases of lactic acidosis or suspected lactic acidosis were identified during 615 person-years of follow-up on-HAART either on adverse event reporting or through review of serious adverse events and deaths.

Nausea and vomiting was reported among 41 subjects (incidence 10 episodes per 100 person-years; 95% CI 7.3–14) pre-HAART and 143 subjects (incidence 27 episodes per 100 person-years; 95% CI 22–31) on-HAART. Subjects receiving cotrimoxazole had a higher rate of nausea or vomiting (HR 1.6; $P = 0.004$).

Neurocerebellar data were only collected on-HAART. On-HAART, 187 subjects (incidence 37 episodes per 100 person-years; 95% CI 32–43) developed neurocerebellar symptoms (Table 3), 11 of whom had grade 3 symptoms, most frequently at week 2 (Fig. 2). Five subjects had a change or discontinuation of HAART after neurocerebellar symptoms. Subjects receiving cotrimoxazole had a higher rate of neurocerebellar symptoms (HR 1.7; $P < 0.001$).

Discussion

In this South African setting, HAART containing efavirenz, lamivudine, and zidovudine was well tolerated with a minimal increase in clinical and laboratory events from the pre-HAART level. Furthermore, most events occurred within the first 12 weeks of therapy, and were effectively managed by either symptomatic care or, in a few cases, change to another regimen.

Perhaps most importantly, despite a concern for potentially worsening anemia, we found the opposite to occur in our cohort. On-HAART, grade 3 and 4 anemia occurred with an incidence similar to pre-HAART. In addition, we observed a sustained overall rise in hemoglobin after week 6. Our finding of increasing hemoglobin contrasts with studies conducted in high-income countries. The Women's Interagency HIV Study demonstrated an association between zidovudine and persistent anemia; subjects who received a regimen not containing zidovudine had resolution of anemia, whereas those who received zidovudine did not [13]. It is unclear whether sex played a role as theircohort was entirely female. Another study from a male cohort also reported a decline in hemoglobin among those subjects treated with zidovudine, however, but not those receiving stavudine [14]. A meta-analysis of six clinical trials conducted in high-income settings also identified a decline in hemoglobin, 0.4 g/dl at 24 weeks and 0.2 g/dl at 48 weeks after the initiation of a regimen containing zidovudine but not stavudine [15]. The difference between our observations and reports from high-income country cohorts may reflect more advanced HIV disease and higher levels of concomitant disease in our African population [16–18].

On the other hand, zidovudine probably contributed to neutropenia. Despite the high rates of grade 3 or 4 neutropenia, however, we did not detect evidence of severe infection, consistent with a previous study [18]. The one neutropenia-related death occurred in a subject with

disseminated tuberculosis and advanced HIV disease. In that subject, the neutropenia may have been a result of those conditions rather than HAART.

The large proportion of subjects with grade 1 and 2 neutropenia suggests that the current ACTG grading scale is not optimal for a southern African population. This finding is consistent with several studies that have reported lower means and ranges for neutrophil counts among healthy individuals of African compared with European origin. For example, the neutrophil reference ranges based on studies of individuals of African descent in the United Kingdom (900–4200 cells/μl) and in Uganda (840–3370 cells/μl) overlap ACTG ranges for grade 1 and 2 neutropenia [19,20]. In contrast, the reference range derived from a population of European descent is 1500–7800 cells/μl, well above grade 1 neutropenia. Therefore for a European population, the ACTG grading for neutropenia with grade 1 neutropenia starting at a neutrophil count of 1000 cells/μl may be suitable, whereas a scale with different ranges for grade 1 and 2 neutropenia may be more appropriate for other populations.

Possible peripheral neuropathy occurred at a similar rate before and after HAART initiation and within previously reported ranges [21]. We were unable to determine whether any cases of peripheral neuropathy occurred as a result of antiretroviral toxic neuropathy. Most subjects with peripheral neuropathy during HAART, however, also had peripheral neuropathy identified before HAART initiation, making such an association unlikely.

Efavirenz was probably responsible for the large proportion of subjects with neurocerebellar symptoms. Neurocerebellar toxicity affected 22% of subjects assessed at the week 2 clinical evaluation. The high proportion of subjects with early neurocerebellar toxicity and rapid decline in the number of subjects with this symptom is consistent with previous reports from high-income countries of efavirenz-containing HAART regimens [22,23].

We noted more neutropenia, rashes, nausea or vomiting, and neurocerebellar symptoms among subjects receiving cotrimoxazole prophylaxis while on-HAART. Cotrimoxazole is known to cause neutropenia, can cause a variety of hypersensitivity rashes, and is associated with nausea providing a potential explanation for the increase in these events among individuals receiving cotrimoxazole. It is unclear how cotrimoxazole may have been associated with neurocerebellar effects and this could have been a chance finding. Given the reported survival benefits of cotrimoxazole, we do not suggest any reduction in its use [24,25].

We believe the value of this study is enhanced by the comprehensiveness of our laboratory follow-up and the structured history and physical examination forms. To apply our findings to other settings, however, limitations must be recognized. Notably, our population was predominantly male, and malaria, a known risk factor for anemia, was uncommon. Some subjects with low baseline hemoglobin were not started on zidovudine, and therefore a small number of subjects who may have had a higher risk of severe anemia were not included. An additional limitation is the lack of a comparator group on a different HAART regimen. We believe comparing pre-HAART to on-HAART data allows some estimation of adverse events associated with the regimen. We may, however, have underestimated pre-HAART adverse events as ascertainment was limited by a shorter assessment time, assessments were not as frequently scheduled, laboratory testing was mostly obtained on the basis of clinical indication rather than routine monitoring, and subjects may have been sicker around the time of starting HAART than during the pre-HAART period. Equally intense pre-HAART and on-HAART monitoring may have found a higher rate of clinical events pre-HAART. This would lead to the finding of an even safer on-HAART profile. We also raise the issue that some subjects with clinical events were switched to other regimens or may have left care as

a result of side effects, thus the decline in period prevalence of a given adverse event may partly reflect the loss of the most susceptible subjects. We expect the impact of any such bias to be small because of the small number of subjects who switched regimen for adverse events.

Our findings regarding clinical events occurring during the first 12 months of therapy with a regimen consisting of zidovudine, lamivudine, and efavirenz may be of use both for selecting first-line HAART regimens as well as scheduling clinical and laboratory investigations after starting HAART. Further evaluations of the tolerability of zidovudine in other African settings are important, however, especially among women and in regions with a high prevalence of endemic malaria. In addition, direct comparisons conducted in African settings between regimens containing zidovudine, stavudine, tenofovir, or abacavir would add valuable information for designing future HAART regimens.

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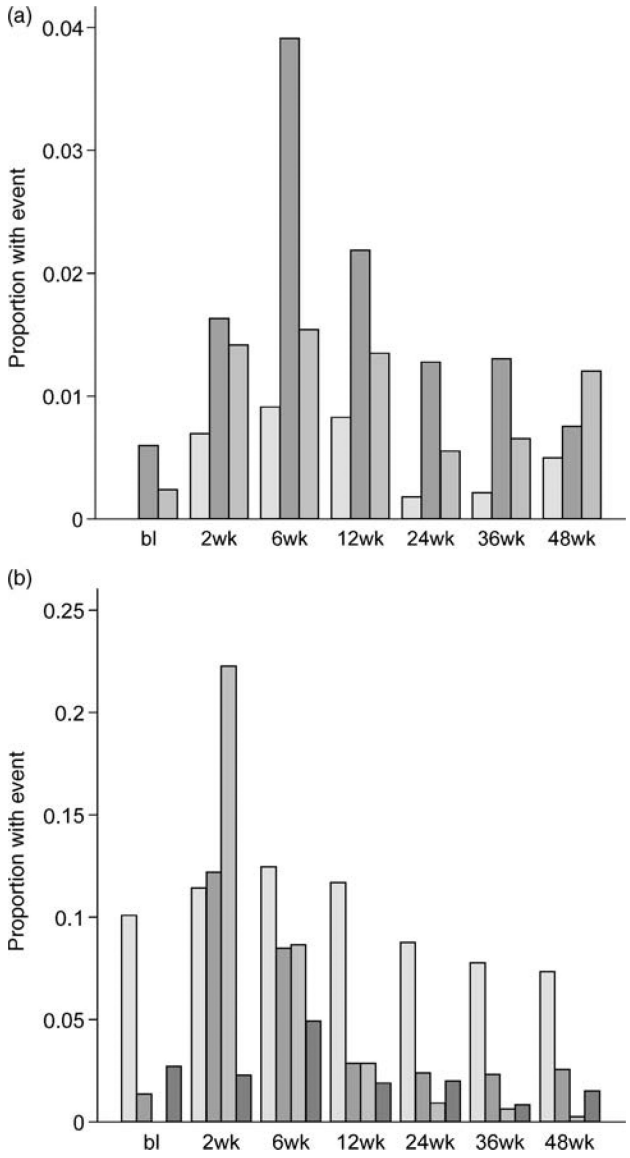

Fig. 1. Proportion at each time interval with grade 3 or 4 laboratory events or any clinical events

(a) Laboratory events. Anemia; neutropenia; hepatotoxicity. (b) Clinical events. Rash; nausea/vomiting; neurocerebellar; neuropathy. Number of subjects evaluated during each time interval: baseline, 853; 2 weeks, 628; 6 weeks, 705; 12 weeks, 661; 24 weeks, 589; 36 weeks, 507; 48 weeks, 451. No baseline neurocerebellar data were available. bl, Baseline; wk, week after HAART initiation.

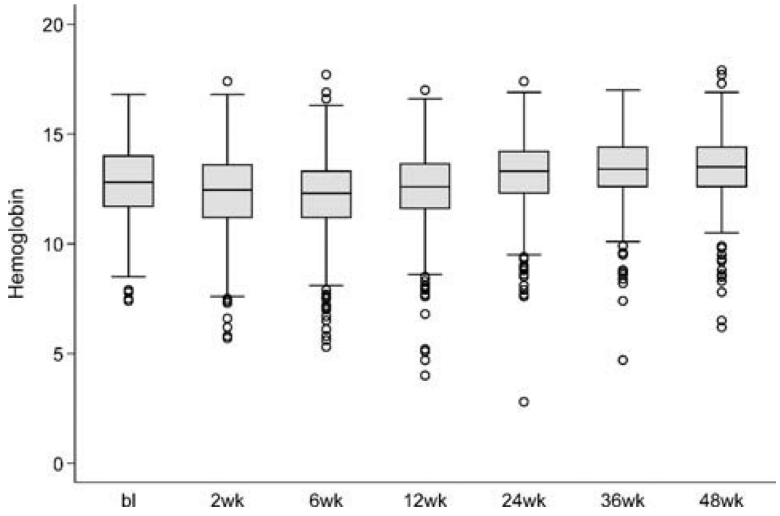

Fig. 2. Box plot of hemoglobin at baseline and follow-up time intervals

Horizontal line, median; box, interquartile range; whiskers, adjacent values; circles, outlier values. bl, Baseline; wk, week.

Table 1

Adverse events grading scales.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Anemia, hemoglobin (gm/dl)	8.0–9.5	7.0–7.9	6.5–6.9	< 6.5
Neutropenia, absolute neutrophil count (/μl)	1000–1500	750–999	500–749	< 500
Hepatotoxicity (if baseline < ULN)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Hepatotoxicity (if baseline > ULN)	1.25–2.5 × baseline	2.6–3.5 × baseline	3.6–5 × baseline	> 5 × baseline
Clinical	Mild and transient, not requiring medical intervention	Moderate, mild to moderate limitation in activity and no to minimal medical intervention required	Severe, marked limitation in activity requiring intervention	Life-threatening, intervention required and hospitalization probable

ULN, upper limit of normal.

Table 2

Baseline characteristics and key HAART outcomes.

Characteristic [*n*]		No. or median
Sex [850]	Male (%)	835 (98)
Age (years) [850]	Median (IQR)	40 (36–45)
Weight (kg) [850]	Median (IQR)	64 (59–70)
CD4 cell count (cells/μl) [850]	Median (IQR)	186 (101–282)
Log_{10} HIV RNA (copies/ml) [529]	Median (IQR)	4.7 (4.3–5.2)
WHO stage [850]	1 and 2 (%)	46 (7)
	3 (%)	327 (38)
	4 (%)	477 (56)
Hemoglobin (g/dl) [842]	Median (IQR)	12.8 (12–14)
Neutrophil (cells/μl) [834]	Median (IQR)	2300 (1600–3100)
ALT/AST maximum[a] (IU/l) [834]	Median (IQR)	36 (29–50)
HIV RNA < 400 copies/ml [335/255]	24 weeks (%)	255 (76)
	48 weeks (%)	191 (75)
Cotrimoxazole	Pre-HAART (%)	485 (57)
	On-HAART (%)	428 (50)
Isoniazid	Pre-HAART (%)	12 (1.4)
	On-HAART (%)	44 (5.2)
Deaths during first year of HAART [887]	(%)	34 (4.0)

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; WHO, World Health Organization.

[a]Upper limit of normal for ALT and AST is 40 IU/l.

Table 3

Prevalence of maximum grade of events on HAART up to 12 months after initiation for all events and up to 12 months pre-HAART for laboratory evaluations (clinical events were not graded pre-HAART).

Event	*n*	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Anemia					
Pre-HAART	781	79 (10)	22 (2.8)	4 (0.51)	9 (1.2)
On-HAART	774	56 (7.2)	21 (2.7)	4 (0.52)	13 (1.7)
Neutropenia					
Pre-HAART	681	127 (19)	21 (3.1)	11 (1.6)	4 (0.59)
On-HAART	769	287 (37)	59 (7.7)	42 (5.5)	8 (1.0)
Hepatotoxicity					
Pre-HAART	547	169 (31)	79 (14)	21 (3.8)	7 (1.3)
On-HAART	772	200 (26.0)	43 (5.6)	14 (1.8)	20 (2.6)
Rash;on-HAART	788	28 (3.6)	19 (2.4)	1 (0.1)	0
Neuropathy; on-HAART	788	21 (2.6)	12 (1.5)	2 (0.2)	0
Nausea or vomiting; on-HAART	805	45 (5.6)	32 (4.0)	3 (0.4)	0
Lactic acidosis; on-HAART	788	0	0	0	0
Neurocerebellar; on-HAART	789	110 (14.0)	66 (8.4)	11 (1.4)	0

Comparisons between the period prevalence of laboratory adverse events pre and on-antiretroviral therapy should be made bearing in mind that laboratory evaluations were undertaken less frequently pre-HAART.