Journal of Antimicrobial Chemotherapy (2006) **58**, 637–644
doi:10.1093/jac/dkl313

Monitoring the toxicity of antiretroviral therapy in resource limited settings: a prospective clinical trial cohort in Thailand

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Received 20 April 2006; returned 10 June 2006; revised 20 June 2006; accepted 6 July 2006

***Background*: One of the many challenges which come together with the implementation of antiretroviral therapy (ART) in settings with limited resources is the monitoring of toxicity. This monitoring increases costs of ART and strains resources. We therefore investigated the necessity for laboratory toxicity monitoring of ART in Thailand.**

***Design, methods and participants*: A prospective Thai cohort of 417 HIV-infected patients were enrolled in randomized clinical trials investigating ART. Time-dependent occurrence of grade III/IV abnormal laboratory values as defined by the AIDS Clinical Trial Group was analysed.**

***Results*: During a median observation period of 3.7 years (2.4–4.3) 142 grade III/IV toxicities occurred in 101 (24.2%) patients. Hepatic toxicity (*n* = 33, 7.9%), hypercholesterolaemia (*n* = 57, 13.7%), hypertriglyceridaemia (*n* = 26, 6.2%), anaemia (*n* = 16, 3.8%) and low platelet counts (*n* = 8, 1.9%) were frequently observed. Anaemia and low platelets occurred early and during the first 2 years of ART. Hepatic toxicity was seen early and throughout the observation period. Hypertriglyceridaemia and hypercholesterolaemia occurred throughout the observation period, and increased over time. Hypercreatininaemia and hyperglycaemia occurred once after 120 and 132 weeks. ART was changed or interrupted for grade III/IV hepatic toxicity, anaemia and hyperglycaemia only. The incidence rate for grade III/IV toxicity was between 5.56 (95% CI, 6.76–18.02) for low platelet counts and 41.18 (31.77–53.39) per 1000 patient years for hypercholesterolaemia. Antiretrovirals used were zidovudine, stavudine, lamivudine, zalcitabine, didanosine, efavirenz, saquinavir, ritonavir and indinavir.**

***Conclusions*: Grade III/IV toxicity is frequently observed in Thai patients treated with ART. The simple and inexpensive monitoring of ALT and haemoglobin could prevent most serious short-term toxicity. Long-term toxicity can be addressed with a yearly monitoring of triglycerides, cholesterol, glucose and creatinine if nephrotoxic drugs are used.**

Keywords: developing countries, laboratory tests, HIV infections, HAART

Introduction

Antiretroviral therapy (ART) has proven to be highly effective in the treatment of HIV infection in industrialized countries[1,2] as well as in countries with limited resources.[3–10] But ART also has significant toxicity that requires monitoring.[11–27] Laboratory tests performed on a regular basis are usually used to detect severe toxicity before it becomes clinically apparent and harmful. These tests however are costly and require patient visits, phlebotomy, and appropriate infrastructure and equipment. So far, due to

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financial constraints and the lack of appropriate infrastructure, ART is mostly used in developed countries where such infrastructure is available. However, considerable efforts are being undertaken worldwide to expand the access to ART in resource limited settings.[5,28–30] One of the many challenges which comes together with the implementation of ART in such areas is the monitoring of toxicity.[31,32] Knowing when toxicity is most likely to occur, and what parameters call for a change in therapy, would help to avoid unnecessary examinations and costs. The interval at which safety monitoring is performed varies considerably depending on local practice, availability of tests and resources. Despite the fact that safety laboratory examinations are considered to be the standard of care, evidence on when to perform which test is scarce. Most data are available from clinical trials with an emphasis on maximal safety. Also, some randomized clinical trials evaluating the efficacy of antiretrovirals (ARV) were not powered to detect side effects. Especially in resource limited settings like in Thailand, safety laboratory monitoring significantly adds to the costs of ART.[33,34] With cheaper ARV becoming available, an increasing number of HIV-infected patients will be treated and will have to be monitored for side effects.[5–7] To provide evidence on how safety monitoring could be most efficiently performed we conducted an analysis in patients treated within different trials and with different antiretroviral drugs in Thailand.

Methods

Study design

The study population included HIV-infected adults participating in randomized controlled trials of ART at HIV-NAT, Bangkok, Thailand, who initiated therapy between December 1996 and December 2002. Patients were recruited from the HIV outpatient clinic of the Chulalongkorn Hospital and the anonymous clinic of the Thai Red Cross in Bangkok, Thailand. All protocols were approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. All patients gave written informed consent. In accordance with trial protocols, clinical and laboratory data were collected at screening (within 4 weeks before ART commencement), baseline (just prior to ART commencement) and every 6 weeks to 12 weeks depending on the trial protocols up to week 378. Pathological grade III/IV results were graded according to the AIDS Clinical Trial Group (ACTG) toxicity grading system (http://aactg.s-3.com): haemoglobin < 7.4 g/dL, platelets < 50 000 platelets/mm^3, ALT > 5× upper limit, creatinine > 1.9× upper limit, triglycerides > 8.49 mmol/L, cholesterol > 7.77 mmol/L, glucose <2.2 and >13.9 mmol/L. Other tests used in the studies but excluded from the analysis were amylase, neutrophils, lymphocytes, monocytes, eosinophils, basophils, CD8, lactate. Reasons for exclusion were that measurements were available only for a few patients (amylase, lactate) and that no grade III/IV toxicity occurred (all of these tests).

Data analysis and statistics

In order to detect patterns in the occurrence of toxicity, the database was screened for haemoglobin, leucocyte count, platelet count, ALT, serum creatinine, cholesterol, triglycerides and glucose. Relevant events defined as grade III or IV toxicity were analysed separately. Univariate and multivariate Cox regression analyses were used to detect factors associated with severe (grade III and IV) toxicity. Variables that were statistically significant in the univariate models then would be selected to be in the multivariate models to see whether they still had the same effects. Incidence rates for each endpoint per 1000 patients per year were also calculated. Nelson-Aalen function was used to calculate failure rates in each endpoint. For statistical analysis STATA version 8.2 (StataCorp, USA) was used. Level of significance in this paper is 0.05 and all P values in the study are two-sided.

Results

A total of 417 patients participating in HIV-NAT 001 (n = 111), 002 (n = 78), 003 (n = 106), 005 (n = 104) and 009 (n = 18)[35–43] trials between December 1996 and December 2002 were analysed. Drug regimens used in the different trials were zidovudine/zalcitabine standard versus half dose,[37] dual nucleoside plus boosted saquinavir,[35,36,40,42] didanosine/stavudine versus zidovudine/lamivudine,[38] zidovudine/lamivudine/didanosine,[39,43] zidovudine/lamivudine/boosted indinavir[44] and boosted indinavir/efavirenz.[41] Exclusion criteria in the protocols were (i) protease inhibitor-experienced; (ii) liver function tests >5 times upper normal limit, creatinine >2 times upper normal limit.

Median (IQR) observation period was 3.7 years (2.4–4.3) accounting for 1677 patient years. Mean (SD) time on HAART was 2.09 (1.6) years. Baseline characteristics of the patients are shown in Table 1. As expected in a cohort with predominately heterosexual transmission (89.0%), female to male ratio

Table 1. Baseline characteristics of patients at inclusion into trials, and overall exposure to antiretrovirals

Characteristic	
Number of patients	417
Age [years (SD)]	32.2 (7.2)
Female/male [n (%)]	224/193 (53.7/46.3)
Transmission category [n (%)]	
heterosexual	371 (89.0)
homosexual	30 (7.2)
injecting drug users	3 (0.7)
heterosexual/bisexual	10 (2.4)
other	3 (0.7)
CDC clinical stage [n (%)]	
A	224 (53.8)
B	159 (38.0)
C	34 (8.2)
Viral load [$\log_{10}$ copies/mL (IQR)]	4.3 (3.7–4.9)
CD4 cells [cells/mm^3 (IQR)]	283 (179–392)
ARV naive/experienced	295/122 (70.7/29.3)
Drugs ever used [n (%)]	
zidovudine	372 (89.2)
lamivudine	307 (73.6)
didanosine	217 (52.0)
stavudine	189 (45.3)
zalcitabine	111 (26.6)
efavirenz	62 (14.9)
indinavir	165 (39.6)
saquinavir	95 (22.8)
ritonavir boosting dose	192 (46.0)

JAC antiviral

was balanced (1.16). A total of 142 grade III/IV toxicity events occurred in 101 patients within a maximum observation period of 378 weeks. When severe toxicity occurred, patients most frequently experienced hypercholesterolaemia (n = 57, 13.7%), elevation of ALT (n = 33, 7.9%), triglycerides (n = 26, 6.2%) and a decline in haemoglobin (n = 16, 3.8%) followed by low platelet counts (n = 8, 1.9%). No hypoglycaemia occurred. Hyperglycaemia and high creatinine in a patient taking indinavir were observed only once. The time-dependent occurrence of grade III/IV toxicity on ART is shown in Figure 1. Whereas anaemia is observed predominately during the first 2 years of ART, elevation of liver enzymes, triglycerides and cholesterol occurred throughout the observation period. The first grade III/IV anaemia (n = 3) and ALT elevation (n = 5) occurred at week 12, the first low platelet count (n = 1) at week 6. First grade III/IV hyperlipidaemia was observed after 12 weeks on ART. Only one isolated incidence of elevated creatinine and one hyperglycaemia occurred after 120 and 132 weeks, respectively. ART was interrupted in 15 of the 16 (93.8%) patients who experienced severe anaemia and changed in 2 (12.5%) without discontinuation (Table 2). Hepatic toxicity was observed in 33 patients and triggered interruption of ART in 14 (42.4%). One patient

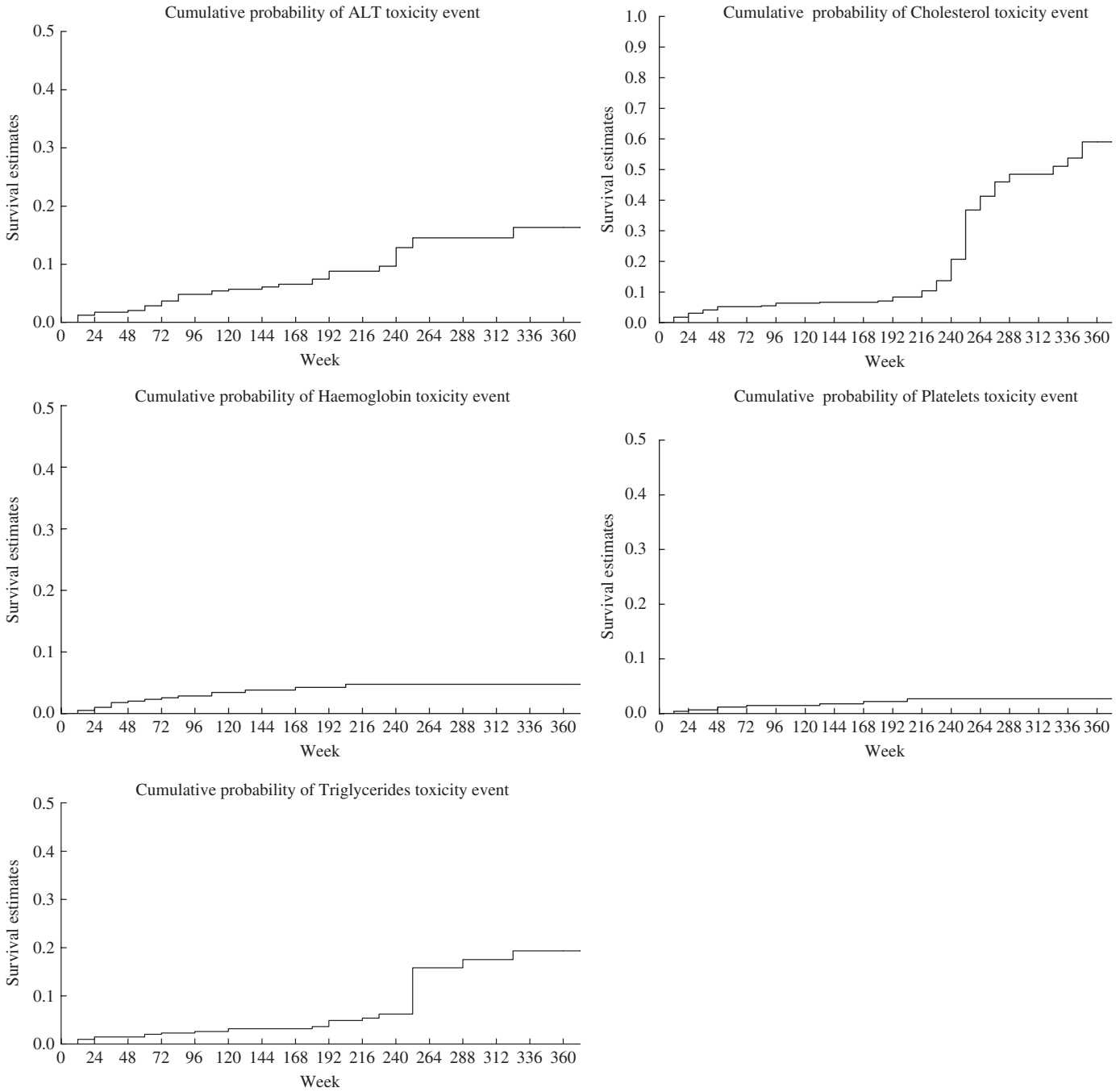

Figure 1. Occurrence of grade III/IV toxicity over time shown with Nelson Aalen's plots.

Table 2. Occurrence, management and devolution of grade III/IV toxicity events per patient who experienced toxicity

Toxicity	No. of patients	ART changed[a]	ART interrupted[a]	Resolution[b]	Persistence/recurrence
ALT >5× upper limit	33	8	14	20	13
Haemoglobin < 7.4 g/L	16	2	15	15	1
Platelets < 50 000 platelets/mm^3	8	0	0	8	0
Cholesterol > 7.77 mmol/L	57	0	0	15	42
Triglycerides > 8.49 mmol/L	26	0	0	12	14
Hyperglycaemia > 13.9 mmol/L	1	0	1	0	1
Creatinine >1.9× upper limit	1	–	–	–	–

[a]Multiple mentioning.
[b]Toxicity of grade II or less during follow up.

experienced hyperglycaemia and his therapy was interrupted. No therapy was interrupted because of low platelet counts and grade III/IV hyperlipidaemia. Also, no change in the ARV was triggered by abnormal creatinine (Table 2). Incidence rates per 1000 patient years (with 95% confidence interval) of severe toxicity were 5.56 (2.78–11.13) for low platelet counts, 41.18 (31.77–53.39) for hypercholesterolaemia, 11.04 (6.76–18.02) for severe anaemia, 18.42 (12.54–27.05) for hypertriglyceridaemia and 23.86 (16.96–33.56) for elevated liver enzymes. We used Cox proportional hazards models to determine factors related to grade III/IV toxicity (Table 3). In the univariate analysis anaemia was associated with the use of zidovudine. Older age was significantly associated with liver toxicity. Hyperlipidaemia was associated with older age, advanced HIV disease, and treatment with efavirenz and indinavir, whereas patients naive to ART, patients with higher CD4 count, and patients using zidovudine and didanosine had lower lipid values. In the multivariate analysis older age, the use of indinavir, the inverse correlation with higher CD4 count, didanosine and ARV naive status remained significantly associated with hyperlipidaemia.

Discussion

Significant toxicity of ART was frequently observed in this Thai cohort of patients treated within various clinical trials. Grade III/IV toxicity of ART occurred with an incidence rate 5.56–41.18 per 1000 patient years. A total of 142 grade III/IV laboratory adverse events were recorded in 101 (24.2%) patients. Due to toxicity, therapy had to be changed or interrupted in 30 of the 417 (7.2%) patients analysed. No mortality was attributed to drug toxicity.

In accordance with population-based studies in industrialized countries [12,14,16,23,27,45] our data show that toxicity is a significant problem in Thai patients treated with ART. The incidence of grade III/IV laboratory adverse events was higher than that in industrialized countries,[12,27,45] but similar to investigations in other resource limited settings.[10,46] One reason for this could be the lack of therapeutic alternatives. Many patients had to continue their treatment despite low-grade toxicity. Switching ARV for any-grade toxicity is indeed the most frequent reason to change ARV in industrialized countries.[17,23,47] Switches for low-grade toxicity may have prevented grade III/IV toxicity. Accordingly switches due to grade III/IV laboratory toxicity occurred in 6.7% of Thai patients. This is about twice as frequent as in industrialized countries.[47] Hepatic toxicity was frequently observed. This may be due to fact that chronic hepatitis B or C co-infection is common in HIV-infected Thai patents.[48] In our study 8% suffered from chronic viral hepatitis. It has been shown that such co-infection puts patients at a higher risk for developing grade III/IV liver enzyme elevations.[21,48] Grade III/IV elevation in ALT was judged by the treating clinicians to be serious, and ART was frequently interrupted due to ALT elevation. The other abnormalities that caused changes in therapy were severe anaemia and hyperglycaemia. Low platelet counts resolved while on ART and were probably not drug related. Thus, monitoring of only ALT and haemoglobin would have been enough to detect nearly all of the significant short-term toxicity.

No change in therapy was triggered by hyperlipidaemia. However, newer data shows an increased cardiovascular risk for patients treated with ART.[16] So far cardiovascular mortality is not an extensive problem for HIV-infected persons in developing countries. The high mortality of untreated HIV infection combined with younger age and a high proportion of female patients make a cardiovascular event unlikely. This may change if ART becomes more widely accessible, and life expectancy of HIV-infected patients increases also in the economically less developed countries. Due to the lack of funding to perform testing there is no data on cardiovascular toxicity of HAART in Thai patients. However, this needs to be followed carefully as HAART becomes more widely available in this country. We did show that hyperlipidaemia develops steadily over time, suggesting that continuous monitoring at a low frequency, i.e. every 1–2 years, is sufficient to detect this long-term cardiovascular risk factor. Nevertheless, ART has shown to be beneficial even without laboratory monitoring for side effects.[4] Indeed the rate of life-threatening toxicity in our cohort is still well below the rate of progression to AIDS without ART. A cohort of patients in an industrialized country showed a progression to AIDS of 15.1 per 100 patient years 6 months prior to ART.[49] The same analysis also showed a striking reduction in the progression to AIDS 3 and 6 months after starting ART form 15.1 to 7.7 and 2.2 per 100 patient years, respectively.[49] Other cohorts in industrialized countries have reported progression rates to new AIDS-defining events of 2.6–4.8 per 100 patient years.[2,50,51] In our cohort progression to new AIDS-defining events and mortality were 1.7 and 0.7 per 100 patient years.[8] Tuberculosis, which is endemic in Thailand, was the most frequent new AIDS-defining disease (14 of 29 events). The impact of ART in these Thai patients is thus at least as significant as in industrialized countries. But severe toxicity was frequently observed and would probably have caused some

Table 3. Hazard ratios (HR) with 95% confidence interval from Cox proportional hazards models for factors related to grade III/IV toxicity

Factors	ALT grade III/IV	Haemoglobin grade III/IV	Platelets grade III/IV	Triglycerides grade III/IV	Cholesterol grade III/IV
Baseline CD4 per 100 cells/mm^3	0.89 (0.70–1.13)	0.80 (0.58–1.10)	0.99 (0.63–1.55)	0.68 (0.49–0.93)*	**0.78 (0.64–0.97)**
Baseline HIV RNA per 1 log$_{10}$	1.24 (0.84–1.84)	1.19 (0.69–2.05)	0.70 (0.40–1.25)	1.87 (1.13–3.07)*	1.17 (0.85–1.61)
Age per year	1.05 (1.01–1.10)*	1.03 (0.97–1.10)	1.00 (0.94–1.08)	**1.05 (1.01–1.10)**	**1.08 (1.05–1.12)**
Female	0.55 (0.26–1.14)	1.95 (0.71–5.36)	0.65 (0.15–2.75)	0.46 (0.20–1.06)	0.61 (0.36–1.03)
Naive to ART	1.67 (0.56–4.99)	0.63 (0.21–1.52)	1.65 (1.77–15.35)*	**0.16 (0.04–0.58)**	–
CDC classification					
CDC class A	1.00	1.00	1.00	1.00	1.00
CDC class B	0.69 (0.32–1.46)	1.04 (0.37–2.91)	0.98 (0.23–4.11)	1.83 (0.77–4.28)	2.54 (1.44–4.47)*
CDC class C	0.43 (0.06–3.29)	0.88 (0.11–7.05)	1.36e–18 (4.66e–19–3.98e–18)	5.69 (1.66–19.00)*	6.34 (2.44–16.25)*
Treatment					
mono/dual ART	1.00	1.00	1.00	1.00	1.00
triple ART	1.44 (0.66–3.16)	0.20 (0.03–1.54)	4.23 (0.95–18.86)	1.42 (0.59–3.42)	3.39 (1.88–6.11)*
>3 drugs	–	2.66 (0.82–8.64)	2.01e–15 (4.8e-16–8.44e–15)	3.20 (0.90–11.34)	5.73 (2.48–13.25)*
Ever used zidovudine	0.95 (0.28–3.19)	6.86e14 (3.67e14–1.28e15)*	2.49e14 (1.01e14–6.17e14)	0.28 (0.11–0.73)	0.16 (0.08–0.33)*
Ever used lamivudine	0.74 (0.35–1.60)	0.96 (0.31–2.97)	2.23 (0.27–18.26)	0.47 (0.20–1.08)	0.69 (0.37–1.26)
Ever used stavudine	1.10 (0.52–2.31)	0.95 (0.37–2.41)	1.50 (0.32–7.00)	0.77 (0.37–1.58)	0.60 (0.37–0.97)*
Ever used didanosine	1.25 (0.57–2.72)	0.71 (0.28–1.82)	4.82 (0.58–40.25)	0.58 (0.29–1.19)	**0.18 (0.09–0.37)**
Ever used zalcitabine	–	–	–	–	–
Ever used efavirenz	1.32 (0.64–2.71)	1.14 (0.34–3.80)	0.76 (0.10–5.56)	4.79 (2.16–10.58)*	–
Ever used indinavir	0.82 (0.40–1.66)	1.83 (0.60–5.62)	0.71 (0.12–4.07)	4.41 (1.98–9.82)*	**5.80 (1.62–20.77)**
Ever used saquinavir	0.85 (0.37–1.94)	1.22 (0.40–3.71)	0.31 (0.03–2.85)	0.69 (0.27–1.79)	15.07 (3.32–68.36)*
Ever used ritonavir	0.80 (0.39–1.65)	2.30 (0.81–6.59)	0.33 (0.07–1.52)	5.21e+15 (3.06e+15–8.85e+15)*	7.91 (2.82–22.32)*

Bold font: significant hazard ratios in the multivariate analysis.
*Significant hazard ratio in the univariate analysis only.

additional morbidity and mortality without proper management. In this context it is interesting how toxic events occurred over time (see Figure 1). Haematological toxicity happened early and was observed during the first 2 years of follow up. To detect such toxicity, safety monitoring has to start early, 12 weeks at the latest, and continue for the first 2 years of treatment. Whereas hepatic toxicity can occur early and may continue to arise even after 150 weeks. Therefore, monitoring starting after 12 weeks on treatment and continuing during the whole treatment period is required to detect it. Hypertriglyceridaemia occurred without distinct patterns throughout the observation period and became more frequent in the later course of ART. This is particularly true for hypercholesterolaemia, which predominately occurred after more than 200 weeks on therapy. This was because patients became older during the observation period and the use of boosted protease inhibitors was more frequent. Both factors were associated with hyperlipidaemia in the multivariate analysis. Grade III/IV renal toxicity and hyperglycaemia were very rare and happened only after more than 2 years on treatment. But grade I/II nephrotoxicity was frequently observed in patients taking indinavir in HIV-NAT studies.[44] So checking creatinine on a yearly basis should be considered.

In order to determine patients at particular risk for toxicity, we analysed various factors that are shown in Table 3. Grade III/IV hepatotoxicity was weakly associated with older age. As expected, hyperlipidaemia was associated with the use of protease inhibitors like indinavir. Older patients developed hypercholesterolaemia more frequently, while the use of didanosine at baseline was associated with lower cholesterol. Overall we could not find any predictive risk factors for the development of toxicity, suggesting that all patients taking ART should be monitored for side effects.

Some limitations in our study should be considered. The number of ARVs used is restricted. Therefore the conclusions can only be generalized with some caution to any combination of antiretroviral drugs. On the other hand many drugs have overlapping toxicity. And newer drugs tend to have even fewer side effects than the one used. For example, tenofovir may require toxicity monitoring including more frequent measurements of creatinine and excluding monitoring for toxicity the drug does not have. Therefore the main conclusion that toxicity can be addressed with just a very few tests is not affected by the limited choice of drugs. Another limitation is the sample size. Some factors related to grade III/IV toxicity may not have been detected because of too small numbers. And the selected nature of participants within clinical trials may have led to an underestimation of toxicity. On the other hand, the long follow up strengthens the conclusions. And the standardized setting within randomized trials has reduced cofounders and selection bias.

Grade III/IV toxicity is frequently observed in Thai patients treated with ART. Although the decrease in the incidence of progression of HIV infection induced by ART largely outweighs toxic effects, life-threatening toxicity occurs. Focusing toxicity monitoring on the few parameters which trigger a change in therapy such as ALT and haemoglobin could prevent most of the severe short-term toxicity of ART and further increase its beneficial effects in countries with limited resources. Where possible, long-term toxicity should be addressed with a yearly monitoring of triglycerides, cholesterol, glucose and creatinine if nephrotoxic drugs are used.

Acknowledgements

We are thankful to all the HIV-NAT patients, as well as the physicians, research nurses, laboratory technicians and administrative staff who contributed to patient care. Part of the data was presented at the Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, USA, 2006. *Sponsorship*: The HIV-NAT trials included in the study had financial support from Hoffmann-LaRoche, Bristol Myers Squibb, GlaxoSmithKline and Merck. HIV-NAT was responsible for the conduction of all studies. HIV-NAT, NCHECR and IATEC were responsible for the design and the evaluation of the studies, as well as the final publications. Reto Nüesch was funded by a grant of the Swiss National Science Foundation.

HIV-NAT Study Team: physicians: P. P., K. R., C. D., Chaiwat Ungsedhapand, Jintanat Ananworanich, Saskia Autar, Wadchara Pumpradit, Anchalee Avihingsanon, Torsak Bunupuradah, Thanyawee Puthanakit, Jasper van der Lugt; administrative manager: Theshinee Chuenyam; study nurses: Narumon Subsri, Jeeranan Sawatatat, Sukontha Saenawat, Arpa Chemchaitrakool, Khanitta Sujaikeaw, Seangla Tammawong, Jintana Intasan, Duanghathai Sutthichom, Nitaya Jeanpan, Sineenart Chautrakarn, Tippawan Hoksiew, Sewita Wannakayont, Peeraporn Keaw-on, Siripan Wattanaporn, Jirat Labsanaprem, Bulan See-ngam, Saowanee Jomtong, Sangla Najai; laboratory: Sasiwimol Ubolyam, Jongkol Sankote, Apicha Mahanontharit, Bunruan Sopa, Matinee Laopraynak, Amnat Phooprang, Theeradej Boonmangum, Patcharee Pongprayoon, AB Rayayoi, Janyaporn Sangsawad; pharmacy: Thantip Nuchapong, Vajira Tongphatana, Ratree Longcharoen, Orathai Chaiya, Taksin Panpuy; data management/logistics: Chowalit Phadungphon, John Liddy, Ekkasit Thodsanit, Noppong Hirunwadee, Orm-rudee Rit-im, Wanchai Tongsri; statistics: Steve Kerr, Puntarika Pornprasit, Pich Boonyarak; monitors: Saijai Wicharuk, Kobkeaw Laohajinda, Siriporn Nonnoi, Natnipa Wannachai, Nitiya Chomchey, Thidarat Jupimai.

Transparency declarations

Reto Nüesch has received honorarium from GlaxoSmithKline. Jintanat Ananworanich has received travel grants and honorarium from Hoffmann-LaRoche. Kiat Ruxrungtham has received travel grants, consultancy fees and honoraria from various pharmaceutical companies including Hoffmann-LaRoche, Merck, Sharp and Dohme, Bristol-Myers-Squibb and Abbott. Praphan Phanuphak has received honoraria from Bristol-Myers-Squibb and research grants from Bristol-Myers-Squibb, Hoffmann-LaRoche, GlaxoSmithKline and Merck, Sharp and Dohme. All other authors confirm that they have not accepted any financial contribution which may have affected the conclusions of this paper. Neither do they own stocks and other participation from companies involved in this work.

References

1. Palella FJ, Delaney KM, Moorman AC *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338**: 853–60.

2. Mocroft A, Ledergerber B, Katlama C *et al*. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003; **362**: 22–9.

3. Zhou J, Kumarasamy N, Ditangco R *et al*. The TREAT Asia HIV Observational Database: baseline and retrospective data. *J Acquir Immune Defic Syndr* 2005; **38**: 174–9.

4. Weidle PJ, Malamba S, Mwebaze R *et al*. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet* 2002; **360**: 34–40.

5. Phanuphak P. Antiretroviral treatment in resource-poor settings: what can we learn from the existing programmes in Thailand? *AIDS* 2004; **18** Suppl 3: S33–8.

6. Teixeira PR, Vitoria MA, Barcarolo J. Antiretroviral treatment in resource-poor settings: the Brazilian experience. *AIDS* 2004; **18** Suppl 3: S5–7.

7. Marins JR, Jamal LF, Chen SY *et al*. Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003; **17**: 1675–82.

8. Duncombe C, Kerr SJ, Ruxrungtham K *et al*. HIV disease progression in a patient cohort treated via a clinical research network in a resource limited setting. *AIDS* 2005; **19**: 169–78.

9. Wolff MJ, Beltran CJ, Vasquez P *et al*. The Chilean AIDS cohort: a model for evaluating the impact of an expanded access program to antiretroviral therapy in a middle-income country—organization and preliminary results. *J Acquir Immune Defic Syndr* 2005; **40**: 551–7.

10. Wester CW, Kim S, Bussmann H *et al*. Initial response to highly active antiretroviral therapy in HIV-1C-infected adults in a public sector treatment program in Botswana. *J Acquir Immune Defic Syndr* 2005; **40**: 336–43.

11. French M, Amin J, Roth N *et al*. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 Infection: the OzCombo 2 study. *HIV Clin Trials* 2002; **3**: 177–85.

12. Fellay J, Boubaker K, Ledergerber B *et al*. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001; **358**: 1322–7.

13. Brindeiro RM, Diaz RS, Sabino EC *et al*. Brazilian Network for HIV Drug Resistance Surveillance (HIV-BResNet): a survey of chronically infected individuals. *AIDS* 2003; **17**: 1063–9.

14. Bonfanti P, Valsecchi L, Parazzini F *et al*. Incidence of adverse reactions in HIV patients treated with protease inhibitors: a cohort study. Coordinamento Italiano Studio Allergia e Infezione da HIV (CISAI) Group. *J Acquir Immune Defic Syndr* 2000; **23**: 236–45.

15. Benbrik E, Chariot P, Bonavaud S *et al*. Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells. *J Neurol Sci* 1997; **149**: 19–25.

16. Friis-Moller N, Weber R, Reiss P *et al*. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS* 2003; **17**: 1179–93.

17. Hansel A, Bucher HC, Nuesch R *et al*. Reasons for discontinuation of first highly active antiretroviral therapy in a cohort of proteinase inhibitor-naive HIV-infected patients. *J Acquir Immune Defic Syndr* 2001; **26**: 191–3.

18. Heath KV, Hogg RS, Singer J *et al*. Antiretroviral treatment patterns and incident HIV-associated morphologic and lipid abnormalities in a population-based chort. *J Acquir Immune Defic Syndr* 2002; **30**: 440–7.

19. Joly V, Flandre P, Meiffredy V *et al*. Efficacy of zidovudine compared to stavudine, both in combination with lamivudine and indinavir, in human immunodeficiency virus-infected nucleoside-experienced patients with no prior exposure to lamivudine, stavudine, or protease inhibitors (novavir trial). *Antimicrob Agents Chemother* 2002; **46**: 1906–13.

20. Ofotokun I, Pomeroy C. Sex differences in adverse reactions to antiretroviral drugs. *Top HIV Med* 2003; **11**: 55–9.

21. Wit FW, Weverling GJ, Weel J *et al*. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis* 2002; **186**: 23–31.

22. Yozviak JL, Doerfler RE, Woodward WC. Effectiveness and tolerability of nevirapine, stavudine, and lamivudine in clinical practice. *HIV Clin Trials* 2001; **2**: 474–6.

23. Dieleman JP, Jambroes M, Gyssens IC *et al*. Determinants of recurrent toxicity-driven switches of highly active antiretroviral therapy. The ATHENA cohort. *AIDS* 2002; **16**: 737–45.

24. Ananworanich J, Moor Z, Siangphoe U *et al*. Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs. *AIDS* 2005; **19**: 185–92.

25. Hagberg L, Janson GL. Clinical and laboratory signs of mitochondrial dysfunction secondary to nucleoside analogue antiretroviral therapy are reversible. *Scand J Infect Dis* 2001; **33**: 558.

26. The Australian HIV Observational Database. Rates of combination antiretroviral treatment change in Australia, 1997–2000. *HIV Med* 2002; **3**: 28–36.

27. Colette JS, Sabin CA, Lampe FC *et al*. The relationship between CD4 cell count nadirs and the toxicity profiles of antiretroviral regimens. *Antivir Ther* 2005; **10**: 459–67.

28. Brown P. Cheaper AIDS drugs due for Third World. *Nature* 2000; **405**: 263.

29. Cohen J. AIDS treatment. A step toward cheaper anti-HIV therapy. *Science* 2005; **307**: 653.

30. Piot P, Feachem RG, Lee JW *et al*. Public health. A global response to AIDS: lessons learned, next steps. *Science* 2004; **304**: 1909–10.

31. Wainberg MA. Generic HIV drugs—enlightened policy for global health. *N Engl J Med* 2005; **352**: 747–50.

32. Harries AD, Nyangulu DS, Hargreaves NJ *et al*. Preventing antiretroviral anarchy in sub-Saharan Africa. *Lancet* 2001; **358**: 410–4.

33. Creese A, Floyd K, Alban A *et al*. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet* 2002; **359**: 1635–43.

34. Kaufmann GR, Smith D, Bucher HC *et al*. Potential benefit and limitations of a broad access to potent antiretroviral therapy in developing countries. *Expert Opin Investig Drugs* 2002; **11**: 1303–13.

35. Cardiello PG, Hassink E, Ananworanich J *et al*. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis* 2005; **40**: 594–600.

36. Nuesch R, Ananworanich J, Sirivichayakul S *et al*. Development of HIV with drug resistance after CD4 cell count-guided structured treatment interruptions in patients treated with highly active antiretroviral therapy after dual-nucleoside analogue treatment. *Clin Infect Dis* 2005; **40**: 728–34.

37. Kroon ED, Ungsedhapand C, Ruxrungtham K *et al*. A randomized, double-blind trial of half versus standard dose of zidovudine plus zalcitabine in Thai HIV-1-infected patients (study HIV-NAT 001). HIV Netherlands Australia Thailand Research Collaboration. *AIDS* 2000; **14**: 1349–56.

38. Ruxrungtham K, Kroon ED, Ungsedhapand C *et al*. A randomized, dose-finding study with didanosine plus stavudine versus didanosine alone in antiviral-naive, HIV-infected Thai patients. *AIDS* 2000; **14**: 1375–82.

39. Ungsedhapand C, Kroon ED, Suwanagool S *et al*. A randomized, open-label, comparative trial of zidovudine plus lamivudine versus zidovudine plus lamivudine plus didanosine in antiretroviral-naive HIV-1-infected Thai patients. *J Acquir Immune Defic Syndr* 2001; **27**: 116–23.

40. Cardiello PG, Samor T, Burger D *et al*. Pharmacokinetics of lower doses of saquinavir soft-gel caps (800 and 1200 mg twice daily) boosted with itraconazole in HIV-1-positive patients. *Antivir Ther* 2003; **8**: 245–9.

41. Boyd MA, Aarnoutse RE, Ruxrungtham K *et al*. Pharmacokinetics of indinavir/ritonavir (800/100 mg) in combination with efavirenz (600 mg) in HIV-1-infected subjects. *J Acquir Immune Defic Syndr* 2003; **34**: 134–9.

42. Ananworanich J, Siangphoe U, Hill A *et al*. Highly active antiretroviral therapy (HAART) retreatment in patients on CD4-guided

therapy achieved similar virologic suppression compared with patients on continuous HAART: the HIV Netherlands Australia Thailand Research Collaboration 001.4 study. *J Acquir Immune Defic Syndr* 2005; **39**: 523–9.

43. Ungsedhapand C, Srasuebkul P, Cardiello P *et al*. Three-year durability of dual-nucleoside versus triple-nucleoside therapy in a Thai population with HIV infection. *J Acquir Immune Defic Syndr* 2004; **36**: 693–701.

44. Boyd M, Mootsikapun P, Burger D *et al*. Pharmacokinetics of reduced-dose indinavir/ritonavir 400/100 mg twice daily in HIV-1-infected Thai patients. *Antivir Ther* 2005; **10**: 301–7.

45. van Leeuwen R, Katlama C, Murphy RL *et al*. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003; **17**: 987–99.

46. Djomand G, Roels T, Ellerbrock T *et al*. Virologic and immunologic outcomes and programmatic challenges of an antiretroviral treatment pilot project in Abidjan, Cote d'Ivoire. *AIDS* 2003; **17** Suppl 3: S5–15.

47. d'Arminio Monforte A, Lepri AC, Rezza G *et al*. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS* 2000; **14**: 499–507.

48. Law WP, Duncombe CJ, Mahanontharit A *et al*. Impact of viral hepatitis co-infection on response to antiretroviral therapy and HIV disease progression in the HIV-NAT cohort. *AIDS* 2004; **18**: 1169–77.

49. Ledergerber B, Egger M, Erard V *et al*. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999; **282**: 2220–6.

50. Egger M, May M, Chene G *et al*. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002; **360**: 119–29.

51. Cole SR, Hernan MA, Robins JM *et al*. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am J Epidemiol* 2003; **158**: 687–94.