

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

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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/mm³, 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 indinavir⁴⁴ 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 predominantly 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 [<i>n</i> (%)]	224/193 (53.7/46.3)
Transmission category [<i>n</i> (%)]	
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 [<i>n</i> (%)]	
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 [<i>n</i> (%)]	
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)

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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

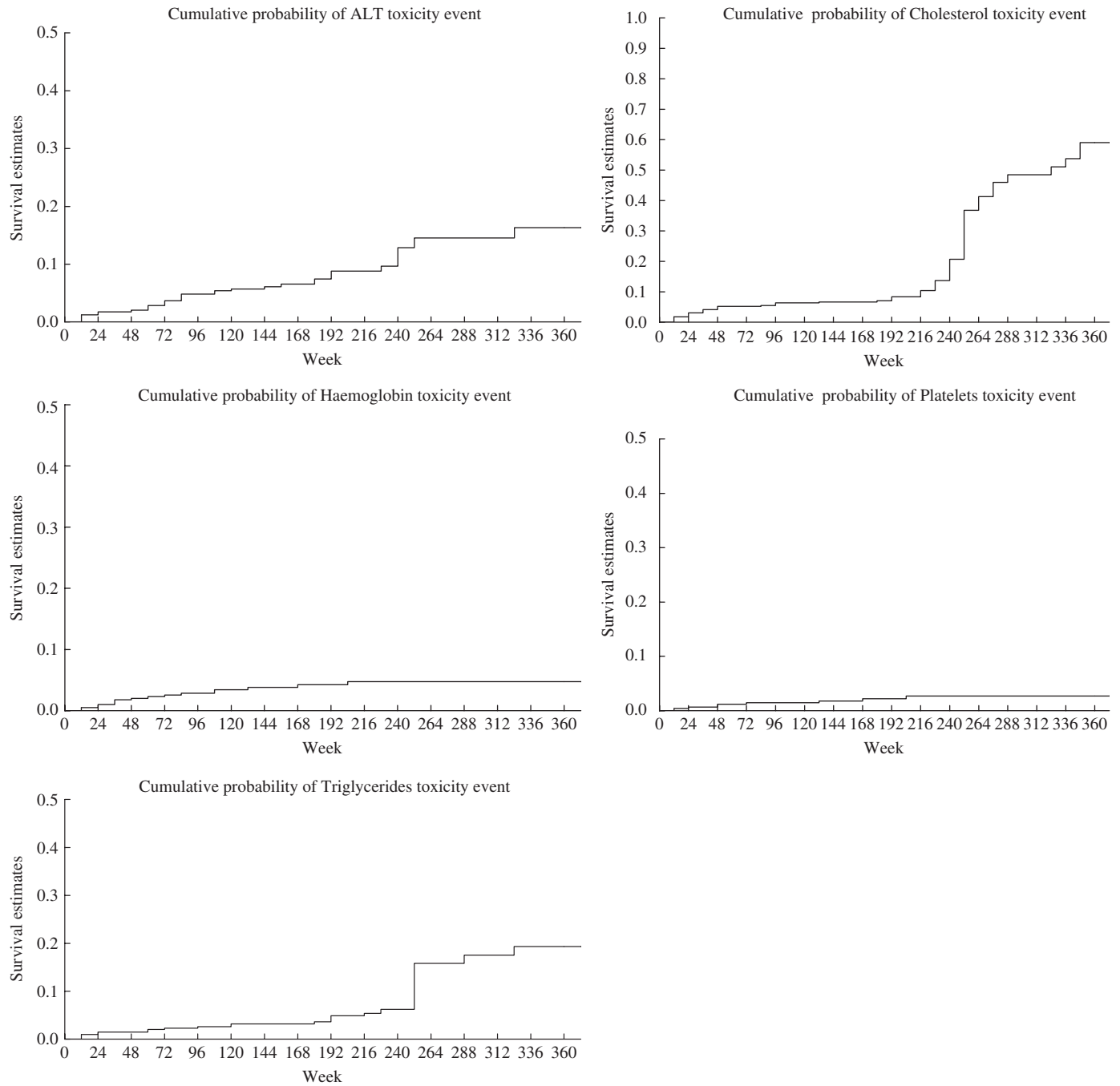


Figure 1. Occurrence of grade III/IV toxicity over time shown with Nelson Aalen's plots.

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	–	–	–	–

^aMultiple mentioning.

^bToxicity 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 from 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.

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