



# Severe hepatotoxicity in a large cohort of Thai HIV-infected patients enrolled in HIV-NAT antiretroviral therapy trials



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## Introduction

Hepatotoxicity is emerging as a major issue for people with HIV infection commenced on antiretroviral therapy. Seropositivity for HBV surface antigen (HBsAg) and HCV antibodies (anti-HCV), as well as a high pretreatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level, have been reported as risk factors for HAART-induced hepatotoxicity.

The incidence and predictors of hepatotoxicity require further examination, particularly in non-Caucasian and developing country populations.

## Method

Hepatotoxicity was examined within a cohort of Thai HIV-infected patients enrolled in eight HIV-NAT randomised controlled trials. All patients (n = 692) received at least two nucleoside analogue reverse transcriptase inhibitors (NRTI), while 135 received a protease inhibitor (PI)-containing regimen and 215 received a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI)-containing regimen.

Severe hepatotoxicity was defined as an increase in ALT level to 5 times the upper limit of normal. Liver function tests were available at baseline and weeks 4, 8, 12, 24, 36, and 48.

Serological testing for HBsAg and anti-HCV was performed retrospectively on stored baseline samples by enzyme-linked immunosorbent assay (Cobas Core EIA, Roche Diagnostic Systems, Branchburg, New Jersey, USA) within the entire cohort.

## Results

Mean age was 32.3 years, 52% were male, 11% had CDC class C HIV disease at baseline, and 22% had received prior antiretroviral therapy. Prevalence of HBsAg and anti-HCV was 9.1% (n = 63) and 7.7% (n = 53) respectively. Baseline median ALT levels were comparable across patient groups stratified by hepatitis serological status (table 1).

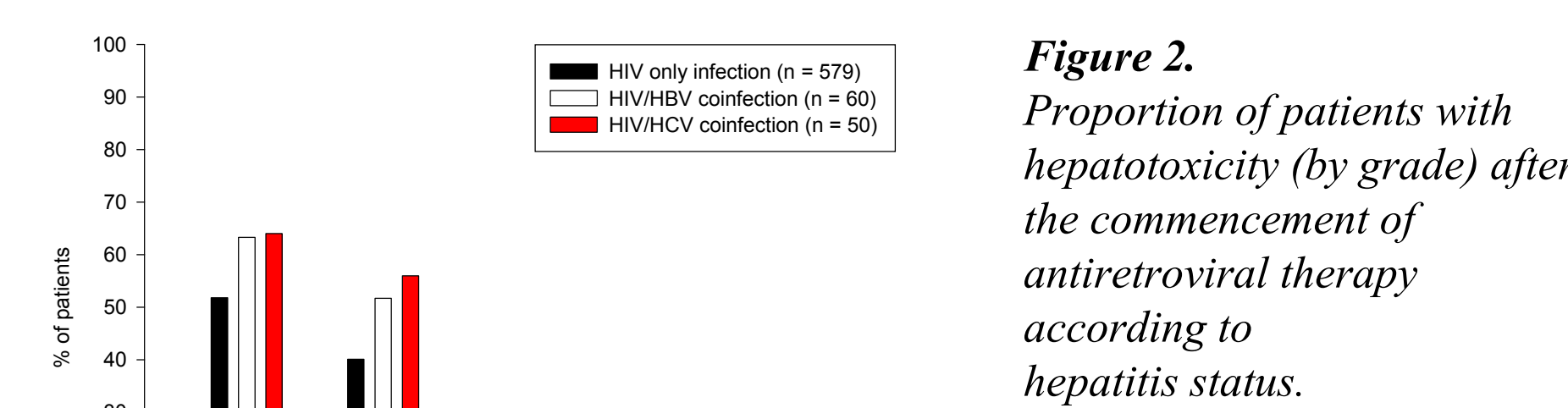
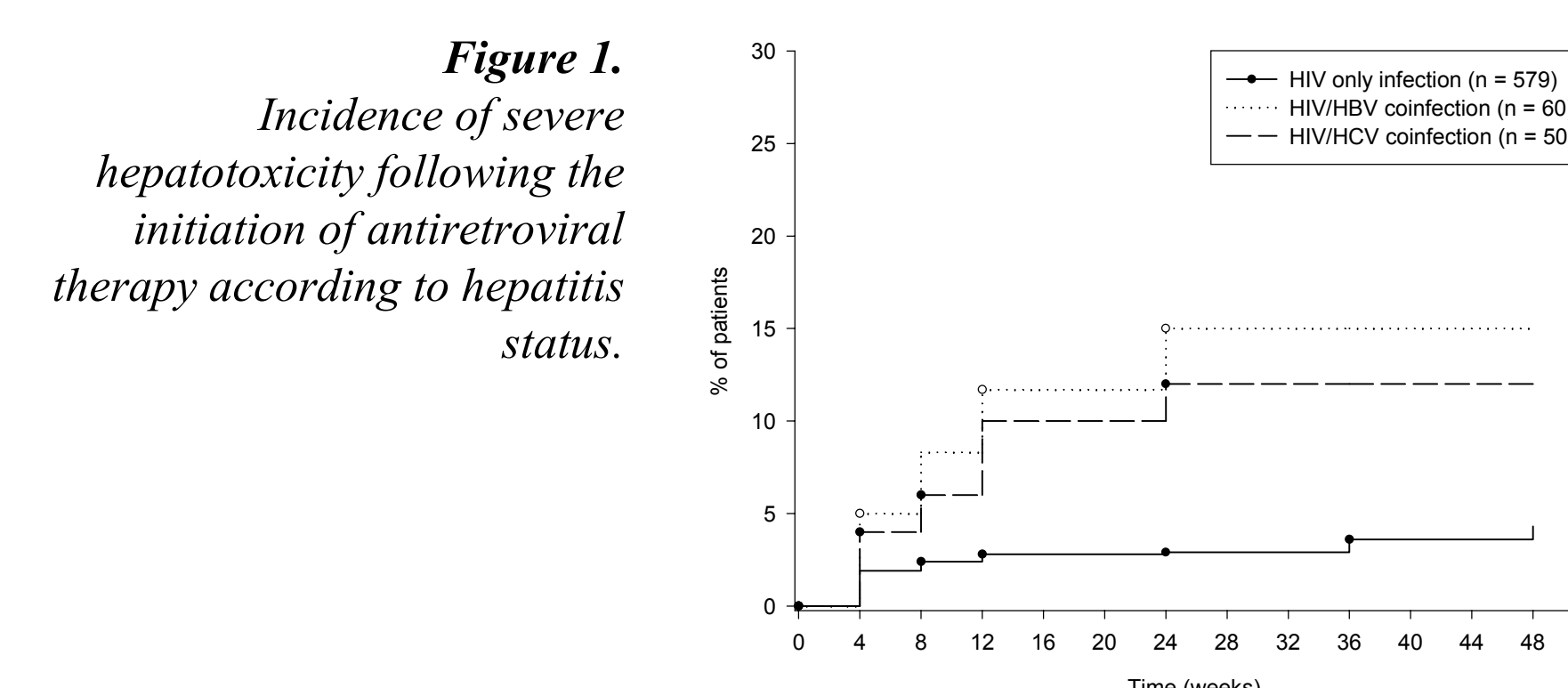
Baseline characteristic	All	HBsAg – anti-HCV –	HBsAg + anti-HCV –	HBsAg – anti-HCV +
Patients [n (%)]	692 (100%)	579 (84%)	60 (9%)	50 (7%)
Age (years) [mean (SD)]	32.3 (7.1)	32.2 (7.1)	31.9 (5.8)	34.0 (7.8)
Sex [n (%)]				
Male	361 (52%)	290 (50%)	33 (55%)	36 (72%)
Female	331 (48%)	289 (50%)	27 (45%)	14 (28%)
Risk group for HIV infection [n (%)]				
Heterosexual	600 (87%)	509 (88%)	53 (88%)	35 (70%)
Homosexual	98 (14%)	80 (14%)	9 (15%)	9 (18%)
Blood recipient	5 (1%)	2 (< 1%)	0 (0%)	3 (6%)
Injecting drug use	5 (1%)	0 (0%)	0 (0%)	5 (10%)
Unknown/other	17 (2%)	15 (3%)	1 (2%)	1 (2%)
CDC class [n (%)]				
A	362 (52%)	305 (53%)	32 (53%)	23 (46%)
B	255 (37%)	220 (38%)	13 (22%)	21 (42%)
C	75 (11%)	54 (9%)	15 (25%)	6 (12%)
Weight (kg) [mean (SD)]	57.6 (10.8)	57.7 (10.7)	56.8 (11.4)	58.7 (10.95)
CD4 cell count ( $\times 10^6/L$ ) [median (IQR)]	260 (140-390)	256 (140-387)	270 (134-407)	317 (175-462)
CD8 cell count ( $\times 10^6/L$ ) [median (IQR)]	880 (624-1218)	832 (624-1203)	967 (585-1284)	1037 (758-1387)
HIV RNA undetectable prior to start of study [n (%)]	72 (10%)	58 (10%)	8 (13%)	6 (12%)
HIV RNA ( $\log_{10}$ copies/mL) [median (IQR)]	4.4 (3.7-4.9)	4.4 (3.8-5.0)	4.3 (3.5-4.8)	4.5 (3.4-4.9)
ARV therapy prior to start of study [n (%)]				
Naive	540 (78%)	455 (79%)	45 (75%)	37 (74%)
Experienced	152 (22%)	124 (21%)	15 (25%)	13 (26%)
Liver enzymes (U/L) [median (IQR)]				
ALT	23 (15-37)	22 (15-36)	29 (18-39)	29 (17-54)
AST	25 (20-35)	24 (19-34)	26 (22-38)	29 (23-48)
GGT	29 (17-51)	29 (17-50)	30 (16-45)	45 (27-87)
ALP	69 (56-86)	67 (55-86)	70 (58-89)	82 (68-111)
TBili	2.85 (0.62-6.70)	2.80 (0.60-6.30)	4.15 (0.65-8.43)	1.62 (0.69-7.15)
DBili	1.50 (0.21-2.70)	1.50 (0.20-2.60)	2.10 (0.26-3.55)	1.50 (0.26-3.30)

Table 1. Baseline demographic and clinical characteristics.

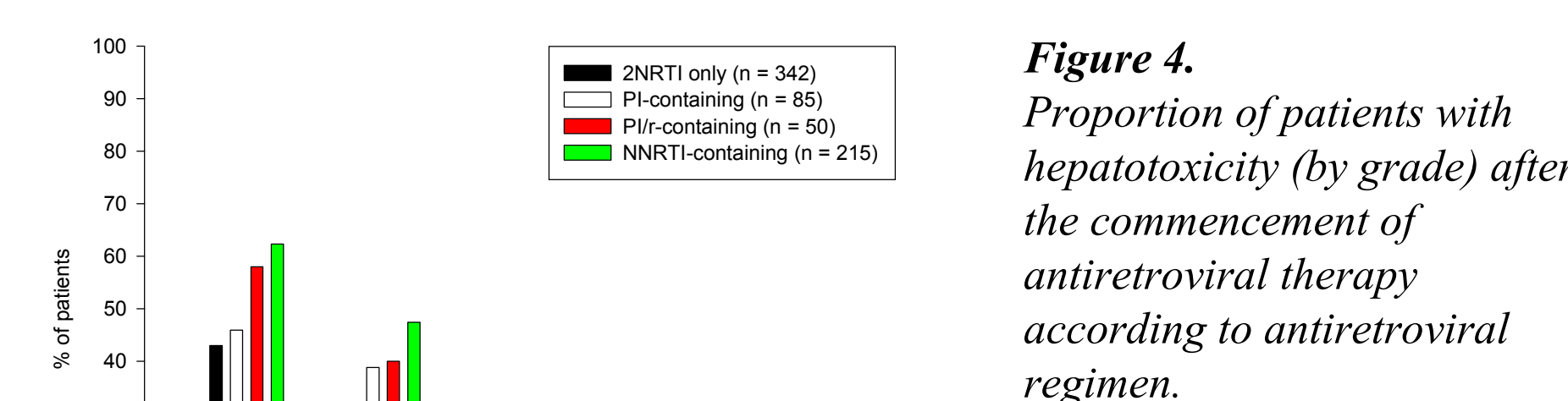
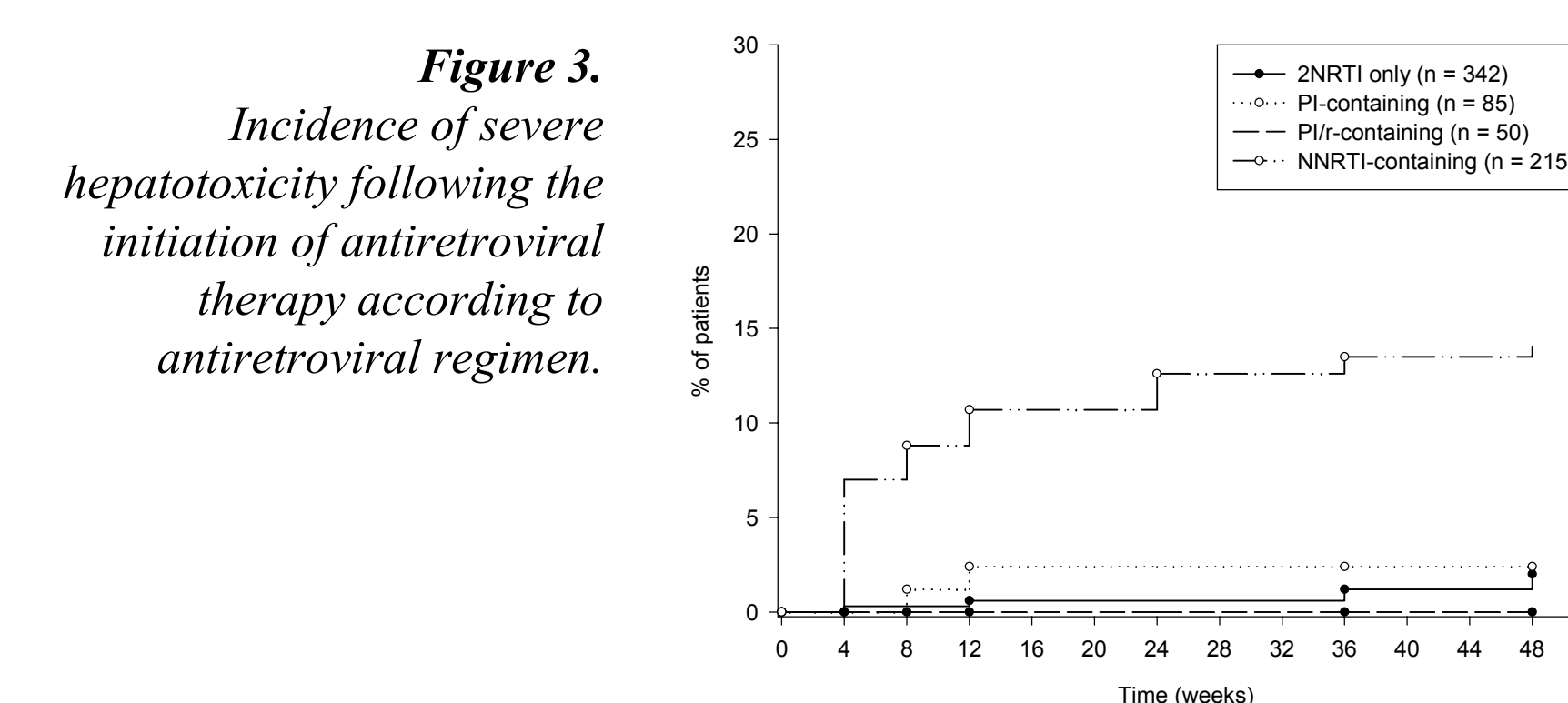
Incidence of severe hepatotoxicity was 6.1/100 person-years (py) (95% CI, 4.3-8.3), but was significantly higher for HIV/HBV (15.3/100 py; 95% CI, 7.0-29.0) and HIV/HCV (13.3/100 py; 95% CI, 4.9-29.1) coinfecting patients. Median time to severe hepatotoxicity was 56 days and was similar for the three groups (table 2, figures 1 and 2).

Hepatitis serological status	Persons exposed	Cases	Time exposed (person-years)	Cases/100 person-years (95% CI)	Time to LEE (days) [median (IQR)]
HBsAg –, anti-HCV –	579	25	552	4.5 (2.9-6.7)	56 (28-252)
HBsAg +, anti-HCV –	60	9	59	15.3 (7.0-29.0)	56 (28-126)
HBsAg –, anti-HCV +	50	6	45	13.3 (4.9-29.1)	70 (28-105)
All	692	40	659	6.1 (4.3-8.3)	56 (28-168)

Table 2. Incidence and median time to development of severe hepatotoxicity according to hepatitis serological status.



Incidence of severe hepatotoxicity was significantly higher among patients receiving NNRTI-containing regimens (14.1/100 py; 95% CI, 9.5-20.1) compared with 2NRTI-containing regimens (6.1/100 py; 95% CI, 4.8-8.3), protease inhibitor (PI)-containing regimens (2.1/100 py; 95% CI, 0.3-7.7) or PI/low dose ritonavir-containing regimens (0.0/100 py; 95% CI, 0.0-7.4) (table 3, figures 3 and 4).



Antiretroviral regimen	Persons exposed	Cases	Time exposed (person-years)	Cases/100 person-years (95% CI)	Time to LEE (days) [median (IQR)]
2NRTI only	342	7	323	2.2 (0.9-4.5)	252 (168-336)
PI-containing	85	2	94	2.1 (0.3-7.7)	70 (56-84)
PI/r-containing	50	0	45	0.0 (0.0-7.4)	—
NNRTI-containing	215	30	213	14.1 (9.5-20.1)	28 (28-84)
All	692	40	659	6.1 (4.3-8.3)	56 (28-168)

Table 3. Incidence and median time to development of severe hepatotoxicity according to antiretroviral regimen.

These findings were confirmed by univariate Cox regression analyses (table 4).

Predictor	Relative risk (95% CI)	P
Baseline characteristics		
Age $\geq 30$ years	1.51 (0.75-3.02)	0.25
Male sex	1.57 (0.81-3.03)	0.18
Hepatitis serological status		
HBsAg –, anti-HCV –	1	
HBsAg +, anti-HCV –	3.91 (1.73-8.83)	0.001
HBsAg –, anti-HCV +	3.02 (1.18-7.75)	0.02
Risk group for HIV infection		
Heterosexual	1	
Homosexual	1.27 (0.57-2.84)	0.55
AIDS status		
CD4 cell count $\geq 250 \times 10^6$ cells/L	0.48 (0.23-0.95)	0.05
CD8 cell count $\geq 750 \times 10^6$ cells/L	0.98 (0.50-1.91)	0.96
HIV RNA undetectable	0.21 (0.03-1.55)	0.13
Naive to ARV therapy	3.65 (1.11-11.99)	0.03
ARV therapy		
2NRTI only	1	
PI-containing	1.01 (0.21-4.83)	0.99
PI/ritonavir-containing	1.17 (0.58-2.29)	0.70
NNRTI-containing	6.78 (3.04-15.07)	0.0001
Alanine aminotransferase > ULN	1.19 (0.57-2.49)	0.65
Follow-up characteristics		
CD4 cell increase $\geq 100 \times 10^6$ cells/L	1.07 (0.52-2.18)	0.86
CD8 cell increase $\geq 200 \times 10^6$ cells/L	1.03 (0.54-1.98)	0.92

Table 4. Relative risks of severe hepatotoxicity after the commencement of antiretroviral therapy for all patients.

## Conclusion

Incidence of severe hepatotoxicity among Thai HIV-infected patients receiving antiretroviral therapy appears similar to other racial groups. The highest risk of severe hepatotoxicity was among patients with HIV/viral hepatitis coinfection and those receiving NNRTIs. A combination of immune reconstitution reactivation of viral hepatitis and direct therapeutic toxicity may explain these findings.