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HEPATOLOGY

Hepatitis B and C virus coinfection in The TREAT Asia HIV Observational Database

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Abstract

Background and Aim: Most studies of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection with HIV have been conducted among Western patient populations. This study aims to assess rates of HBV and HCV coinfection, and their impact on response to antiretroviral therapy and mortality, using data from The TREAT Asia HIV Observational Database (TAHOD), a multi-center cohort of patients with HIV in the Asia–Pacific region.

Methods: Patients who had been tested either HBV surface antigen (HBsAg) or HCV antibody were included. Patients who ever tested positive for HBV or HCV were regarded as coinfected for the duration of the study.

Results: Results of hepatitis tests were available for 55% (HBV) and 49% (HCV) of 2979 TAHOD patients, with prevalence of HBV and HCV coinfection both at approximately 10%. Mean CD4 change at 180 days after antiretroviral treatment initiation was 118.8 cells/μL and patients with either HBV or HCV had a lower but non-significant CD4 increase compared with patients with HIV only. Median time to reach undetectable viral load (<400 copies/mL) was 148 days and was not independently associated with HBV or HCV. In univariate analysis, patients with HCV had increased mortality (unadjusted hazard ratio, HR 2.80, $P = 0.007$). However, neither HBV (adjusted HR 0.80, 95% confidence interval CI 0.24–2.64, $P = 0.710$) nor HCV (adjusted HR 1.06, 95% CI 0.40–2.79, $P = 0.905$) was associated with increased mortality after adjustment for other covariates. Both HBV and HCV remained independently associated with elevated alanine aminotransferase (ALT) in the multivariate model (HBV, adjusted HR 1.94, 95% CI 1.04–3.62, $P = 0.037$; HCV, adjusted HR 2.74, 95% CI 1.47–5.12, $P = 0.002$).

Conclusion: The impact of hepatitis coinfection on immunological and virological responses to antiretroviral therapy and HIV disease progression among this Asian cohort are similar to that seen in Western countries. The longer-term impact of hepatitis coinfection on both HIV disease and liver disease morbidity and mortality needs to be monitored.

Introduction

Infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the 10 leading causes of death from infectious disease.[1] Worldwide, it is estimated that there are 40 million people living with HIV, 370 million people with chronic HBV infection and 130 million with chronic HCV infection.[2–4] Among HIV patient populations, HBV and HCV are more prevalent due to overlapping transmission routes.[5] The introduction of highly active antiretroviral therapy (HAART) has led to a marked reduction of morbidity and mortality in HIV-infected patients,[6,7] with subsequently increased importance of comorbidities such as chronic liver disease.[8,9]

The impact of viral hepatitis coinfection on HIV natural history remains uncertain. There is conflicting evidence regarding the effect of HBV and HCV on HIV disease progression and survival. Injecting drug use is a potential confounder in the case of HCV. Some studies have suggested poorer outcomes in coinfected patients,[10,11] while other studies have not.[12,13] HIV/HCV coinfection appears to be associated with a slightly poorer immunological response to antiretroviral treatment, but immunological responses appear unaffected by HBV coinfection, and virological responses are unaffected by HCV or HBV coinfection.[13–19] HIV increases HBV- and HCV-related liver disease progression and coinfected patients receiving HAART have increased risk of hepatotoxicity.[9,20,21]

Most studies of HIV/HBV and HIV/HCV coinfection have been conducted among Western patient populations. Understanding HBV and HCV coinfection with HIV is particularly important in Asian countries due to high background HBV and HCV prevalence,[5] and the significant role injecting drug use plays in transmission of HIV in the region.[22] Using data from The TREAT Asia (Therapeutic Research, Education and AIDS Training in Asia) HIV Observational Database (TAHOD), a multicenter, prospective cohort, the impact of HBV and HCV coinfection on HIV disease progression and response to antiretroviral treatment among Asian HIV-infected patients was assessed.

Methods

The TAHOD is a collaborative observational cohort study, involving 15 participating sites in 12 cities in the Asia and Pacific region (See Acknowledgments). Detailed methods are published elsewhere,[23] but briefly, each site recruited 200 patients, both treated and untreated with antiretroviral therapy. Recruitment was based on a consecutive series of patients regularly attending a given clinical site from a particular start-up time. Ethics approval for the study was obtained from the University of New South Wales Ethics Committee and from a local ethics committee for each participating TAHOD site.

The following data were collected: (i) patient demographics and baseline data: date of the clinical visit, age, sex, ethnicity, exposure category, date of first positive HIV test, HIV-1 subtype, and date and result of hepatitis B, hepatitis C and syphilis serology; (ii) stage of disease: CD4 and CD8 count, HIV viral load, prior and new AIDS defining illnesses, date and cause of death; (iii) treatment history: prior and current prescribed antiretroviral treatments, reason for treatment changes (e.g. treatment failure, clinical failure and adverse events) and prophylactic treatments for opportunistic infections. Coinfection with HBV was defined as the detection of HBV surface antigen (HBsAg) and coinfection with HCV the detection of anti-HCV antibody. Patients who ever tested positive for HBV or HCV were regarded as coinfected for the duration of the study.

Factors associated with testing for HBV and/or HCV were determined by multiple logistical regression models. Patients were included if they had had either HBsAg or HCV antibody testing performed and had results available. Factors associated with positive HBsAg and positive HCV antibody were also determined by multiple logistic regression models. Immunological and virological responses to antiretroviral treatment after initiating HAART were assessed using change in CD4 count at 180 days, and time to reach HIV viral load undetectable (<400 copies/mL) after initiation of treatment. For CD4 change, patients were included if they started HAART and had CD4 count tests before (within 90 days) and at 180 days (90–270 days) after treatment initiation. Factors associated with CD4 changes were determined by multiple linear regression models. For HIV viral load, patients were included if they started HAART and had at least one subsequent HIV viral load test. Factors associated with undetectable HIV viral load were determined by Cox proportional hazards models. Patients were included in analyses of overall survival if they had at least one prospective follow-up visit. Follow up was censored at the last clinic visit for patients who survived. Factors associated with overall survival after entry to TAHOD were determined using Cox proportional hazards models. Treatment and diagnosis of Centers for Disease Control and Prevention (CDC) category B and C illnesses were included as time-dependent variables. Factors associated with elevated alanine aminotransferase (ALT) levels after initiation of HAART were determined by Cox proportional hazards models. Patients were included if they started HAART and had an ALT test before (within 90 days) and at least one assessment after starting treatment. Patients without ALT tests during follow up were excluded from analyses. Liver toxicity was defined as a follow-up ALT greater than five times upper limit of normal or three times baseline ALT. Follow up was censored at the last clinic visit for patients with no events. Antiretroviral treatment containing nevirapine, efavirenz or other drug was included as a time-dependent variable. All analyses were adjusted by clinical site.

Data were analyzed with STATA package (version 8.2, StataCorp, College Station, TX, USA). Statistical significance was taken as $P < 0.05$ (two-sided). Multivariate models considered for inclusion all variables that were $P < 0.10$ in univariate analyses, and were developed using forward stepwise methods. Non-significant variables were also presented and adjusted for final multivariate models.

Results

By December 2005, a total of 2979 patients have been recruited to TAHOD. HBsAg and HCV antibody tests were available for 1641 (55%) and 1469 (49%) patients, respectively. A total of 1731 patients had test for either HBsAg or HCV antibody. The majority were male (73%), with a median age of 37 years (range 18–83). Chinese (44%) and Thai (19%) were the main ethnic groups. Most patients reported HIV infection through heterosexual (59%) and homosexual contact (23%); only 5% through injecting drug use.

Hepatitis tests vary from less than 10% to more than 90% across TAHOD sites. After adjustment for sites, HBsAg testing was less likely if baseline CD4 count was less than 50 cells/μL (compared with baseline CD4 =50 cells/μL, odds ratio [OR] 0.72, 95% confidence interval [95% CI] 0.53–0.99, $P = 0.042$) or HIV viral load greater than 10 000 copies/mL (compared with HIV viral load <400 copies/mL, OR 0.69, 95% CI 0.50–0.96, $P = 0.029$); HCV antibody testing was more likely if HIV infection was reported through injecting drug use (compared with heterosexual contact, OR 1.68, 95% CI 1.03–2.77, $P = 0.039$).

HBsAg was positive in 171 patients (10.4%) and HCV antibody positive in 153 patients (10.4%). HBsAg and HCV antibody tests were both available in 1379 patients, with an HBV prevalence of 10.4% and HCV 9.6%. There were 15 patients (1.1% of the 1379 patients) who were positive for both HBsAg and HCV antibody. Table 1 summarizes the factors associated with HBV or HCV coinfection. After adjustment for sites, HBsAg-positive patients were more likely to report HIV infection through homosexual contact and were marginally older; HCV antibody-positive patients were more likely to report HIV infection through injecting drug use, donating or receiving blood or blood products and other or unknown reasons (excluding homosexual contact). At entry to TAHOD, there were no differences in HIV disease stage, CD4 counts and HIV viral load according to hepatitis coinfection status.

Nearly one in five of patients coinfected with either HBV (37 of 171, 22%) or HCV (32 of 153, 21%) have not started antiretroviral therapy. In coinfected patients who started treatment, stavudine

Table 1 Factors associated with HBV or HCV coinfection

	HBsAg testing						HCV antibody testing					
	No.	No. positive (%)	Univariate		Multivariate†		No.	No. positive (%)	Univariate		Multivariate†	
			OR	*P*	OR (95% CI)	*P*			OR	*P*	OR (95% CI)	*P*
Total	1 641	171 (10.4)					1 469	153 (10.4)				
Gender												
Male	1 191	138 (11.6)					1 097	125 (11.4)				
Female	450	33 (7.3)	0.60	0.013	0.75 (0.48, 1.17)	0.201	372	28 (7.5)	0.63	0.036	0.78 (0.46, 1.35)	0.382
Age (year)												
≤30	349	29 (8.3)					323	45 (13.9)				
31–40	724	71 (9.8)	1.20	0.430	1.32 (0.82, 2.12)	0.248	633	63 (10.0)	0.68	0.067	1.12 (0.66, 1.92)	0.665
≥41	567	71 (12.5)	1.58	0.049	1.61 (0.99, 2.60)	0.055	512	44 (8.6)	0.58	0.016	1.19 (0.67, 2.14)	0.549
Missing	1	0 (0.0)	ND	ND	ND	ND	1	1 (100.0)	ND	ND	ND	ND
Mode of infection												
Heterosexual contact	995	87 (8.7)					818	41 (5.0)				
Homosexual contact	359	50 (13.9)	1.69	0.006	1.83 (1.12, 3.00)	0.017	372	23 (6.2)	1.25	0.407	1.25 (0.62, 2.53)	0.536
Injecting drug use	68	6 (8.8)	1.01	0.982	1.12 (0.42, 3.01)	0.823	71	47 (66.2)	37.1	<0.001	24.95 (12.17, 51.13)	<0.001
Blood products	44	6 (13.6)	1.65	0.271	0.55 (0.18, 1.63)	0.277	44	31 (70.5)	45.2	<0.001	89.95 (31.58, 256.20)	<0.001
Others	219	28 (12.8)	1.50	0.110	0.69 (0.25, 1.92)	0.481	164	11 (6.7)	1.36	0.378	2.91 (1.00, 8.49)	0.050
CDC clinical classification for HIV infection at entry to TAHOD												
Category A	792	81 (10.2)					702	66 (9.4)				
Category B	201	23 (11.4)	1.13	0.615	0.99 (0.54, 1.81)	0.979	172	18 (10.5)	1.13	0.672	1.08 (0.49, 2.37)	0.849
Category C	648	67 (10.3)	1.01	0.944	1.02 (0.70, 1.48)	0.923	595	69 (11.6)	1.26	0.198	1.04 (0.64, 1.70)	0.859
CD4 Count at entry to TAHOD (cells/μL)												
≤50	120	9 (7.5)					110	16 (14.6)				
51–100	104	9 (8.7)	1.17	0.752	1.13 (0.42, 3.06)	0.806	99	12 (12.1)	0.81	0.608	0.96 (0.33, 2.77)	0.938
101–200	242	28 (11.6)	1.61	0.232	1.69 (0.74, 3.83)	0.212	225	21 (9.3)	0.60	0.156	0.95 (0.38, 2.37)	0.917
201–300	295	33 (11.2)	1.55	0.262	1.78 (0.79, 4.03)	0.167	261	25 (9.6)	0.62	0.166	1.51 (0.62, 3.69)	0.368
≥301	713	79 (11.1)	1.54	0.241	1.83 (0.84, 4.00)	0.128	642	56 (8.7)	0.56	0.058	1.45 (0.63, 3.34)	0.387
Not tested	167	13 (7.8)	1.04	0.929	1.31 (0.51, 3.31)	0.575	132	23 (17.4)	1.24	0.545	1.47 (0.56, 3.84)	0.429
HIV viral load at entry to TAHOD (copies/mL)												
<400	621	63 (10.1)					586	43 (7.3)				
400–10 000	113	12 (10.6)	1.05	0.878	0.92 (0.47, 1.81)	0.817	106	15 (14.2)	2.08	0.022	1.72 (0.81, 3.63)	0.158
≥10 001	199	18 (9.1)	0.88	0.651	0.67 (0.38, 1.21)	0.184	200	17 (8.5)	1.17	0.593	0.56 (0.26, 1.17)	0.123
Not tested	708	78 (11.0)	1.10	0.607	1.01 (0.63, 1.60)	0.979	577	78 (13.5)	1.97	0.001	1.12 (0.62, 2.01)	0.715

†Adjusted for TAHOD sites. CDC, Centers for Disease Control and Prevention; CI, confidence interval; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ND, not done; OR, odds ratio; TAHOD, The TREAT Asia HIV Observational Database.

Table 2 CD4 change at 180 days after initiation of HAART

	Mean CD4 change		SD	Univariate		Multivariate	
	No.	(cells/μL)		Difference†	*P*	Difference† (95% CI)	*P*
Total	486	118.8	121.7				
HBsAg							
Negative	385	118.6	126.5				
Positive	63	116.7	108.1	–1.9	0.910	3.6 (–28.6, 35.8)	0.825
Not tested	38	124.1	91.6	5.4	0.793	5.8 (–34.8, 46.4)	0.778
HCV antibody							
Negative	371	119.0	115.4				
Positive	43	103.7	115.9	–15.4	0.434	–8.2 (–46.5, 30.2)	0.675
Not tested	72	126.8	153.6	7.8	0.621	–2.7 (–34.1, 28.8)	0.868
Gender							
Male	364	118.6	118.9				
Female	122	119.3	130.0	0.7	0.958	–2.2 (–28.0, 24.6)	0.867
Age (year)							
≤30	89	139.1	151.8				
31–40	216	122.2	121.9	–16.9	0.269	–15.7 (–45.6, 14.2)	0.301
≥41	181	104.8	102.3	–34.3	0.029	–35.5 (–66.3, –4.8)	0.024
Mode of infection							
Heterosexual contact	350	121.3	128.2				
Homosexual contact	75	128.3	111.0	6.9	0.654	4.5 (–26.5, 35.4)	0.777
Injecting drug use	19	79.1	100.7	–42.3	0.140	–46.4 (–102.4, 9.7)	0.105
Blood products	11	67.2	59.1	–54.2	0.146	–28.7 (–101.8, 44.5)	0.442
Others	31	109.8	90.3	–11.5	0.613	–6.6 (–53.9, 40.7)	0.784
CDC clinical classification for HIV infection at treatment initiation							
Category A	230	109.9	109.9				
Category B	50	114.7	176.8	4.8	0.801	15.4 (–21.9, 52.7)	0.418
Category C	206	129.8	117.7	19.9	0.088	37.2 (12.6, 61.7)	0.003
CD4 Count before initiation of treatment (cells/μL)							
≤50	187	108.2	84.9				
51–100	69	93.0	83.9	–15.3	0.371	–8.3 (–42.1, 25.4)	0.628
101–200	132	132.1	136.3	23.9	0.083	37.7 (9.2, 66.1)	0.010
201–300	61	148.6	137.7	40.2	0.024	56.6 (20.3, 92.9)	0.002
≥301	37	124.0	213.6	15.8	0.468	33.0 (–11.2, 77.2)	0.143
HIV viral load at treatment initiation							
<400	14	61.0	94.9				
400–10 000	13	100.6	138.8	39.6	0.398	38.7 (–52.0, 129.5)	0.402
≥10 001	236	119.1	113.4	58.1	0.083	63.9 (–1.3, 129.2)	0.055
Not tested	223	123.1	130.0	62.1	0.064	64.4 (–1.0, 129.7)	0.053

†Differences were compared with the first category of each variable. CDC, Centers for Disease Control and Prevention; CI, confidence interval; HAART, highly active antiretroviral therapy; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; SD, standard deviation.

(d4T) + lamivudine (3TC) + nevirapine (NVP; 16% in HBV and 18% in HCV positive patients, respectively) and zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV; 13% in HBV and 15% in HCV positive patients, respectively) were the most frequently use treatment combinations, regardless of patient's hepatitis status.

Data for mean CD4 change at 180 days after initiation of HAART were available for a total of 486 patients who had been tested for either HBsAg or HCV antibody. In univariate analysis (Table 2), patients with HBV had similar mean CD4 change compared with HBV-negative patients (117 *vs* 119 cells/μL, $P = 0.91$), while patients with HCV had a slightly lower mean CD4 change compared with HCV-negative patients (104 *vs* 119 cells/μL, $P = 0.43$). These differences remained non-significant after adjustment for independent predictors. Mean CD4 changes at 360 days after treatment initiation were also similar for hepatitis-coinfected and HIV-mono-infected patients (HBV positive *vs* negative, 164 *vs* 160 cells/L, $P = 0.89$; HCV positive *vs* negative, 141 *vs* 166 cells/L, $P = 0.39$). These differences remained non-significant after adjustment for independent variables.

Time to undetectable HIV viral load after initiation of HAART was assessable in 405 patients who had been tested for either HBsAg or HCV antibody (Table 3). Similar to immunological responses, there were no clear differences between patients with or without hepatitis (median days reaching undetectable viral load: HBV-positive patients *vs* HBV-negative patients, 146 days *vs* 148 days, $P = 0.860$; HCV-positive patients *vs* HCV-negative patients, 148 days *vs* 144 days, $P = 0.427$). The effect of coinfection remained non-significant after adjustment for independent predictors.

Table 3 Time to undetectable HIV viral load after initiation of HAART

	No. patients	No. reach undetectable viral load	Rate (/100 pys)	Median days reaching undetectable viral load	Univariate		Multivariate	
					HR	*P*	HR (95% CI)	*P*
Total	405	379	117.2	148.0				
HBsAg								
Negative	319	299	116.8	148.0				
Positive	54	52	123.2	145.5	1.03	0.860	1.14 (0.84, 1.54)	0.413
Not tested	32	28	112.0	135.0	0.93	0.733	0.98 (0.64, 1.49)	0.907
HCV antibody								
Negative	320	304	127.6	143.5				
Positive	40	35	112.6	148.0	0.87	0.427	0.95 (0.64, 1.40)	0.780
Not tested	45	40	74.0	182.5	0.66	0.013	0.73 (0.52, 1.04)	0.083
Gender								
Male	303	282	123.6	135.0				
Female	102	97	101.9	175.0	0.83	0.116	0.83 (0.64, 1.07)	0.154
Age (year)								
≤30	71	67	121.1	144.0				
31–40	175	166	112.8	166.5	0.91	0.522	0.94 (0.70, 1.25)	0.655
≥41	159	146	120.8	133.5	0.99	0.971	1.09 (0.81, 1.47)	0.574
Mode of infection								
Heterosexual contact	294	278	113.8	161.0				
Homosexual contact	74	71	142.2	135.0	1.18	0.209	0.99 (0.75, 1.30)	0.953
Injecting drug use	16	15	207.4	109.0	1.68	0.052	1.27 (0.74, 2.17)	0.392
Blood products	9	6	81.6	95.0	0.75	0.494	0.77 (0.34, 1.74)	0.522
Others	12	9	61.8	176.0	0.57	0.098	0.46 (0.24, 0.91)	0.025
CDC clinical classification for HIV infection at treatment initiation								
Category A	205	198	153.8	132.0				
Category B	29	24	72.6	203.0	0.50	0.001	0.59 (0.39, 0.88)	0.011
Category C	171	157	97.2	181.0	0.64	<0.001	0.73 (0.58, 0.92)	0.008
CD4 Count before initiation of treatment (cells/μL)								
≤50	158	143	99.3	168.0				
51–100	54	50	104.6	156.5	1.02	0.905	0.97 (0.70, 1.34)	0.841
101–200	113	107	125.8	148.0	1.21	0.142	1.16 (0.88, 1.53)	0.293
201–300	46	45	158.2	119.0	1.53	0.014	1.39 (0.98, 1.99)	0.068
≥301	34	34	188.6	129.0	1.71	0.005	1.54 (1.03, 2.29)	0.034
HIV viral load at treatment initiation								
≥10 001	227	210	135.5	112.0				
400–10 000	13	12	135.7	107.5	0.96	0.891	1.08 (0.59, 1.96)	0.805
≤400	14	14	184.3	130.0	1.48	0.150	1.64 (0.95, 2.84)	0.076
Not tested	151	143	94.1	210.0	0.70	0.001	0.68 (0.55, 0.85)	0.001

Rate: per 100 person-years (pys). Undetectable HIV viral load: <400 copies/mL. CDC, Centers for Disease Control and Prevention; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HR, hazard ratio.

A total of 1372 patients, who had been tested for either HBsAg or HCV antibody, contributed 1913 person-years of prospective follow up (median follow up 1.55 years, interquartile IQR 0.99–1.83 years). During this time 46 patients died, an overall mortality of 2.40 per 100 person-years (Table 4). Of these, 27 (59%) deaths were reported to be directly attributable to HIV/AIDS. During the study period, no patient was reported to have died of liver-related disease. In univariate analysis, mortality was higher in patients whose mode of infection was blood products and unknown or others, patients who had lower CD4 counts, and patients with a higher HIV viral load at entry to TAHOD. Diagnoses of AIDS-defining illnesses significantly increased overall mortality. Patients receiving HAART had a significantly improved survival. Patients with HBV had similar mortality to patients without HBV (1.72 *vs* 2.38 per 100 person-years, unadjusted HR 0.72, $P = 0.58$), however, in univariate analyses patients with HCV had significantly higher mortality than patients without HCV (5.89 *vs* 2.05 per 100 person-years, unadjusted HR 2.80, $P = 0.007$). The effect of HCV coinfection on survival lost statistical significance after adjustment for independent risk factors (adjusted HR 1.06, 95% CI 0.40–2.79, $P = 0.91$). The effect of HBV coinfection remained non-significant (adjusted HR 0.80, 95% CI 0.24–2.64, $P = 0.71$).

A total of 362 patients who had been tested for either HBsAg or HCV antibody had an ALT test within 90 days of HAART initiation. During 723 years of follow up, 66 patients had an elevated ALT test (five times upper limit of normal [ULN], or three times baseline level), a rate of 9.12 per 100 person-years (Table 5). In univariate analysis, patients with HBV had marginally higher rate

Table 4 Overall survival after entry to TAHOD

	No. patients	Person-years	No. death	Rate (/100 pys)	Univariate		Multivariate	
					HR	*P*	HR (95% CI)	*P*
Total	1372	1913.1	46	2.40				
HBsAg								
Negative	1168	1641.7	38	2.38				
Positive	126	174.9	3	1.72	0.72	0.578	0.80 (0.24, 2.64)	0.710
Not tested	78	96.5	4	4.15	1.66	0.335	1.17 (0.40, 3.46)	0.777
HCV antibody								
Negative	1020	1414.3	29	2.05				
Positive	124	152.9	9	5.89	2.80	0.007	1.06 (0.40, 2.79)	0.905
Not tested	228	345.9	8	2.31	1.14	0.740	0.86 (0.38, 1.93)	0.706
Gender								
Male	1016	1391.3	33	2.37				
Female	356	521.8	13	2.49	1.07	0.838	1.38 (0.68, 2.78)	0.373
Age (year)								
≤30	277	353.3	11	3.11				
31–40	619	881.9	15	1.70	0.56	0.142	0.57 (0.25, 1.30)	0.182
≥41	476	677.9	20	2.95	0.98	0.947	1.10 (0.50, 2.39)	0.816
Mode of infection								
Heterosexual contact	918	1403.0	24	1.71				
Homosexual contact	292	316.1	7	2.21	1.24	0.623	2.06 (0.86, 4.93)	0.103
Injecting drug use	77	96.6	6	6.21	3.42	0.007	2.04 (0.81, 5.13)	0.130
Blood product	33	36.1	5	13.86	7.87	<0.001	5.99 (2.18, 16.46)	0.001
Others	52	61.4	4	6.51	3.69	0.016	2.99 (0.99, 9.06)	0.052
CDC clinical classification for HIV infection								
Category A	***	920.8	17	1.85				
Category B	***	164.3	6	3.65	1.98	0.151	2.79 (1.02, 7.64)	0.045
Category C	***	828.0	23	2.78	1.51	0.194	1.99 (0.96, 4.10)	0.063
Antiretroviral treatment								
No treatment	***	367.4	19	5.17				
Mono/double treatment	***	59.6	3	5.03	0.98	0.969	0.66 (0.19, 2.33)	0.523
Triple or more treatment	***	1486.1	24	1.62	0.33	<0.001	0.30 (0.16, 0.58)	<0.001
CD4 Count before initiation of treatment (cells/μL)								
≤50	90	123.9	10	8.07				
51–100	77	104.9	5	4.77	0.60	0.353	0.60 (0.20, 1.81)	0.364
101–200	193	282.3	6	2.13	0.27	0.001	0.31 (0.11, 0.86)	0.025
201–300	254	352.7	5	1.42	0.18	0.002	0.22 (0.07, 0.67)	0.008
≥301	606	854.4	6	0.70	0.09	<0.001	0.10 (0.03, 0.28)	<0.001
Not tested	152	194.9	14	7.18	0.89	0.787	0.82 (0.35, 1.90)	0.644
HIV viral load at entry to TAHOD								
<400	565	798.6	7	0.88				
400–10 000	105	140.2	1	0.71	0.82	0.854	0.58 (0.07, 4.81)	0.617
≥10 001	178	227.3	11	4.84	5.44	<0.001	1.73 (0.61, 4.91)	0.305
Not tested	524	747.0	27	3.61	4.12	0.001	1.36 (0.53, 3.50)	0.526

***Time-dependent variable, patients can contribute person-time to more than one category.

Rate: per 100 person-years (pys). CDC, Centers for Disease Control and Prevention; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HR, hazard ratio; TAHOD, The TREAT Asia HIV Observational Database.

of elevated ALT (unadjusted HR 1.80, $P = 0.061$) and patients with HCV had a significantly higher rate (unadjusted HR 2.41, $P = 0.004$). The experience of antiretroviral treatment containing nevirapine, efavirenz or other drugs did not have a significant impact on the rate of elevated ALT. Both HBV and HCV remained significantly associated with elevated ALT in the multivariate model.

Discussion

Hepatitis testing data are available in nearly half of the TAHOD patients, with prevalence of HBV and HCV coinfection each at approximately 10%. Choice of HAART regimen did not seem to be influenced by hepatitis status. Immunological and virological responses to antiretroviral treatment were similar among patients

Table 5 Rates of elevated liver enzyme test after initiation of HAART

	No. patients	Person-years	No. events	Rate (/100 pys)	Univariate		Multivariate	
					HR	*P*	HR (95% CI)	*P*
Total	362	723.2	66	9.13				
HBsAg								
Negative	285	563.3	46	8.71				
Positive	42	92.4	13	14.07	1.80	0.062	1.94 (1.04, 3.62)	0.037
Not tested	35	65.5	7	10.38	1.23	0.604	1.09 (0.48, 2.46)	0.833
HCV antibody								
Negative	276	580.6	46	7.92				
Positive	49	63.2	14	22.15	2.40	0.005	2.74 (1.47, 5.12)	0.002
Not tested	37	79.4	6	7.56	0.99	0.983	0.91 (0.38, 2.16)	0.826
Gender								
Male	281	578.5	56	9.68				
Female	81	144.7	10	6.91	0.68	0.263	0.77 (0.39, 1.53)	0.461
Age (year)								
≤30	91	163.9	24	14.64				
31–40	157	334.8	27	8.06	0.58	0.055	0.53 (0.30, 0.92)	0.024
≥41	114	224.4	15	6.68	0.47	0.021	0.38 (0.20, 0.74)	0.004
Mode of infection								
Heterosexual contact	211	474.0	35	7.38				
Homosexual contact	77	192.5	16	8.31	1.13	0.685	0.92 (0.49, 1.71)	0.783
Injecting drug use	25	28.7	9	31.40	3.44	0.001	2.27 (0.91, 5.67)	0.080
Blood products	19	9.6	4	41.54	3.38	0.023	2.63 (0.79, 8.80)	0.115
Others	30	18.5	2	10.84	0.88	0.861	0.85 (0.20, 3.61)	0.824
CDC clinical classification for HIV infection at treatment initiation								
Category A	148	311.6	33	10.59				
Category B	38	68.8	2	2.91	0.27	0.071	0.35 (0.08, 1.48)	0.154
Category C	176	342.7	31	9.04	0.85	0.530	0.85 (0.51, 1.41)	0.523
CD4 Count before initiation of treatment (cells/μL)								
≤50	130	262.8	22	8.37				
51–100	47	84.3	10	11.87	1.38	0.402	1.43 (0.67, 3.07)	0.356
101–200	79	150.7	12	7.96	0.92	0.820	0.94 (0.46, 1.94)	0.874
201–300	36	73.4	8	10.91	1.28	0.553	1.27 (0.56, 2.89)	0.570
≥301	19	46.2	5	10.83	1.36	0.531	1.38 (0.51, 3.76)	0.529
Not tested	31	105.9	9	8.50	1.01	0.989	0.92 (0.42, 2.04)	0.836
HIV viral load at treatment initiation								
≥10 001	159	363.8	33	9.07				
400–10 000	13	31.4	2	6.36	0.71	0.633	1.23 (0.37, 4.06)	0.739
<400	12	26.6	3	11.28	1.16	0.803	0.76 (0.18, 3.21)	0.710
Not tested	178	301.3	28	9.29	0.92	0.750	0.92 (0.55, 1.54)	0.739
Antiretroviral treatment (ARV)								
ARV containing NVP	***	201.4	19	9.43				
ARV containing EFV	***	319.5	29	9.08	1.08	0.801	1.07 (0.58, 1.97)	0.833
Others	***	202.3	18	8.90	1.20	0.587	1.12 (0.57, 2.19)	0.750

***Time-dependent variable, patients can contribute person-time to more than one category.

Rate: per 100 person years (pys). Hepatotoxicity: alanine aminotransferase > five times upper limit of normal or three times of baseline level.

CDC, Centers for Disease Control and Prevention; CI, confidence interval; EFV, efavirenz; HAART, highly active antiretroviral therapy; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HR, hazard ratio; NVP, nevirapine; TAHOD, The TREAT Asia HIV Observational Database.

with and without hepatitis, and hepatitis coinfection status had no independent effect on survival. Coinfection with HBV or HCV, however, was independently associated with elevated ALT levels in patients on HAART.

Estimated prevalence of HBV is high in the Asia–Pacific region, with at least 8% of the population chronically infected and 70–90% having serological evidence of previous HBV infection.[5] HCV prevalence in this region is estimated to be 2.0–2.9% of the general population.[5] The prevalence of HBV or HCV coinfection observed in our study is similar to a Thai HIV-infected cohort which reported HBV and HCV prevalence of 8.7% and 7.2%, respectively;[20] the majority of patients were infected through heterosexual contact. In studies from Western countries,[15,18] where injecting drug users form a large proportion of the patient population (30–40%), HCV prevalence is higher (30–50%), even though in the general population, the prevalence is low (1–2%).

The prevalence of HIV and hepatitis coinfection depends on several factors, including geographic location and background population HBV and HCV prevalence, age and distribution of HIV and hepatitis risk-exposure categories.

Combinations of d4T + 3TC + NVP and AZT + 3TC + EFV are the most frequently used antiretroviral treatment regimens in HIV-infected patients in the Asia–Pacific region, as the individual agents are available as generics and also in convenient fixed-dose combinations.[24,25] In this study, choice of antiretroviral treatment regimen did not seem to be influenced by HBV or HCV status, which may reflect the limited treatment options available in the region, but may also indicate that hepatitis coinfection status was not considered when patients initiated HAART.

Coinfection with HBV or HCV did not significantly influence immunological or virological responses to HAART. CD4 cell recovery at 180 days and 360 days after initiating HAART were similar for hepatitis-coinfected and HIV-mono-infected patients, even after multivariate adjustments. No effect of HBV coinfection on CD4 recovery after HAART has been reported in several previous studies.[13,15,26] HCV coinfection was associated with a smaller CD4 cell increase in some studies.[14,15,19] Law *et al*.[17] observed in HIV-infected patients with HBV or HCV an initially delayed CD4 count recovery at week four after HAART treatment, but at week 48 the CD4 count increase was similar to the patients only infected with HIV. Sulkowski *et al*.[16] and Rockstroh *et al*.[18] did not find an association between HCV coinfection and CD4 recovery after HAART. Neither HBV nor HCV coinfection influenced virological response to HAART, consistent with other studies.[13–15,18]

Overall survival was similar after adjustment, regardless of hepatitis status, although patients with HCV coinfection had higher mortality in univariate analysis. Law *et al*.[17] reported no association between hepatitis coinfection and progression to AIDS or death, as did Lincoln and colleagues,[13] with both studies having a follow up about 12 months. Some studies with larger populations and longer follow up, however, have found hepatitis coinfection independently associated with all-cause mortality[14,26] and/or liver-related mortality.[18,26] Although the number of patients recruited in this study is relatively large, the median follow up of 1.5 years and relatively small number of events would have limited the power to detect a small change in mortality risk resulting from hepatitis coinfection.

Guitton and colleagues,[27] using data from the French Pharmacovigilance Database, reported that hepatic adverse drug reactions are more frequent in HBV and HCV coinfected HIV patients. HCV coinfection also caused more frequent treatment discontinuation due to toxicity in the EuroSIDA study.[28] Similarly, HBV and HCV coinfection were associated with severe hepatotoxicity in the HIV-NAT Cohort in Thailand.[20] The association between hepatitis coinfection and elevated ALT levels in patients on antiretroviral treatment in our study is consistent with the literature, even though liver enzymes were often not monitored. Monitoring liver enzymes varied across TAHOD sites (about 20% of total and 25–30% of hepatitis coinfection patients), and testing levels for hepatitis coinfection were suboptimal. We found no significant difference in rates of hepatotoxicity between nevirapine- and efavirenz-containing regimens. This contrasts with a Thai study that found higher rates of hepatotoxicity in patients receiving nevirapine compared with efavirenz within a randomized trial setting.[20] The lack of effect found in our analyses might, to some extent, reflect the observational nature of our study including the lack of standardized liver enzyme assessment.

Apart from suboptimal hepatitis testing and liver enzyme assessments in TAHOD patients, there are other limitations in our study. Information about alcohol consumption is not recorded in TAHOD, and so could not be assessed in our analyses. Treatment information for viral hepatitis is also unavailable, although access to non-antiretroviral therapy based HBV and HCV treatments is limited in most Asia–Pacific countries. TAHOD is comprised of urban-based clinical sites and the results of this study may not be able to be generalized to patients in rural areas where access to antiretroviral treatments is more limited. Although this is the largest patient population studied in the Asia–Pacific region, the relatively short follow up and limited number of endpoints gives relatively low statistical power to detect the effect of viral hepatitis coinfection on HIV disease in terms of immunological and virological response to antiretroviral treatment and survival.

Our study shows that HBV- or HCV-coinfected HIV patients can benefit from HAART as demonstrated by immunological and virological responses and overall survival. There is evidence of increased hepatotoxicity in coinfected patients, which points out the necessity for improved monitoring of liver function and adverse events in patients on treatment, especially in high-risk groups such as injecting drug users.[22]

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