

# Impact of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Co-infections on Immunological Responses to HAART in the TREAT Asia HIV Observational Database (TAHOD)



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## Introduction

The mortality rate associated with human immunodeficiency virus (HIV) infection has declined drastically among patients receiving highly active antiretroviral therapy (HAART) [1,2]. Globally, an estimated 33 million, 350 million and 170 million people are chronically infected with HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV), respectively, making these diseases three of the top 10 causes of infectious diseases deaths [3-5]. Among the 33 million HIV patients worldwide, about 2-4 million are chronically infected with HBV and 4-5 million are chronically infected with HCV [6]. Due to high rates of hepatitis co-infections among HIV patients, liver disease is now a leading cause of death among HIV-HCV co-infected patients and is becoming an important cause of death among HIV-HBV co-infected patients [7]. Nevertheless, there is no clear-cut consensus among hepatologists, virologists, and infectious diseases experts on the treatment and management of HIV patients chronically co-infected with HBV and HCV [8].

Several studies conducted in Western countries reported that when HAART is initiated, HIV-1-positive patients co-infected with HBV and/or HCV are at increased risks of developing side effects, such as liver enzyme elevation [9,10]. However, there is limited data exclusively detailing the prevalence of HIV, HBV, and HCV co-infections and how the hepatitis co-infections impact the immunological responses to HAART among Asian HIV-positive patients. The aims of this study were to assess the HBV and HCV co-infection rates and to evaluate their impact on the disease progression of HIV/AIDS patients from TAHOD.

## Methods

The TAHOD is a multi-center observational cohort study. Patients from seventeen AIDS treatment centers in the Asia-Pacific were enrolled. Each center recruited two hundred patients who were regularly attending the clinics and were either treated or not treated with antiretroviral therapy [11].

Data on socio-demographics, clinical observations, laboratory test results, exposure history, and treatment history were collected at each participating center. During the study period, those who ever tested positive for HBV surface antigen (HBsAg) or anti-HCV antibody were considered co-infected with HBV or HCV, respectively.

Clinical and demographic risk factors associated with HBV or HCV co-infections were determined through multivariate logistic regression analysis. The impact of hepatitis co-infections on CD4 changes was evaluated by multiple linear regression analyses. Cox proportional hazard models were built to determine the factors associated with elevated ALT levels and survival. Data collected from the beginning of the study until March 2009 were included in analysis.

**Table 3. Overall survival after entry to TAHOD**

	No. patients	Person-years	No. death	Rate (100 person-years)	Univariate		Multivariate*	
					HR (95% CI)	p-value	HR (95% CI)	p-value
<b>Total</b>	4,463	16,734.35	181	1.11				
<b>HBsAg</b>								
Negative	2,621	9,001.87	89	0.99	1			
Positive	305	1,097.21	10	0.91	0.92 (0.48, 1.77)	0.798	0.74 (0.34, 1.61)	0.45
Not tested	1,537	6,627.27	82	1.31	1.17 (1.01, 1.34)	0.042	1.15 (0.98, 1.35)	0.463
<b>HCV antibody</b>								
Negative	1,613	7,869.43	64	0.81	1			
Positive	1,137	7,869.43	17	1.62	2.36 (1.18, 4.03)	0.012	2.00 (0.83, 4.87)	0.147
Not tested	1,712	7,620.97	84	1.31	1.62 (1.18, 2.21)	0.003	1.21 (0.84, 1.75)	0.303
<b>Gender</b>								
Male	2,309	11,609.15	134	1.15	1			
Female	1,150	4,751.85	47	0.99	0.84 (0.61, 1.18)	0.316	0.85 (0.57, 1.28)	0.441
<b>Age (year)</b>								
≤30	1,139	3,840.61	9	1.01	1			
31-40	2,002	7,385.89	62	0.84	0.86 (0.57, 1.28)	0.444	0.81 (0.52, 1.27)	0.36
>41	1,402	5,122.86	80	1.56	1.56 (1.07, 2.29)	0.022	1.47 (0.94, 2.29)	0.088
<b>Mode of infection</b>								
Household contact	3,032	11,534.12	136	1.09	1			
Injecting drug use	834	3,047.17	13	1.63	0.38 (0.21, 0.66)	0.001	0.46 (0.24, 0.89)	0.021
Others	281	1,023.33	19	1.35	2.82 (1.74, 4.57)	0.001	2.36 (1.36, 4.07)	0.002
Blood products	76	298.35	8	2.68	2.53 (1.24, 5.18)	0.011	2.56 (1.14, 6.00)	0.028
Others	281	871.34	14	1.61	1.33 (0.77, 2.32)	0.306	1.62 (0.84, 3.13)	0.149
<b>CDC clinical classification for HIV infection</b>								
Category A	607	680.56	5	0.73	1			
Category B	509	1,912.62	17	0.89	1.22 (0.45, 3.31)	0.695	0.91 (0.34, 2.55)	0.888
Category C	2,073	7,994.54	119	1.57	2.21 (0.90, 5.42)	0.082	2.09 (0.82, 5.11)	0.123
<b>Antiretroviral treatment</b>								
Not treatment	—	1,984.11	44	2.22	1			
Monotherapy treatment	—	129.14	4	3.1	1.56 (0.36, 6.33)	0.398	1.17 (0.35, 3.94)	0.796
HAART	—	14,626.10	133	0.91	0.64 (0.31, 0.82)	0.001	0.28 (0.17, 0.44)	0.001
<b>CD4 count before initiation of treatment (cells/μL)</b>								
≤50	620	2,039.53	24	1.18	1			
51-100	323	1,104.69	11	1.18	1.01 (0.51, 1.98)	0.985	1.11 (0.55, 2.24)	0.764
101-200	481	1,753.53	12	0.69	0.59 (0.30, 1.18)	0.138	0.73 (0.34, 1.58)	0.431
201-300	287	1,021.03	9	0.89	0.79 (0.35, 1.64)	0.467	1.59 (0.71, 3.58)	0.239
≥301	153	614.85	5	0.33	0.29 (0.07, 1.22)	0.001	0.26 (0.07, 2.59)	0.383
Not tested	2,701	9,848.88	121	1.23	1.07 (0.69, 1.66)	0.765	0.96 (0.59, 1.57)	0.885
<b>HIV viral load at entry to TAHOD</b>								
≤1000	44	187.87	2	1.06	1			
>1000	77	367.7	0	—	—			
Not tested	535	2,105	11	0.52	0.47 (0.10, 2.13)	0.329	0.11 (0.13, 8.02)	0.99
Not tested	307	1,375.75	168	1.22	1.06 (0.26, 2.49)	0.911	1.56 (0.21, 11.4)	0.66

\*Adjusted for mode of infection, CDC clinical classification for HIV infection, CD4 count before initiation of treatment, and HIV viral load at entry to TAHOD  
 \*Missing value for multivariate analysis

**Table 4. Hazard rates of elevated liver enzyme test after initiation of HAART**

	No. patients	Person-years	No. events	Rate (100 py)	Univariate		Multivariate	
					HR (95% CI)	p-value	HR (95% CI)	p-value
<b>Total</b>	862	3579.25	199	5.56				
<b>HBsAg</b>								
Negative	573	2,229.47	131	5.62	1			
Positive	89	391.84	25	6.38	1.19 (0.78, 1.83)	0.419	1.18 (0.77, 1.82)	0.437
Not tested	200	957.94	43	5.01	0.89 (0.64, 1.23)	0.552	0.84 (0.51, 1.36)	0.471
<b>HCV antibody</b>								
Negative	556	2,471.11	123	5.01	1			
Positive	142	201.46	27	13.4	2.15 (1.42, 3.27)	0.001	2.21 (1.21, 3.77)	0.001
Not tested	224	674.44	49	5.21	1.05 (0.74, 1.47)	0.76	1.16 (0.72, 1.86)	0.551
<b>Gender</b>								
Male	679	2,938.78	149	5.07	1			
Female	181	639.78	48	7.57	1.34 (0.97, 1.85)	0.081	1.37 (0.98, 1.91)	0.063
<b>Age (year)</b>								
≤30	40	201.16	7	3.78	1			
31-40	343	1,452.97	90	6.19	1.18 (0.81, 1.74)	0.388	1.22 (0.85, 1.79)	0.313
>41	526	1,465.02	122	8.4	0.96 (0.65, 1.43)	0.853	1.00 (0.67, 1.49)	0.986
<b>Mode of infection</b>								
Household contact	547	2,428.48	125	5.15	1			
Injecting drug use	173	749.36	34	4.54	0.86 (0.59, 1.25)	0.43	0.87 (0.59, 1.27)	0.464
Blood products	60	244.43	22	25.3	2.96 (1.49, 6.09)	0.001	2.65 (1.48, 4.74)	0.001
Others	61	231.2	9	3.89	0.69 (0.35, 1.36)	0.284	0.69 (0.35, 1.36)	0.282
<b>CDC clinical classification for HIV infection at treatment initiation</b>								
Category A	49	201.16	4	1.99	1			
Category B	128	477.17	29	6.14	2.68 (0.94, 7.62)	0.065	2.48 (0.97, 6.30)	0.076
Category C	678	2,157.45	129	5.96	2.73 (1.70, 4.01)	0.048	2.47 (0.91, 7.72)	0.09
<b>CD4 count before initiation of treatment (cells/μL)</b>								
≤50	244	503.18	64	12.7	1			
51-100	122	511.25	29	5.65	0.88 (0.57, 1.36)	0.564	0.89 (0.58, 1.39)	0.621
101-200	186	520.19	40	5.33	0.81 (0.55, 1.20)	0.299	0.83 (0.56, 1.23)	0.354
201-300	118	448.84	18	4.01	0.59 (0.35, 0.99)	0.046	0.61 (0.36, 1.04)	0.069
≥301	64	294.19	14	4.75	0.77 (0.43, 1.37)	0.376	0.79 (0.44, 1.42)	0.423
Not tested	328	529.66	69	13.42	0.86 (0.69, 1.09)	0.927	0.94 (0.62, 1.43)	0.772
<b>HIV viral load at treatment initiation</b>								
≤1000	318	1,586.23	69	4.35	1			
>1000	38	174.22	11	6.31	1.40 (0.87, 2.14)	0.304	1.34 (0.71, 2.50)	0.371
Not tested	20	80.53	6	7.45	1.55 (0.67, 3.57)	0.305	1.37 (0.68, 3.65)	0.248
Not tested	486	178.27	113	6.5	1.13 (0.91, 1.77)	0.083	1.25 (0.81, 1.91)	0.168

## Results

**Risk factors associated with HBV and HCV co-infections**  
 • In total, 2926 (64%) and 2471 (54%) TAHOD patients were tested for HBV and HCV infections, respectively. Of those ever tested, 10.4% were HBsAg-positive and 13.7% had anti-HCV antibodies.  
 • Sex, mode of infection, CD4 count and HIV clinical stage at entry to TAHOD were associated with HBV infection, whereas sex and mode of infection were associated with HCV infection.

**Table 1. Socio-demographic and clinical risk factors associated with HBV and HCV co-infections**

	No.	No. positive (%)	HBsAg testing (UVA)		Multivariate*		No.	No. positive (%)	HCV antibody testing (UVA)		Multivariate*	
			OR (95% CI)	p-value	OR (95% CI)	p-value			OR (95% CI)	p-value	OR (95% CI)	p-value
<b>Total</b>	2,926	305 (10.4)				2,471	338 (13.7)					
<b>Gender</b>												
Male	2,045	250 (12.2)				1,780	272 (15.3)					
Female	881	55 (6.2)	0.48 (0.35, 0.65)	0.001	0.46 (0.33, 0.63)	0.001	69 (6.9)	0.58 (0.44, 0.78)	0.001	0.49 (0.35, 0.67)	0.001	
<b>Age</b>												
≤30	70	72 (9.9)				605	124 (20.5)					
31-40	1,272	135 (10.6)	1.09 (0.80, 1.47)	0.596	1.13 (0.83, 1.55)	1,041	107 (10.3)	0.85 (0.65, 0.76)	0.016	0.86 (0.65, 1.20)	0.428	
>41	924	98 (10.6)	1.08 (0.79, 1.49)	0.621	1.05 (0.75, 1.48)	879	76 (9.4)	0.40 (0.30, 0.55)	0.001	0.81 (0.56, 1.16)	0.247	
<b>Mode of infection</b>												
Household contact	2,008	187 (9.3)				1,556	109 (7.0)					
Household contact	531	73 (14.1)	1.59 (1.20, 2.12)	0.001	1.80 (1.30, 2.37)	0.001	20 (4.8)	0.67 (0.43, 1.04)	0.072	1.00 (0.54, 1.87)	0.992	
Injecting drug use	200	21 (10.5)	1.14 (0.71, 1.84)	0.584	1.46 (0.78, 2.74)	0.237	21 (10.7)	4.32 (3.01, 6.85)	0.001	28.56 (17.42, 48.62)	0.001	
Blood products	56	7 (12.5)	1.39 (0.62, 3.12)	0.422	1.74 (0.38, 1.85)	0.254	34 (30.5)	16.64 (9.40, 29.45)	0.001	27.07 (12.98, 58.66)	0.001	
Others	120	15 (12.5)	1.28 (0.83, 2.34)	0.288	1.25 (0.66, 2.36)	0.49	102 (10.9)	1.54 (0.75, 2.90)	0.274	1.62 (1.01, 2.61)	0.002	
<b>CD4 count at entry to TAHOD (</b>												