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ORIGINAL RESEARCH

HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy

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Objectives
To assess the prevalence and risk factors for HBV and HCV coinfection in the Australia HIV Observational Database (AHOD), and examine outcomes of HIV disease following initiation of highly active antiretroviral therapy (HAART).

Methods
Analyses were based on 2086 participants recruited to AHOD by September 2002. Of these, 1605 (77%) had been tested for HBV surface antigen, 1704 (82%) for anti-HCV antibody and 1453 (70%) for both. Demographic and clinical predictors of HBV and HCV coinfection were examined. The impact of HBV and HCV coinfection on HIV disease progression was assessed by Kaplan-Meier survival curves and Cox proportional hazard model of time to AIDS events and death.

Results
Among those tested, prevalence of HBV surface antigen and HCV antibody were 6.3% and 13.1%, respectively (4.8% and 10.7%, respectively, among the entire cohort). In multivariate analyses, the only independent risk factor for HIV/HBV coinfection was coinfection with HCV. Independent risk factors for HIV/HCV coinfection were HIV exposure category (with people who reported injecting drug use [MSM & IDU, IDU only] or receipt of blood or blood products at markedly increased risk) and HBV coinfection. HIV disease outcomes following first initiation of a HAART regimen were similar for HIV/HBV and HIV/HCV coinfected patients compared with HIV-only patients in terms of AIDS-free survival and detectable HIV virus during the first 12 months. However, patients coinfected with HIV/HCV appeared to have a poorer response to HAART in terms of CD4 count changes, with a CD4 count increase of 32 cells/μL (95% CI 1–67) less than HIV-only patients.

Conclusions
Coinfection with HBV or HCV is relatively common among HIV-infected participants in AHOD. HIV disease outcomes following HAART do not appear to be adversely affected by HBV/HCV coinfection, except for slightly poorer CD4 count responses in HIV/HCV coinfected patients.

Keywords: coinfection, hepatitis B, hepatitis C, highly active antiretroviral therapy, HIV

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Introduction

Hepatitis B and C viral infections are highly prevalent among HIV-infected persons, generally as a result of shared transmission routes [1]. Improved survival due to the success of highly active antiretroviral therapy (HAART) has enabled conditions with long latency, such as chronic viral hepatitis, to become a major source of comorbidity in HIV-infected populations [2]. HIV modifies the natural history of hepatitis B virus (HBV), with higher rates of chronic HBV infection, replicative disease, and progression to advanced liver disease among persons with HIV/HBV coinfection [2]. The impact of HBV on HIV natural history is less certain [1, 3].

HIV also modifies the natural history of hepatitis C virus (HCV) infection, with clear evidence of higher HCV viral load and accelerated liver disease progression in persons with HIV/HCV coinfection [4]. As with HBV, there is contradictory evidence on the effects of HCV on HIV disease progression [5]. Several studies before the era of HAART showed no impact of HCV on HIV disease progression [6, 7], while others suggested accelerated HIV disease progression [8, 9]. A recent longitudinal cohort

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study demonstrated inhibited CD4 cell recovery following commencement of HAART in persons with HIV/HCV coinfection [10], but evidence is limited on clinical progression.

Further longitudinal studies are, therefore, required to assess the impact of HBV and HCV on HIV disease progression in the era of HAART. The Australian HIV Observational Database (AHOD) is a longitudinal study that has been collecting information (including hepatitis status) on a cohort of HIV-infected patients since September 1999 [11]. This analysis aimed to assess the seroprevalence of HBV and HCV within the AHOD population, to identify characteristics associated with coinfection with chronic viral hepatitis, and investigate the effect of coinfection on immunological, virological and clinical progression of HIV infection.

Methods

Patients and data variables

The AHOD collects data from 26 sites, including hospitals, sexual health clinics and general practitioners from around Australia. Data are transferred electronically to the National Centre in HIV Epidemiology and Clinical Research (NCHECR), and updated every 6 months. Core data variables collected on patients include sex, date of birth, date of most recent visit, HIV exposure category, HBV status, HCV status, CD4 and CD8 T lymphocyte counts, HIV viral load counts, antiretroviral and opportunistic infection prophylaxis treatments, AIDS defining illnesses, and date of death.

Risk factors of HBV and HCV coinfection

HBV infection was defined by a positive HBV surface antigen (HBsAg), and HCV infection by a positive anti-HCV antibody. Prevalence of HBV infection, HCV infection and HBV/HCV coinfection was calculated for those with recorded test results for HBsAg and anti-HCV antibody. Due to possible testing bias, further prevalence estimates were calculated for the entire population with the assumption that all untested patients were negative. Risk factors for coinfection with HBV and HCV were determined in cross-sectional analyses using logistic regression models. If a patient's HBV or HCV test was prior to entry to the cohort, or if the test date was missing, analyses were based on date at cohort entry. If the test date was after entry to the cohort, analyses were based on the data at this test date. Univariate analyses were initially performed on each covariate. The nominal covariates were tested for significance using χ^2 tests for heterogeneity and the ordinal covariates were tested for significance using tests for trend. All tests were performed at the 5% significance level. Missing values of the nominal covariates were dropped for the tests of trend, but retained when calculating and reporting the odds ratios. Multivariate logistic models were used to test the predictors after adjusting for the other covariates. The models were built using forward step-wise methods based on the significance tests described above.

Outcomes of HBV/HCV coinfected patients following HAART

The three endpoints used to test the clinical, virological and immunological progression of coinfected patients were time to AIDS or death, detectable viral load at 12 months and time-weighted CD4 cell counts to 24 months. For the analyses, only patients who had received HAART and had recorded test results for both HBV and HCV were included. The patients were grouped by no hepatitis infection, infection with HBV only, HCV only and coinfection with HBV and HCV. Baseline was defined as the date the patient commenced HAART. No distinction was made between patients being tested for hepatitis before or after baseline. The impact of hepatitis coinfection on the clinical progression of HIV was assessed with Kaplan-Meier survival curves and a Cox proportional hazard model of the time to first AIDS defining illness or death. Patients who did not progress to the endpoint were censored at the date of the last recorded visit. The effect of hepatitis coinfection on viraemia at 12 months after baseline was assessed by logistic regression among patients with baseline viral load measurement. The effect of hepatitis coinfection on immunological progression was assessed by fitting a linear model on time-weighted average changes in CD4 counts from baseline to 24 months. In addition to having received HAART, patients were required to have a baseline CD4 count and at least one follow-up CD4 count to be included in the analysis.

Covariates tested for inclusion in all multivariate models were age group, sex, HIV exposure category, viral load at baseline, CD4 cell count at baseline and antiretroviral therapy immediately prior to baseline. Each covariate was tested at the 5% level using the chi-squared test for heterogeneity if it was a nominal variable or a *t*-test for trend if it was ordinal.

Results

Prevalence and risk factors of HBV/HIV and HCV/HIV coinfection

Of the 2086 AHOD participants, 1605 (77%) had a HBsAg result, 1704 (82%) had a anti-HCV antibody result, and

1453 (70%) had results for both tests. One hundred and one patients tested positive for HBsAg, a HBV prevalence of 6.3% for those with a test result and 4.8% for the entire cohort. Two hundred and twenty-three patients tested positive for anti-HCV antibody, a HCV prevalence of 13.1% for those with a test result and 10.1% for the entire cohort. Thirty-eight patients tested positive for HBsAg and anti-HCV antibody, a HBV/HCV coinfection prevalence of 2.6% for those with a recorded result for both tests and 1.8% for the entire cohort.

HCV-RNA results were reported for 218 patients who also had a HCV antibody result. Of HCV antibody positive patients with HCV-RNA results ($n = 107$), 88 (82%) were HCV-RNA positive. Of HCV antibody negative patients with HCV-RNA results ($n = 111$), 5 (4.5%) were HCV-RNA positive.

Risk factors of HBV and HCV coinfection

In univariate analysis, risk factors for HBV coinfection were HIV exposure through transfusion of blood products, and HCV coinfection (Table 1). Following adjustment in multivariate analysis, only HCV coinfection remained significant. Prevalence of HBV coinfection was 6.2% for men who have sex with men (MSM), 8.7% for MSM who also reported injecting drug use (MSM & IDU), 3.0% for IDUs, and 9.9% for heterosexuals.

Risk factors for HCV coinfection in univariate analysis were female sex, HIV exposure categories (MSM & IDU, IDUs, recipients of blood products), HBV coinfection, CD4 count of less than 200 cells/μL [3], and younger age (Table 2). Following adjustment in multivariate analysis, HIV exposure category and HBV coinfection remained significantly associated with HCV coinfection. Prevalence of HCV coinfection was similar for MSM & IDU (50%), IDUs (63.9%), and recipients of blood products (57.1%), and considerably higher than both MSM (8.7%) and heterosexuals (9.9%).

As HCV coinfection and HBV infection were associated, the relationship between HCV coinfection and prior HBV exposure (as measured by HBV core antibody status) was examined. There was a significant association between HCV coinfection and prior HBV exposure (OR = 1.74; 95% CI 1.26–2.39, $P = <0.001$).

Impact of hepatitis coinfection on disease progression

A total of 1271 (60.9%) AHOD patients commenced HAART, and 181 progressed to an AIDS event. Time to

Table 1 Factors associated with HBV/HIV coinfection

		HBV−		HBV +		Univariate				Multivariate			
		n	%	*n*	%	OR	95% CI	*P*	*P**	OR	95% CI	*P*	*P**
Overall		1504	101										
Sex	Male	1410	93.75	98	97.02								
	Female	94	6.25	3	2.97	0.46	(0.14–1.48)	0.191	0.191	0.44	(0.14–1.43)	0.174	0.174
Exposure	MSM	1086	72.20	73	72.27								
	MSM & IDU	84	5.58	8	7.92	1.42	(0.66–3.04)	0.371		1.13	(0.50–2.55)	0.767	
	IDU	32	2.12	1	0.99	0.46	(0.06–3.45)	0.454		0.32	(0.04–2.50)	0.280	
	Hetero	128	8.51	8	7.92	0.93	(0.44–1.97)	0.850		0.94	(0.44–2.00)	0.874	
	Blood	11	0.73	3	2.97	4.06	(1.11–14.86)	0.035		3.13	(0.82–11.93)	0.094	
	Other & NR	163	10.84	8	7.92	0.73	(0.34–1.54)	0.410	0.234	0.71	(0.33–1.50)	0.365	0.551
Age (years)	<30	96	6.38	3	2.97								
	30–39	563	37.43	47	46.53	2.67	(0.81–8.75)	0.105		2.63	(0.80–8.65)	0.110	
	40 +	845	56.18	51	50.49	1.93	(0.59–6.31)	0.276	0.717	1.96	(0.60–6.42)	0.266	0.801
Coinfected	No	1230	81.78	72	71.28								
with HCV	Yes	135	8.97	16	15.84	2.02	(1.14–3.58)	0.015		2.02	(1.14–3.58)	0.015	
	NR	139	9.24	13	12.37	1.60	(0.86–2.96)	0.136	0.028	1.60	(0.86–2.96)	0.136	0.028
RNA at BL	<400	639	42.49	47	46.53								
(copies/mL)	400–9999	342	22.74	17	16.83	0.68	(0.38–1.19)	0.178		0.66	(0.37–1.18)	0.162	
	10000 +	294	19.55	16	15.84	0.74	(0.41–1.32)	0.312		0.73	(0.41–1.32)	0.303	
	NR	229	15.22	21	20.79	1.25	(0.73–2.13)	0.420	0.212†	1.20	(0.70–2.06)	0.504	0.208†
CD4 at BL	<200	182	12.10	17	16.83								
(cells/μL)	200–499	516	34.31	30	29.70	0.62	(0.33–1.15)	0.133		0.62	(0.33–1.16)	0.136	
	500 +	606	40.29	32	31.68	0.56	(0.31–1.04)	0.067		0.58	(0.31–1.07)	0.082	
	NR	200	13.30	22	21.78	1.18	(0.61–2.29)	0.629	0.101†	1.16	(0.59–2.25)	0.665	0.144†
Previous ADI	No	1197	79.58	75	74.25								
	Yes	307	20.41	26	25.74	1.35	(0.85–2.15)	0.202	0.202	1.38	(0.87–2.20)	0.176	0.176

P-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. †patients with NR data were not included for testing trend. MSM, men who have sex with men; IDU, injecting drug user; BL, baseline; ADI, AIDS defining illness; *P**, overall *P*.

Table 2 Factors associated with HCV/HIV coinfection

		HCV−		HCV +		Univariate			*P**	OR	95% CI	*P*	*P**
Overall		1481		223									
Sex	Male	1402	94.67	203	91.03								
	Female	79	5.33	20	8.97	1.75	(1.05–2.92)	0.033	0.033	1.41	(0.70–2.84)	0.335	0.335
Exposure	MSM	1129	76.23	107	47.98								
	MSM & IDU	51	3.44	51	22.87	10.55	(6.82–16.31)	<0.001		10.45	(6.74–16.20)	<0.001	
	IDU	13	0.88	23	10.31	18.67	(9.19–37.91)	<0.001		19.46	(9.56–39.58)	<0.001	
	Hetero	128	8.64	14	6.28	1.15	(0.64–2.07)	0.632		1.14	(0.634–2.06)	0.651	
	Blood	6	0.40	8	3.59	14.07	(4.79–41.30)	<0.001		13.18	(4.44–39.04)	<0.001	
	Other & NR	154	10.39	20	8.97	1.37	(0.83–2.27)	0.223	<0.001	1.36	(0.82–2.27)	0.231	<0.001
Age (years)	<30	111	7.49	22	9.86								
	30–39	560	37.81	109	48.88	0.98	(0.59–0.85)	0.944		1.11	(0.63–1.95)	0.721	
	40 +	810	54.69	92	41.25	0.57	(0.34–0.95)	0.031	0.001	0.82	(0.46–1.46)	0.499	0.149
Coinfected	No	1198	80.89	178	79.82								
with HBV	Yes	59	3.98	18	8.07	2.05	(1.18–3.56)	0.010		2.17	(1.19–3.95)	0.011	
	NR	224	15.12	27	12.11	0.81	(0.53–125)	0.339	0.018	0.89	(0.56–1.42)	0.636	0.030
RNA at BL	<400	649	43.82	92	41.26								
(copies/mL)	400–9999	320	21.61	49	21.97	1.08	(0.74–1.57)	0.684		1.00	(0.67–1.50)	0.988	
	10000 +	294	19.85	44	19.73	1.05	(0.72–1.55)	0.782		0.90	(0.59–1.38)	0.636	
	NR	218	14.72	38	17.04	1.23	(0.82–1.85)	0.321	0.737†	1.02	(0.65–1.60)	0.923	0.659†
CD4 at BL	<200	164	11.07	32	14.35								
(cells/μL)	200–499	507	34.23	81	36.32	0.82	(0.52–1.28)	0.379		0.80	(0.49–1.31)	0.379	
	500 +	627	42.23	72	32.28	0.59	(0.37–0.92)	0.021		0.68	(0.42–1.12)	0.130	
	NR	183	12.36	38	17.04	1.06	(0.63–1.78)	0.813	0.011†	0.94	(0.53–1.66)	0.830	0.602†
Previous ADI	No	1187	80.15	178	79.82								
	Yes	294	19.85	45	20.18	1.02	(0.72–1.45)	0.909	0.909	0.92	(0.63–1.36)	0.688	0.388

P-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. †patients with NR data were not included for testing trend. MSM, men who have sex with men; IDU, injecting drug user; BL, baseline; ADI, AIDS defining illness. *P**, overall *P*.

AIDS or death was not associated with hepatitis coinfection ($P = 0.37$, logrank test) (Fig. 1). The hazard ratios from the Cox proportional hazard model for progression to AIDS or death are presented in Table 3. In univariate analysis, factors associated with clinical progression were higher HIV viral load, lower CD4 count, and dual antiretroviral therapy prior to HAART. In the multivariate model, only lower CD4 count was associated with increased clinical progression.

There were 901 AHOD patients who commenced HAART and had a baseline viral load measurement (Table 4). Similar to clinical progression, there was no association between hepatitis coinfection status and virological response following HAART ($P = 0.92$). In multivariate analysis, factors associated with poorer virological response were higher baseline HIV viral load and antiretroviral therapy prior to HAART.

There were 940 AHOD patients who commenced HAART and had a baseline CD4 count and at least one follow-up CD4 count recorded. Baseline CD4 cell count were similar for the following groups: HIV only (mean: 303 cells/μL; SD: 223), HIV/HBV (mean: 274 cells/μL; SD: 210), HIV/HCV (mean: 300 cells/μL; SD 236), and HIV/HBV/HCV (mean: 270 cells/μL SD: 181) ($P = 0.80$). HBV coinfection did not impact on CD4 count response following HAART, however, in the multivariate analysis HCV was associated with CD4 count response (Table 5). The time-weighted average increase in CD4 count following commencement of HAART was approximately 32 cells/μL [3] less in patients with HCV coinfection compared to those without hepatitis coinfection ($P = 0.040$). In multivariate analysis, factors associated with a poorer CD4 response following commencement of HAART were antiretroviral therapy prior to HAART, and baseline CD4 cell count. Patients coinfected with HCV continued to have a lower response in time-weighted CD4 count following HAART compared to those without hepatitis infection, although of borderline significance ($P = 0.061$).

Discussion

In a large cohort of Australian HIV-infected patients, several clinically relevant findings were seen. The mode of HIV acquisition was predictive HCV coinfection, with particularly strong associations between parenteral modes and HCV coinfection. The CD4 response following commencement of HAART was impaired in patients with HCV coinfection, however, the effect was modest and was not associated with either impaired virological response or more rapid clinical progression.

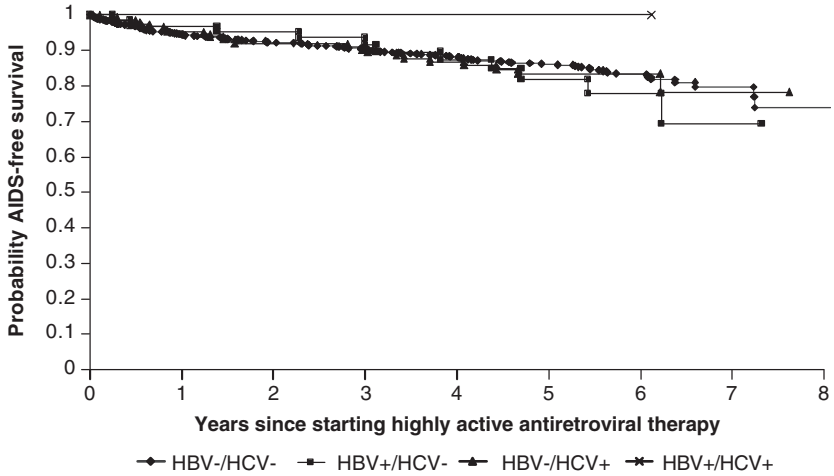

Fig. 1 Time to first AIDS defining illness or death by hepatitis B and C coinfection status.

Table 3 Time to first AIDS defining illness or death

		Non-events		Events		Univariate				Multivariate			
		n	%	*n*	%	HR	95% CI	*P*	*P**	HR	95% CI	*P*	*P**
Overall		1090		181									
Hepatitis Status	HBV−/HCV−	889	81.56	147	81.21								
	HBV + /HCV−	52	4.77	12	6.62	1.34	(0.74–2.41)	0.330		1.27	(0.71–2.29)	0.423	
	HBV−/HCV +	130	11.92	22	12.15	1.05	(0.67–1.65)	0.824		0.99	(0.63–1.56)	0.985	
	HBV + /HCV +	19	1.74	0	0	–	–	–	0.810	–	–	–	0.885
Sex	Male	1022	93.76	173	95.58								
	Female	68	6.24	8	4.42	0.73	(0.36–1.48)	0.382	0.382	0.82	(0.40–1.66	0.576	0.576
Age (years)	< 30	161	14.77	30	16.57								
	30–39	460	42.20	74	40.88	0.83	(0.54–1.27)	0.384		0.84	(0.55–1.29)	0.436	
	40 +	469	43.03	77	42.54	0.84	(0.55–1.29)	0.429	0.547	0.85	(0.56–1.30)	0.453	0.552
Exposure category	MSM	783	71.83	138	76.24								
	Other	280	25.69	40	22.10	0.91	(0.64–1.29)	0.603		0.88	(0.61–1.25)	0.465	
	NR	27	2.48	3	1.66	0.70	(0.22–2.21)	0.547	0.743	0.65	(0.21–2.04)	0.458	0.601
RNA at BL	< 400	188	17.25	16	8.84								
(copies/mL)	400–9999	382	35.04	39	21.55	1.09	(0.61–1.94)	0.781		1.02	(0.57–1.84)	0.933	
	10000 +	256	23.49	54	29.83	2.00	(1.14–3.50)	0.015		1.49	(0.84–2.64)	0.168	
	NR	264	24.22	72	39.78	2.14	(1.24–3.70)	0.006	0.003	1.37	(0.71–2.62)	0.345	0.082
CD4 at BL	< 200	226	20.74	67	37.02								
(cells/μL)	200–499	413	37.89	46	25.41	0.43	(0.30–0.63)	< 0.001		0.43	(0.30–0.63)	< 0.001	
	500 +	232	21.28	13	7.18	0.24	(0.13–0.44)	< 0.001		0.24	(0.13–0.44)	< 0.001	
	NR	219	20.09	55	30.39	0.84	(0.59–1.20)	0.330	< 0.001	0.84	(0.59–1.20)	0.330	< 0.001
Previous ART	None	666	61.10	77	42.54								
	Mono	63	5.78	11	6.08	1.26	(0.67–2.28)	0.467		1.11	(0.59–2.10)	0.739	
	Double	361	33.11	93	51.38	1.64	(1.21–2.22)	0.002	0.006	1.42	(1.04–1.94)	0.026	0.081

P-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. †patients with NR data were not included for testing trend. MSM, men who have sex with men; BL, baseline; ART, antiretroviral therapy. *P**, overall *P*.

The prevalence of HBV, HCV and HBV–HCV coinfection in this cohort is considerably higher than the general Australian population. Recent Australian population level estimates for HCV and chronic HBV infection are 1.1% [12] and 0.5% [13], respectively. The corresponding figures among HIV-infected patients in the AHOD cohort of 6–14% for both HCV and chronic HBV infection reflect overlapping modes of transmission for these three blood-borne viruses. The prevalence of HBV coinfection among Australian HIV-infected patients is similar to several other

Table 4 Detectable viral load at 12 months after baseline

		Undetectable		Detectable		Univariate				Multivariate			
		n	%	*n*	%	OR	95% CI	*P*	*P**	OR	95% CI	*P*	*P**
Overall		431		470									
Hepatitis status	HBV−/HCV−	352	81.67	399	80.93								
	HBV + /HCV−	21	4.87	27	5.48	1.13	(0.63–2.04)	0.675		1.04	(0.54–2.01)	0.903	
	HBV−/HCV +	51	11.83	61	12.37	1.05	(0.71–1.57)	0.792		1.16	(0.74–1.81)	0.520	
	HBV + /HCV +	7	1.62	6	1.22	0.76	(0.25–2.27)	0.618	0.919	0.91	(0.26–3.17)	0.878	0.929
Sex	Male	397	92.11	470	95.33								
	Female	34	7.89	23	43.67	0.57	(0.33–0.99)	0.044	0.044	0.70	(0.36–1.34)	0.279	0.279
Age (years)	<30	62	14.39	72	14.60								
	30–39	180	41.76	214	43.41	1.02	(0.69–1.52)	0.907		0.96	(0.62–1.46)	0.845	
	40 +	189	43.85	207	41.99	0.94	(0.64–1.40)	0.770	0.653	0.85	(0.55–1.31)	0.470	0.392
Exposure category	MSM	292	67.75	368	74.65								
	Other	139	32.25	125	26.60	0.71	(0.54–0.95)	0.021	0.21	0.72	(0.53–0.99)	0.042	0.042
RNA at baseline	<400	144	33.41	36	7.30								
(replicates/mL)	400–9999	152	35.27	225	45.64	5.92	(3.89–9.00)	<0.001		6.80	(4.39–10.53)	<0.001	
	10000 +	109	25.29	153	31.03	5.61	(3.61–8.72)	<0.001		6.33	(4.01–9.99)	<0.001	
	NR	26	6.03	79	16.02	12.15	(6.84–21.58)	<0.001	<0.001	13.91	(7.68–25.20)	<0.001	<0.001
CD4 at baseline	<200	89	20.65	126	25.56								
(cells/μL)	200–499	201	46.64	183	37.12	0.64	(0.46–0.90)	0.010		0.75	(0.51–1.09)	0.133	
	500 +	113	26.22	112	22.72	0.70	(0.48–1.02)	0.064		1.11	(0.72–1.72)	0.617	
	NR	28	6.50	72	14.60	1.82	(1.09–3.04)	0.023	0.069	1.12	(0.50–2.54)	0.777	0.527
Previous ART	None	309	71.69	261	52.94								
	Mono	20	4.64	21	4.26	1.24	(0.66–2.34)	0.501		1.53	(0.76–3.08)	0.235	
	Double	102	23.67	211	42.80	2.45	(1.83–3.27)	<0.001	<0.001	2.81	(2.05–3.89)	<0.001	<0.001

P-values reported for Wald's Chi-squared test of homogeneity in nominal covariates and *t*-test for trend in ordinal covariates. †patients with NR data were not included for testing trend. MSM, men who have sex with men; BL, baseline; ART, antiretroviral therapy. *P**, overall *P*.

Table 5 Time weighted average change in CD4 counts from baseline

		Average time-weighted		Univariate				Multivariate change in CD4 count				
		n	Mean	St. Dev.	D**	95% CI	*P*	*P**	D	95% CI	*P*	*P**
Overall		940	180.72	173.58								
Hepatitis	HBV−/HCV−	772	185.20	174.86								
Status	HBV + /HCV−	48	171.22	148.05	−13.98	−64.61, 36.66	0.588		−12.39	−60.85, 36.07	0.616	
	HBV−/HCV +	108	150.27	177.99	−34.93	−69.91, 0.04	0.050		−32.12	−65.70, 1.46	0.061	
	HBV + /HCV +	12	204.20	124.51	19.00	−80.04, 118.03	0.707	0.241	13.09	−81.64, 107.82	0.786	0.287
Sex	Male	880	181.28	173.99								
	Female	60	172.42	168.65	−8.86	−54.34, 36.61	0.702	0.702	−10.26	−53.84, 33.32	0.644	0.644
Age	<30	142	169.69	175.34								
(years)	30–39	396	202.80	176.82	33.11	−0.05, 66.26	0.050		38.04	6.21, 69.87	0.019	
	40 +	402	162.85	167.64	−6.84	−39.93, 26.25	0.685	0.137	5.54	−26.30, 37.37	0.733	0.484
Exposure	MSM	683	181.48	177.63								
Category	Other & NR	257	178.69	162.66	−2.79	−27.73, 22.15	0.826	0.826	−12.74	−36.73, 11.26	0.298	0.298
Viral load	<400	181	164.69	180.32								
at baseline	400–9999	383	193.20	175.31	28.51	−2.13, 59.16	0.068		11.09	−18.56, 40.73	0.463	
	10000 +	281	185.94	154.05	21.25	−11.13, 53.64	0.198		7.50	−23.98, 38.99	0.640	
	NR	95	145.45	154.05	−19.24	−62.29, 23.81	0.381	0.286	−23.78	−66.52, 18.96	0.275	0.464
CD4	<200	339	192.85	15.19								
at baseline	200–499	449	199.46	161.23	6.61	−17.38, 30.61	0.589		−0.31	−23.81, 23.20	0.980	
(cells/μL)	500 +	152	98.28	225.53	−94.57	−127.12, −62.02	<0.001	<0.001	−103.54	−135.44, −71.64	<0.001	<0.001
Previous	None	547	210.99	181.51								
ART	Mono	50	129.37	165.88	−81.62	−130.92, −32.32	<0.001		−81.36	−129.48, −33.24	0.001	
	Double	343	139.927	150.55	−71.06	−94.04, −48.08	<0.001	<0.001	−75.55	−98.09, −53.02	<0.001	<0.001

P-values reported for Wald's Chi-squared test of homogeneity in nominal covariates and *t*-test for trend in ordinal covariates. †patients with NR data were not included for testing trend. **Mean differences in time-weighted change in CD4 cell count. MSM, men who have sex with men; BL, baseline; ART, antiretroviral therapy. *P**, overall *P*.

industrialized countries [14]. In contrast, the prevalence of HCV coinfection is lower than the 20–30% seen in countries such as the USA, Spain and Italy [15–17], where injecting drug use contributes a larger proportion of HIV infection than in Australia [18].

Independent predictors for HBV and HCV coinfection were found within AHOD. An association between HBV infection and HCV infection indicates shared transmission routes, in particular parenteral exposure [19]. Approximately 12% of people diagnosed with HIV in Australia have reported either injecting drug use or receipt of blood products, including 4% who reported both injecting drug use and homosexual contact [18]. The major determinant of HCV coinfection in AHOD was route of HIV transmission, with more than half of patients who acquired HIV through parenteral routes found to have HCV coinfection. In addition, patients who reported both male homosexual contact and injecting drug use had a HCV coinfection prevalence of above 50%. The majority of men in this category may have acquired HIV through sexual contact and HCV through parenteral exposure, as HIV prevalence among injecting drug users in Australia has remained at low levels throughout the HIV epidemic [18]. Approximately 9% of both heterosexual and male homosexual patients (with no reported injecting drug use) were reported to be HCV coinfected. Possible explanations for HCV infection in these two groups are sexual transmission, underreporting of injecting drug use, or other parenteral exposure, such as tattooing or body piercing.

Among AHOD patients commenced on HAART, those with HCV coinfection had an impaired CD4 count response. This finding, including the magnitude of the effect, is consistent with that found in the Swiss Cohort Study [10], with both studies demonstrating an approximately 40 cells/μL [3] lower CD4 count increase in the 24 months following commencement of HAART. Direct HCV pathogenicity on lymphocytes has been suggested as the mechanism for this effect, and earlier treatment of HCV coinfection in people with HIV proposed as a consequence [10]. Delayed CD4 recovery in patients with HCV coinfection is not related to differences in virological control as shown in our study and by others [10, 20, 21]. Longer-term follow-up and further studies are required to examine the impact of delayed CD4 recovery on clinical progression, as two recent studies have shown no impact [20] and increased progression [21] among patients with HCV coinfection. In contrast to HCV, coinfection with HBV does not appear to influence CD4 count recovery following commencement of HAART, although our study appears to be the first to examine this issue.

There are several limitations to our study that should be considered in relation to the findings. First, HBV and HCV status was based on clinician reporting to the AHOD database rather than through a standardized serological survey. Second, HBV and HCV status was not available for all patients in AHOD. As AHOD includes information on over 2000 patients, and 77–82% of patients had HBV and HCV testing, clinically significant associations with coinfection should have been detected. Third, HCV coinfection status was based on antibody rather than HCV RNA detection, and HBV coinfection status in some cases may have been based on a single positive HBsAg result. However, the vast majority in both HBV and HCV coinfection categories could be expected to have chronic viral hepatitis. The limited HCV-RNA testing among patients with a positive HCV antibody result suggested that 82% had chronic HCV infection. Finally, no assessment of liver disease outcomes was conducted. Although liver biopsy-based information is not available, cause of death is being collected in AHOD, therefore, liver disease-associated mortality will be monitored prospectively.

As survival for patients with HIV infection continues to improve, therapeutic toxicity and comorbid conditions, such as chronic viral hepatitis will be major management issues. Longitudinal monitoring such as that undertaken in observational cohort studies will be a crucial means of examining the changing natural history of HIV disease. Factors such as the impact of hepatitis coinfection on antiretroviral therapy choice, toxicity, and regimen change should also be examined in such cohorts.

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Appendix: The Australian HIV Observational Database

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Sydney Sexual Health Centre; R. Finlayson and J. Clemons, Taylor Square, Darlinghurst; D. Ellis, The Medical and Vein Centre, Coffs Harbour; D. Baker*, J. Kidd and R. McFarlane, 407 Bourke Street, Surry Hills; and K. Petoumenos*, M. Law*, D. Smith*, NCHECR, Darlinghurst.

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South Australia

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Queensland

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Victoria

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