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ORIGINAL RESEARCH

Antiretroviral treatment change among HIV, hepatitis B virus and hepatitis C virus co-infected patients in the Australian HIV Observational Database

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Objectives

To assess the impact of highly active antiretroviral therapy (HAART) on rates of change of antiretroviral treatment among patients co-infected with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) in the Australian HIV Observational Database (AHOD).

Methods

Analysis was based on 805 of the 2218 patients recruited to the AHOD by March 2003, who had commenced HAART after 1 January 1997, who had recorded test results for HBV surface antigen and anti-HCV antibody, and who had follow-up of more than 3 months. The effect of hepatitis co-infection on the rate of antiretroviral treatment change after commencing HAART was assessed using a random-effect Poisson regression model.

Results

Among those included in the analyses, the prevalences of HBV and HCV were 4.8% and 12.8%, respectively. The overall rate of combination antiretroviral treatment change was 0.74 combinations per year. Factors independently associated with an increased rate of change of combination antiretroviral treatment were: prior AIDS-defining illness; prior exposure to double combination antiretroviral therapy; and antiretroviral treatment class. Co-infection with HBV and/or HCV was not found to be significantly associated with the rate of combination antiretroviral treatment change.

Conclusions

While both HBV and HCV co-infections are relatively common in the AHOD, they do not appear to be serious impediments to the treatment of HIV-infected patients.

Keywords: antiretroviral, co-infection, HIV, hepatitis B virus, hepatitis C virus

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The use of highly active antiretroviral therapy (HAART) in Australia since 1996 has dramatically reduced the morbidity and mortality of patients with HIV [1,2]. As the survival of HIV-infected patients continues to improve, and despite the obvious success of HAART, the necessity to continue therapy long term introduces other concerns, such as treatment-related toxicity and the management of co-morbid conditions such as chronic viral hepatitis.

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HIV is known to impact on the natural history of hepatitis B virus (HBV) and hepatitis C virus (HCV) disease. There has been evidence of higher rates of chronic HBV infection among HIV/HBV co-infected patients and higher HCV viral loads among those with HIV/HCV co-infection [3]. However, the impact of HBV and HCV on HIV remains ambiguous. Several studies have shown no impact of HBV or HCV co-infection on HIV disease progression [4,5], while others have shown accelerated HIV disease progression [6,7]. Although there has been a slightly poorer CD4 count response in HIV/HCV co-infected patients [4,8], the impact of HAART on disease progression among patients co-infected with HBV and/or HCV remains relatively uncertain, particularly in the presence of treatment-related toxicities.

Hepatotoxicity associated with antiretroviral use has been shown in several studies to be more common in HIV-

infected patients co-infected with HCV or HBV, particularly after initiating antiretroviral treatment [9,10]. The protease inhibitor (PI) ritonavir and, more recently, nonnucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine and efavirenz, have been associated with hepatotoxicity [10]. However, others have found no association between the use of NNRTIs and hepatotoxicity [11].

The aim of the present study was to assess the impact of HAART on rates of change of antiretroviral treatment among patients co-infected with HBV and/or HCV in the Australian HIV Observational Database (AHOD). In a previous study [12], we demonstrated the use of rates of change of antiretroviral therapy to be a useful mid-range surrogate marker of disease progression, and to be more long range than conventional markers such as CD4 count and HIV viral load, but earlier than clinical AIDS-defining illness or death. This may be a good endpoint for examining the response to HAART in co-infected patients, in whom not only would HIV disease progression be expected to lead to increased rates of antiretroviral treatment change, but also significant liver toxicity to treatment would be expected to lead to increased rates of antiretroviral treatment change.

We also assessed the durability of the first HAART regimen, and the durability of HAART regimens including NNRTIs, which have been associated with liver toxicity.

Methods

Patients and data collection

The Australian HIV Observational Database collects data from 27 sites throughout Australia, including hospitals, sexual health clinics and general practitioners. Data are transferred electronically to the National Centre in HIV Epidemiology and Clinical Research (NCHECR) every 6 months. The following core data variables are collected: sex, date of birth, date of first positive HIV test result, 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, including start and stop dates, and AIDS-defining illnesses.

To be included in the present study, patients in the AHOD had to meet the following requirements: (1) initiation of HAART, defined as a combination of at least three antiretroviral agents, after 1 January 1997; (2) recorded test results for both HCV antibodies and HBV surface antigen (HBsAg); and (3) follow-up of at least 3 months from baseline, defined as the date the patient commenced HAART.

Definition of HBV and HCV serological categories

HBV infection was defined as a positive HBV surface antigen (HBsAg) test, and HCV infection as a positive anti-HCV antibody test. No distinction was made between patients being tested for hepatitis before and after initiation of HAART. Co-infection status was classified as follows: HBV and HCV negative; HBV positive only; HCV positive only; and co-infection with HBV and HCV.

Definition of combination change

An antiretroviral treatment change was defined as any change to a combination, including adding or dropping treatments, or reinitiating treatments previously received. In this definition, a treatment interruption of greater than 7 days was also considered a change.

Statistical analyses

For each patient, data were censored at the last date of follow-up, defined as the most recent of the following dates: most recent visit date, date of CD4 or viral load count, or date on which antiretroviral therapy started or stopped. Individual person-years of follow-up were calculated as the time between baseline (initiation of HAART) and the date of last follow-up. Rate of change of antiretroviral treatment was calculated as the number of combination changes over the person-years of follow-up.

The effect of hepatitis co-infection on the rate of antiretroviral treatment change after commencing HAART was assessed using a random-effect Poisson regression model, which allowed for the repeated-event nature of the data [13]. The effect of hepatitis co-infection on time to changing the first HAART combination was assessed with Kaplan–Meier survival curves and Cox proportional hazard models of time to change of first HAART combination.

Covariates tested for inclusion in multivariate models were sex, age group, HIV exposure category, viral load at baseline, CD4 cell count at baseline, AIDS-defining illness prior to baseline, antiretroviral therapy prior to baseline (none, mono or double), treatment class and calendar year. Nominal covariates were tested using χ^2 tests for heterogeneity and ordinal covariates using tests for trend. Missing values were not included when testing ordinal covariates. Multivariate models were obtained using forward selection techniques.

In addition, the association between hepatitis co-infection and time to stopping nevirapine or efavirenz was examined with Kaplan–Meier survival curves and the Wilcoxon test statistic.

All statistical analyses were performed using STATA 8.0 [14].

Results

By March 2003, 2218 HIV-positive patients had been recruited to the AHOD. Of these, 805 met the study inclusion criteria, having commenced HAART after 1 January 1997, recorded test results for HBsAg and anti-HCV antibody, and had follow-up of more than 3 months. The median follow-up overall was 4.1 years, with a total of 3320 person-years.

Thirty-nine patients (4.8%) tested positive for HBsAg only, 103 patients (12.8%) tested positive for anti-HCV antibody only, and 15 patients (1.9%) tested positive for both HBsAg and anti-HCV antibody.

Patient characteristics, by HBV/HCV status, are summarized in Table 1. A greater proportion of those with HCV only were female (13%), and had an HIV exposure category of injecting drug use (IDU) [men having sex with men (MSM) plus IDU, or IDU] (37%), when compared with those with other HBV/HCV status. Patients co-infected with either HBV or HCV were slightly younger than those without HBV or HCV. Approximately 54% of those infected with HIV only were less than 40 years of age, in comparison with 67% of those with HBV only, 65% of those with HCV only, and 87% of those with HBV and HCV.

Rate of change of antiretroviral treatment

The overall mean rate of treatment change after initiating HAART was 0.73 [95% confidence interval (CI): 0.70–0.77] per year for those without HBV/HCV co-infection, 0.71 (95% CI: 0.58–0.86) per year for those with HBV, and 0.83

Table 1 Patient characteristics by hepatitis B and C virus status

	HBV − /HCV −		HBV + /HCV −		HBV − /HCV +		HBV + /HCV +	
	n	%	*n*	%	*n*	%	*n*	%
Overall	648		39		103		15	
Sex								
Male	605	93.4	37	94.9	90	87.4	15	100
Female	43	6.6	2	5.1	13	12.6	0	0
Age (years)								
< 30	89	13.7	6	15.4	17	16.5	3	20
30–39	263	40.6	20	51.3	50	48.5	10	66.7
40–49	188	29	11	28.2	30	29.1	1	6.7
50 +	108	16.7	2	5.1	6	5.8	1	6.7
HIV exposure category								
MSM	467	74	25	65.8	45	44	8	53.3
MSM and IDU	22	3.5	4	10.5	21	20	5	33.3
IDU	7	1.1	0	0	16	15	0	0
Heterosexual	69	10.9	5	13.2	7	7	0	0
Blood	3	0.5	1	2.6	1	1	2	13.3
Other and NR	63	10	3	7.9	10	10	0	0
CD4 count (cells/μL)								
< 200	150	23.2	9	23.1	27	26.2	6	40
200–350	147	22.7	9	23.1	19	18.5	2	13.3
350 +	241	37.2	14	35.9	31	30.1	2	13.3
NR	110	17	7	18	26	25.2	5	33.3
HIV viral load (HIV-1 RNA copies/mL)								
< 10 000	131	20.2	8	20.5	14	13.6	2	13.3
10 000–50 000	137	21.1	12	30.8	18	17.5	2	13.3
50 000 +	269	41.5	12	30.8	46	44.7	6	40
NR	111	17.1	7	18	25	24.3	5	33.3
Previous AIDS-defining illness								
No	560	86.4	31	79.5	85	82.5	12	80
Yes	88	13.6	8	20.5	18	17.5	3	20
Previous ART								
None	431	66.5	27	69.2	62	60.2	12	80
Mono	50	7.7	1	2.6	11	10.7	0	0
Double	167	25.8	11	28.2	30	29.1	3	20
Year HAART commenced								
1997–1999	534	82.4	30	76.9	80	77.7	12	80
2000–2002	114	17.6	9	23.1	23	22.3	3	20

Co-infection status: HBV and HCV negative (HBV − /HCV −); HBV positive only (HBV + /HCV −); HCV positive only (HBV − /HCV +); and co-infection with HBV and HCV (HBV + /HCV +).
MSM, men who have sex with men; IDU, injecting drug user; NR, not recorded; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy.

per year for those with HCV (95% CI: 0.75–0.93) and for those with both HBV and HCV co-infection (95% CI: 0.59–1.12).

Rate of change of antiretroviral treatment after commencing HAART was not associated with co-infection status ($P = 0.40$). Table 2 presents factors associated with

Table 2 Factors associated with the rate of combination antiretroviral treatment change after commencing highly active antiretroviral therapy (HAART)

					Univariate				Multivarative			
	n	FU	Count	Rate	IRR	95% CI	*P*	Overall *P**	IRR	95%CI	*P*	Overall *P**
Overall	805	3318	2473	0.745								
Hepatitis status												
HBV–/HCV–	648	2707	1982	0.732								
HBV + /HCV–	39	147	104	0.709	0.91	0.65–1.28	0.593		0.95	0.70–1.29	0.740	
HBV–/HCV +	103	416	346	0.833	1.12	0.91–1.38	0.282		1.14	0.95–1.37	0.157	
HBV + /HCV +	15	50	41	0.828	1.39	0.82–2.33	0.218	0.396	1.40	0.88–2.23	0.150	0.249
Sex												
Male	747	3073	2223	0.723								
Female	58	245	250	1.019	1.30	1.01–1.68	0.043	0.043	1.16	0.92–1.46	0.204	0.204
Age (years)												
< 30	115	439	372	0.846								
30–39	343	1414	1009	0.713	0.91	0.74–1.13	0.388		0.88	0.73–1.07	0.200	
40–49	230	974	696	0.714	0.91	0.72–1.14	0.398		0.85	0.69–1.04	0.109	
50 +	117	490	396	0.808	1.03	0.80–1.34	0.805	0.770	0.99	0.79–1.25	0.960	0.894
HIV exposure												
MSM	545	2263	1661	0.734								
Other	239	1056	812	0.769	1.02	0.88–1.18	0.825	0.825	1.04	0.91–1.18	0.603	0.603
CD4 at baseline (cells/μL)												
< 200	192	771	617	0.801								
200–350	177	672	472	0.702	0.88	0.71–1.08	0.221		1.04	0.86–1.26	0.677	
350 +	288	1194	838	0.702	0.88	0.74–1.06	0.186		0.96	0.81–1.14	0.618	
NR	148	681	546	0.802	0.98	0.80–1.22	0.885	0.220	1.03	0.85–1.24	0.798	0.537
HIV viral load at baseline (HIV-1 RNA copies/mL)												
< 10 000	155	633	491	0.775								
10 000–50 000	169	732	480	0.656	0.84	0.67–1.04	0.117		0.95	0.78–1.16	0.615	
50 000 +	333	1275	941	0.738	0.97	0.80–1.17	0.737		1.09	0.91–1.31	0.326	
NR	148	679	561	0.827	1.04	0.84–1.30	0.701	0.975	1.11	0.91–1.35	0.307	0.164
Previous ADI												
No	688	2817	1979	0.702								
Yes	117	501	494	0.986	1.41	1.17–1.69	0.000	0.000	1.34	1.14–1.58	0.001	0.001
Previous ART												
None	532	2104	1350	0.642								
Mono	62	284	251	0.885	1.36	1.06–1.74	0.015		1.24	0.99–1.55	0.057	
Double	211	931	872	0.937	1.43	1.23–1.66	0.000	0.000	1.29	1.12–1.48	0.000	0.000
Drug class												
PI-based HAART (excludes NNRTI)	1189	1298	934	0.720								
NNRTI-based HAART (excludes PI)	892	1250	567	0.454	0.67	0.59–0.76	0.000		0.70	0.62–0.79	0.000	
NNRTI/PI HAART combination	221	175	178	1.018	1.30	1.06–1.60	0.012		1.29	1.05–1.57	0.013	
Mono or double	426	176	370	2.099	2.61	2.22–3.07	0.000		2.69	2.29–3.14	0.000	
None	608	420	424	1.010	1.16	1.00–1.34	0.046	0.000	1.26	1.09–1.45	0.002	0.000
Time period												
1997/1998	530	632	563	0.891								
1999	656	592	467	0.789	0.91	0.80–1.03	0.135		0.92	0.81–1.04	0.175	
2000	727	683	525	0.769	0.89	0.79–1.01	0.072		0.92	0.81–1.04	0.181	
2001	739	689	461	0.669	0.78	0.69–0.89	0.000		0.78	0.69–0.89	0.000	
2002/03	706	722	457	0.633	0.73	0.64–0.83	0.000	0.000	0.72	0.63–0.83	0.000	0.000

**P*-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. Patients with data not recorded were not included when testing trend.
Co-infection status: HBV and HCV negative (HBV − /HCV −); HBV positive only (HBV + /HCV −); HCV positive only (HBV − /HCV +); and co-infection with HBV and HCV (HBV + /HCV +).
FU, follow-up; IRR, incidence rate ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; NR, not recorded; ADI, AIDS-defining illness; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

the rate of treatment change. In univariate analysis, rates of change were significantly associated with sex ($P = 0.043$), AIDS-defining illness prior to initiating HAART ($P < 0.001$), and exposure to antiretroviral therapy prior to commencing HAART ($P < 0.001$). Antiretroviral treatment class was also found to be associated with the rate of treatment change ($P < 0.001$), as well as the calendar year ($P < 0.001$). Age, HIV exposure category, CD4 at baseline and RNA at baseline were not significantly associated with rate of treatment change.

In multivariate analysis, AIDS-defining illness [incidence rate ratio (IRR) = 1.34; $P < 0.001$] and exposure to double therapy prior to initiating HAART (IRR = 1.29; $P < 0.001$) continued to be associated with increased rates of treatment change. Class of treatment combination also remained significantly associated with rates of change. Combinations that included a NNRTI, but not a PI, were associated with a slower rate of change than combinations that did not include a NNRTI (IRR = 0.70; $P < 0.001$); combinations that included both a NNRTI and a PI were associated with a faster rate of change than combinations that did not include a NNRTI (IRR = 1.29; $P = 0.013$); and mono or double therapies, and no therapy, were associated with increased rates of combination change (IRR = 2.69; $P < 0.001$ and IRR = 1.26; $P = 0.002$, respectively). During more recent time periods, particularly from 2001 onwards, the rates of combination change were also significantly slower compared with earlier years ($P < 0.001$).

Post hoc analysis examined the association between ritonavir-boosted combinations and rates of treatment change. Combinations including stavudine and didanosine and their association with rates of change were also analysed. Results showed that treatment combinations that included ritonavir with at least one other PI did not differ significantly from other PI-containing regimens ($P = 0.92$). However, combinations that included stavudine and/or didanosine demonstrated a significantly faster rate of treatment change compared with combinations excluding these two antiretrovirals ($P = 0.024$).

Time to first treatment change

The median durations spent on first HAART combinations, by co-infection status, are shown in Fig. 1. Overall, the median duration on first HAART combination was 482 days for those without HBV or HCV, 686 days for those with HBV alone, 398 days for those with HCV alone, and 172 days for those with HBV and HCV co-infection.

Time to first treatment change after commencing HAART was not significantly associated with co-infection status ($P = 0.51$). The hazard ratios (HRs) from the Cox proportional hazard model for time to first treatment change after commencing HAART are presented in Table 3. In univariate analysis, AIDS-defining illness prior to commencing HAART, and exposure to double therapy prior to commencing HAART, were associated with a faster time to first treatment change ($P = 0.041$ and $P = 0.009$, respectively). Combinations that included a NNRTI, but not a PI, were associated with a slower time to change than combinations that did not include a NNRTI (HR = 0.63; $P < 0.001$). Age, sex, HIV exposure category, CD4 at baseline, RNA at baseline, and year of first change were not significantly associated with time to first treatment change.

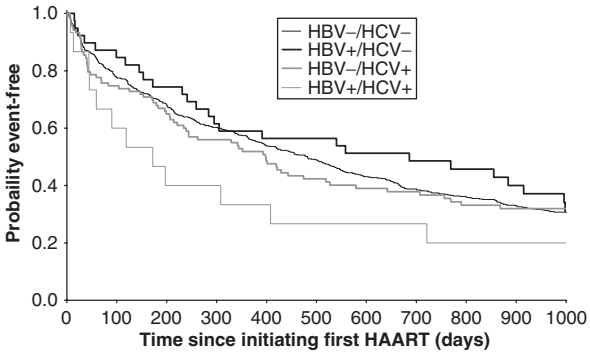

Fig. 1 Time to first antiretroviral treatment change after commencing highly active antiretroviral therapy (HAART), by hepatitis B and C virus co-infection status.

In multivariate analysis, exposure to double therapy prior to initiating HAART (HR = 1.25; $P = 0.014$) was found to be independently associated with a faster time to combination change. In addition, combinations that included a NNRTI, but not a PI, remained significantly associated with a slower time to change than combinations that did not include a NNRTI (HR = 0.64; $P < 0.001$).

Time to stopping nevirapine or efavirenz

Of the 805 patients who met the study inclusion criteria, 611 commenced a HAART combination that included nevirapine or efavirenz at some stage during the follow-up period. Overall, the median time between commencing and stopping either nevirapine or efavirenz was 1344 days. The median durations spent on treatments that included nevirapine or efavirenz, by co-infection status, are shown in Fig. 2. Time to stopping nevirapine or efavirenz was not associated with hepatitis co-infection ($P = 0.86$, Wilcoxon test).

Discussion

In the AHOD, the prevalences of HBV and HCV were 4.8% and 12.8%, respectively. Among the patients who were

Table 3 Time to first antiretroviral combination change after commencing highly active antiretroviral therapy

	Non-events		Events		Univariate				Multivariate			
	n	%	*n*	%	HR	95% CI	*P*	*P**	HR	95% CI	*P*	*P**
Overall	173		632									
Hepatitis status												
HBV −/HCV −	143	82.7	505	79.9								
HBV + /HCV −	7	4.1	32	5.1	1.02	0.72–1.46	0.901		1.02	0.71–1.46	0.925	
HBV −/HCV +	21	12.1	82	13	1.11	0.88–1.40	0.377		1.13	0.90–1.43	0.293	
HBV + /HCV +	2	0.2	13	2.1	1.44	0.83–2.50	0.196	0.507	1.41	0.81–2.45	0.224	0.486
Sex												
Female	17	9.8	41	6.5								
Male	156	90.2	591	93.5	0.99	0.72–1.35	0.932	0.932	0.94	0.68–1.29	0.692	0.692
Age (years)												
< 30	26	15	89	14.1								
30–39	80	46.2	263	41.6	0.80	0.63–1.02	0.075		0.79	0.62–1.01	0.057	
40–49	49	28.3	181	28.6	0.84	0.65–1.08	0.180		0.80	0.62–1.04	0.098	
50 +	18	10.4	99	15.7	1.08	0.81–1.43	0.613	0.378	0.99	0.74–1.33	0.972	0.761
HIV exposure category												
MSM	103	59.5	442	69.9								
Other	70	40.5	190	30.1	0.87	0.74–1.04	0.121	0.121	0.88	0.74–1.04	0.131	0.131
CD4 count at baseline												
< 200	41	23.7	151	23.9								
200–350	53	30.6	124	19.6	0.86	0.68–1.09	0.214		0.96	0.76–1.23	0.764	
350 +	58	33.5	230	36.4	1.05	0.86–1.29	0.635		1.14	0.92–1.40	0.223	
NR	21	12.1	127	20.1	1.15	0.91–1.46	0.247	0.511	1.22	0.96–1.55	0.111	0.245
HIV viral load at baseline (HIV-1 RNA copies/mL)												
< 10 000	33	19.1	122	19.3								
10 000–50 000	31	17.9	138	21.8	1.01	0.80–1.30	0.906		1.07	0.83–1.38	0.582	
50 000 +	87	50.3	246	38.9	0.95	0.76–1.18	0.632		0.97	0.77–1.22	0.792	
NR	22	12.7	126	19.9	1.12	0.87–1.43	0.386	0.541	1.11	0.86–1.43	0.423	0.998
Previous ADI												
No	156	90.2	532	84.2								
Yes	17	9.8	100	15.8	1.25	1.01–1.55	0.041	0.041	1.12	0.90–1.39	0.293	0.293
Previous ART												
None	133	76.9	399	63.1								
Mono	9	5.2	53	8.4	1.27	0.95–1.69	0.106		1.22	0.92–1.63	0.171	
Double	31	17.9	180	28.5	1.27	1.06–1.51	0.009	0.006	1.25	1.05–1.49	0.014	0.011
Drug class combination												
PI-based HAART												
(excludes NNRTI)	52	30.1	370	58.5								
(excludes PI)	115	66.5	230	36.4	0.63	0.54–0.75	0.000		0.64	0.54–0.75	0.000	
NNRTI/PI HAART combination	6	3.5	32	5.1	0.93	0.65–1.33	0.685	0.000	0.89	0.62–1.28	0.522	0.000
Year initiated												
1997	31	17.9	300	47.5								
1998	43	24.9	155	24.5	0.81	0.67–0.99	0.035		0.89	0.73–1.09	0.260	
1999	35	20.2	92	14.6	0.93	0.73–1.18	0.539		1.07	0.84–1.37	0.576	
2000	30	17.3	53	8.4	0.86	0.64–1.16	0.334		1.03	0.76–1.40	0.832	
2001	15	8.7	24	3.8	1.05	0.69–1.59	0.835		1.18	0.78–1.80	0.434	
2002	19	11	8	1.3	0.68	0.34–1.38	0.290	0.297	0.74	0.37–1.51	0.413	0.763

**P*-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. Patients with data not recorded were not included when testing trend.
Co-infection status: HBV and HCV negative (HBV − /HCV −); HBV positive only (HBV + /HCV −); HCV positive only (HBV−/HCV +); and co-infection with HBV and HCV (HBV + /HCV +).
HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; NR, not recorded; ADI, AIDS-defining illness; ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

included in this study (those who commenced HAART after 1997 and had been tested for HBV and HCV infection), the overall rate of combination antiretroviral treatment change was 0.74 combinations per year, varying among the co-infected groups. The rate of combination antiretroviral treatment change was 0.73 per year among patients infected only with HIV, 0.71 per year among HIV/HBV co-infected patients, and 0.83 per year among HIV/HCV co-infected patients and HIV/HBV/HCV co-infected patients.

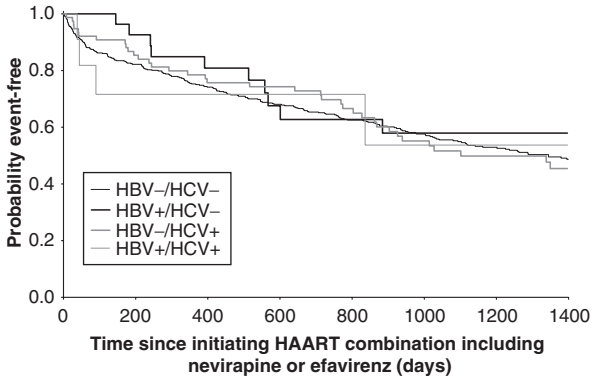

Fig. 2 Time to stopping nevirapine or efavirenz, by hepatitis B and C virus co-infection status.

In this study, factors that were independently associated with an increased rate of change of combination antiretroviral treatment were a previous diagnosis with an AIDS-defining illness (34% faster), and prior exposure to double combination antiretroviral therapy compared with being previously naïve (29% faster). Combinations that included a NNRTI had a 30% slower rate of combination treatment change compared with combinations that included a PI. Co-infection with HBV and/or HCV was not found to be significantly associated with the rate of combination antiretroviral treatment change. Other factors, such as age, sex, exposure category, CD4 count and viral load at baseline, were also not significantly associated with the rate of combination antiretroviral treatment change. Although calendar year was significantly associated with the overall rate of combination change, it was not significantly associated with the first combination change. Co-infection status was also not associated with stopping treatment combinations that included either nevirapine or efavirenz.

Our findings that HBV and/or HCV co-infection was not associated with the rate of change of combination antiretroviral treatment are supported by several other studies. Greub *et al.* [8] found that the probability of changing antiretroviral treatment was not associated with HCV status, but was associated with AIDS at baseline, RNA at baseline, duration of therapy and sex. Sulkowski *et al.* [15] found that HCV co-infection did not alter virological or immunological response to HAART.

In our analysis, patients who were receiving a regimen including a NNRTI had a slower rate of change of antiretroviral treatment than those receiving a PI. Whether this was a result of better tolerability of these compounds or fewer adverse events, such as toxicities, is unknown. Calendar year was also shown to be associated with the rate of combination change overall, more recent time periods having significantly slower rates of change compared with earlier time periods. Such an association was not seen in time to first combination change post-HAART. This is probably a result of the fact that most patients in this cohort had commenced their very first HAART combination before the year 2000.

In the AHOD we also saw that co-infection status was not associated with stopping either nevirapine or efavirenz. In a study with similar demographics to the AHOD, where patients were predominantly homosexual men, no association was found between HBV and HCV infection and hepatotoxicity caused by NNRTI use [11]. Sulkowski *et al.* [10] analysed the outcome of NNRTI-containing HAART in an HIV hospital clinic and also found that the majority of their patients did not develop hepatotoxicity; however, among those who did, it was more common if they were also concurrently using a PI, or if they had HCV or HBC co-infection.

There are several limitations to our study. Firstly, recruitment to the AHOD commenced in June 1999, but a large proportion of the data concerning antiretroviral treatment, HIV disease stage, and HBV and HCV status was collected retrospectively. Hence, the analysis presented in this study is based on retrospective as well as prospective data. Secondly, HBV and HCV status data were not collected in a standardized format, but rather by clinician reporting. HCV status was based on antibody rather than HCV RNA testing, and HBV status, in some instances, may have been based on a single HBsAg antibody result. However, it could be expected that the large majority had chronic HBV and HCV infection. Among the HCV-infected patients, approximately 80% had chronic HCV infection based on the limited HCV RNA testing. Furthermore, no assessment of liver disease outcomes was conducted. Whether the study was sufficiently powered to detect a difference in the rates of change amongst the different co-infection groups is also questionable, given the wide confidence limits for each of these groups. A *post hoc* power analysis determined that at least 35 patients needed to be co-infected with HBV and HCV in order for the difference detected in this study to be significant. In this population, only 15 patients, less than half the required number, were co-infected with both HBV and HCV.

Finally, in this analysis it was not possible to assess whether treatment changes were caused by toxicity, virological failure or other factors. Ascribing reasons for treatment change is difficult, with toxicity, adherence and virological efficacy closely linked. A strength of our analysis is that all treatment changes were included, based on the assumption that more changes, for whatever reason, represent a poorer outcome than fewer changes. This overall rate of change endpoint is also quite a sensitive outcome [12].

Our analyses, both in this paper and in previous work [4], suggest that HIV/HCV and HIV/HBV co-infection are not serious impediments to a patient's treatment for HIV infection. One feature of the HIV epidemic in Australia is that HIV transmission is overwhelmingly through male homosexual content, with very few people living with HIV actually injecting illicit drugs [16]. Whether the poorer outcomes, both in terms of response to treatment as well as in the long-term, as seen in co-infected patients in other studies, reflect ongoing active injecting drug use rather than HCV or HBV co-infection deserves more thorough investigation.

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Appendix 1: The Australian HIV Observational Database

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