

ORIGINAL RESEARCH

Rates of combination antiretroviral treatment change in Australia, 1997–2000

The Australian HIV Observational Database*

Objective

To estimate the rate of combination antiretroviral treatment change and factors associated with combination antiretroviral treatment change among patients recruited in the Australian HIV Observational Database (AHOD).

Methods

Analyses were based on patients in the AHOD who had commenced combination antiretroviral treatment after 1 January 1997. Combination antiretroviral treatment change was defined as the addition or change of at least one antiretroviral drug. A random-effect Poisson regression model was used to assess factors associated with increased rates of combination antiretroviral treatment change.

Results

A total of 596 patients in the AHOD were included in the analysis, with a median follow-up of 2.3 years. The overall rate of antiretroviral treatment change in this group was 0.45 combinations per year. In a multivariate analysis, a low CD4 count ($<$ 200 cells/μL) at baseline was associated with an increased rate of treatment change [rate ratio (RR) = 1.43; 95% confidence interval (CI), 1.13, 1.80; $P = 0.003$)]. Combinations including a nonnucleoside reverse transcriptase inhibitor were also associated with slower rates of change than treatment combinations including a protease inhibitor (RR = 0.64, 95% CI, 0.51, 0.80, $P < 0.001$).

Conclusion

Initiating combination antiretroviral at a CD4 cell count $<$ 200 cells/μL may be associated with poorer patient outcomes. However, the possibility that clinician or patient concerns about low immunological status led to faster rates of treatment change in this group cannot be discounted.

Keywords: combination treatment, HIV, observational database, rates

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Introduction

Combination antiretroviral treatments have been the standard for people with HIV in Australia since mid-1996 [1] and have had a marked effect in reducing morbidity and mortality [2,3]. However, this raises the question of what endpoints are appropriate to use when assessing patient outcomes in observational data. Using rates of AIDS-defining illnesses have become increasingly difficult as such illnesses are now rare, with most HIV-infected patients now living without AIDS for prolonged periods. The HIV viral load and CD4 cell count have long been accepted as good surrogate markers of disease progression. Some studies have looked at short-term virological or immunological endpoints after first initiating antiretroviral therapy [4–6]; however, these endpoints address only the early stages of treatment.

One possible intermediate endpoint to use in HIV observational studies is an assessment of combination antiretroviral

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treatment rates of change. This endpoint has the advantage that it covers the entire time period from when a patient first starts the antiretroviral treatment. Interpretation is fairly straightforward, with a high rate of change considered a poorer outcome. Furthermore, all observational studies can use this endpoint as it is based only on data from the antiretroviral treatments received, which are routinely collected in all cohorts. The aim of the present study was to estimate the rates of change of combination antiretroviral therapy in Australian HIV Observational Database (AHOD) and to investigate its use as a possible surrogate of disease outcome.

Methods

Many HIV treatment clinics around Australia maintain patient information in computerized patient management systems. Most clinical sites collect data on antiretroviral treatment during routine medical care of people with HIV. Data fields common to these HIV specialist clinics identified in the AHOD pilot study [7] included demographic information (such as age, sex, HIV exposure category and date of first HIV positive test), stage of HIV disease, previous and current antiretroviral and prophylactic treatment history.

Ethics approval for the AHOD was obtained from the University of New South Wales' ethics committee (Committee on Experimental Procedures Involving Human Subjects) with further ethics approval from local area health services as appropriate. Patient identifiers were based on a two-by-two name code (first two letters of surname followed by first two letters of first name), date of birth and sex. Written informed consent was based on a two-stage procedure, with an individual first giving consent for inclusion in the database and, secondly, giving explicit consent for their data to be linked with other national and Commonwealth databases.

Data specifications on the AHOD were forwarded to the individual clinical sites. Sites were required to format the data in five separate data sets in either Excel or ASCII format. The core data variables collected from each of the contributing sites were as follows:

(1) *Demographics*. This file includes one record per patient, while the remaining four files have more than one record per patient. Data variables in the demographics file include name code, date of birth, sex, date of most recent visit, HIV exposure category, hepatitis B and C status and date of death.
(2) *Immunology and virology*. These files include data on CD4 and CD8 T lymphocyte counts and HIV viral load counts.
(3) *AIDS defining illness*.
(4) *Antiretroviral treatment uptake* (including reasons for stopping therapy).
(5) *Opportunistic infection prophylaxis*.

As most of these variables are routinely collected as part of clinical care, data on the stages of HIV disease and antiretroviral and prophylactic treatments were collected retrospectively, including all available data from the individual sites. Data exchanges to the AHOD are scheduled biannually, in March and September of each year.

These data were downloaded from each of the sites to the National Centre in HIV Epidemiology and Clinical Research (NCHECR). In order to manipulate site data into a single common format, data from each site were processed separately in Excel and then imported into SAS statistical software [8]. Firstly, patients were provided with individual unique identifiers, based on name code, date of birth and sex and any obvious formatting errors were identified and corrected.

The individual sites were informed of relevant data errors, and corrections were made to the local databases. These corrections were also reported back to the NCHECR. Once data from individual sites were cleaned, they were imported into the SAS. At this point, text variables such as antiretroviral treatment, prophylactic treatment and AIDS-defining illnesses were recorded. Having manipulated the data into a single common format, data from each site were then merged into five separate data sets based on the original five files. Once in their final data set form, duplicate patients were identified, based on 100% name code, date of birth and matches by sex. These duplicates were then re-coded into a single patient record.

Statistical analyses

Combination antiretroviral therapy was defined as a patient receiving two or more antiretrovirals. A combination change was defined as starting one or more antiretroviral drugs not included in the immediately preceding combination. Dropping an antiretroviral from the regimen, or ceasing treatment entirely, does not use up available treatment combinations and therefore was not considered a combination change. However, re-initiating treatments previously received but not included in the immediately preceding combination were included as changes.

Combination treatment regimens were also categorized into three treatment classes. The first treatment class consisted of treatment combinations including a nucleoside reverse transcriptase inhibitor (NRTI) and/or a protease inhibitor (PI) but excluding nonnucleoside reverse transcriptase inhibitors (NNRTIs). The second treatment class consisted of treatment combinations including at least one NNRTI, but excluding PIs. The third treatment class included both a NNRTI and PI.

Included in the analyses were all patients recruited to the AHOD who commenced their first combination

antiretroviral treatment after 1 January 1997. For each patient, data were censored at the last follow-up date, defined as the most recent of the following dates: most recent visit date, date of CD4 or viral load count, date antiretroviral started or date antiretroviral stopped. The person years of follow-up for each patient were taken as the time between commencing the first antiretroviral combination and the last follow-up date. Only patients with a follow-up of at least 3 months were included. Rate of changing antiretroviral treatment was calculated as the number of combination changes over the person years of follow-up.

The time to changing the first, second or third combination was estimated using the Kaplan–Meier method. Factors associated with the rate of changing combination treatment were assessed using the person years method [9]. Factors assessed included age at first combination, sex, CD4 and HIV RNA counts, exposure category, previous AIDS-defining illness, calendar year, number of new combinations and class of drug. In order to allow for the repeated-event nature of the data (that is, patients can have multiple changes), a random-effect Poisson regression model was used to assess factors predictive of increased rates of combination change [9]. Multivariate models were obtained using forward step-wise techniques. All P values of less than 5% were considered significant, and there were no adjustments for multiple comparisons. All statistical analyses were performed using SAS [8] and STATA [10]. Regression analyses were also performed after re-defining a combination change as any change in antiretrovirals, including stopping a single drug.

Table 1 Baseline patient characteristics

Characteristics	*n*	(%)
Sex		
Male	570	(96)
Female	26	(4)
Age (years)		
<30	125	(21)
30–39	263	(44)
40–49	139	(23)
>50	69	(12)
Mean (SD)	38	(9.6)
Exposure category		
Male homosexual contact	459	(77)
Other	107	(19)
Missing	30	
CD4 (cells/μL)		
<200	137	(23)
200–350	123	(21)
>350	263	(44)
Mean (SD)	367	(250)
Missing	73	
HIV viral load (HIV-1 RNA copies/mL)		
$<50\,000$	250	(42)
$\geqslant 50\,000$	272	(46)
Median (LQ–UQ)	55 450	(12 000–220 000)
Missing	74	
Previous AIDS defining illness		
Yes	63	(11)
No	533	(89)

LQ = lower quartile; UQ = upper quartile.

Results

By September 2000, 1476 HIV-positive patients had been recruited to the AHOD and contributed data to the September data exchange. Five hundred and ninety-six patients who commenced combination antiretroviral therapy after 1 January 1997 were included in this analysis. Patient characteristics are summarized in Table 1. The majority of patients were male (96%; mean age 38 years), and infected with HIV through male homosexual contact (81%). At the time of commencing the combination antiretroviral treatment, the mean CD4 count was 367 cells/μL, and the median HIV viral load was 55 450 HIV-1 RNA copies/mL. At the time of first combination, 11% of patients had previously been diagnosed with an AIDS-defining illness.

The median follow-up for these patients was 2.3 years, with a total of 1349 person years. The median durations the patients spent on their first, second and third combinations are shown in Fig. 1. The patients remained on their first combination for a median of 646 days. Out of the 596 patients, 322 started a second combination for a median duration of 623 days. A total of 149 people progressed to a third combination for a median duration of 392 days.

The class of drug combination used by patients as their first, second or third combination is summarized by the baseline CD4 count and the viral load in Table 2. There was a slight trend for a larger proportion of patients with a CD4 count <200 cells/μL and a viral load $>50\,000$ copies/mL to start their first combination therapy with a PI-containing regimen (68% and 60%, respectively). Patients with higher CD4 counts and lower viral loads tended to initiate PI-containing regimens more frequently on their second or subsequent combination (Table 2).

The overall rate of change of combination antiretroviral treatments after the first combination was 0.45 per follow-up year. Table 3 describes the factors associated with an increased rate of change in combination therapy. In univariate analyses, rates of change in the combination antiretroviral therapy were significantly higher for patients with an AIDS-defining illness prior to commencing their first combination [rate ratio (RR) = 1.54, $P = 0.002$] and in patients who commenced combination therapy with a CD4 count <200 cells/μL (RR = 1.53, $P < 0.001$). The antiretroviral

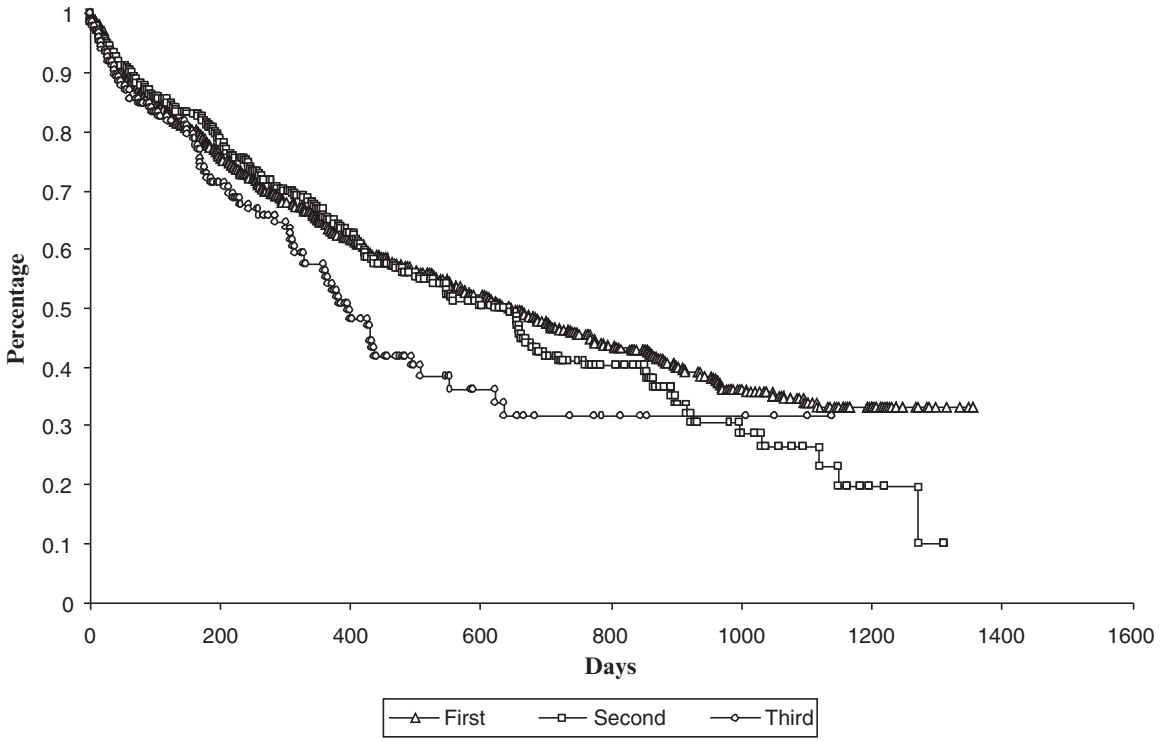

Fig. 1 Duration on first, second and third combination antiretroviral treatments.

treatment class was also found to be associated with the rate of changing combination therapy. Patients whose combination included an NNRTI changed combinations at a significantly slower rate than those whose combination included a PI (RR = 0.61, $P < 0.001$).

In multivariate analyses, the final model included the CD4 cell count and treatment class. Patients with a CD4 count below 200 cells/μL changed combinations at a significantly faster rate (RR = 1.43, $P = 0.003$). Patients whose combination therapy did not include a PI changed at a much slower rate than those whose combination did not include a NNRTI (RR = 0.64, $P < 0.001$). Previous AIDS-defining illnesses did not remain statistically significant when included in the multivariate model along with the CD4 count and treatment class, although the rate of change was still raised (RR = 1.31, $P = 0.078$).

The associations of each of the cofactors were investigated after controlling for CD4 count and treatment class. Although sex was not found to be significant, females changed antiretroviral combinations at a faster rate than males (RR = 1.35, $P = 0.163$). Rates were not statistically significantly different by exposure category (male homosexual contact vs. other), age group (< 30, 30–39, 40–49 and > 50 years), or baseline viral load (< 50 000 vs. = 50 000 HIV-1 RNA copies/mL), calendar year, or whether it is the first, second or third plus combination (Table 3).

Table 4 summarizes, by baseline factors for the first, second and third changes, data showing whether combination changes reflected a substitution of antiretroviral drugs or merely the addition of new drugs to an existing regimen. The majority of changes involved the substitution of one or more antiretrovirals from the immediately preceding regimen. This proportion generally increased from the first to the second and third combination changes for all of the cofactors (age, sex, prior AIDS-defining disease, exposure category, CD4 count and viral load).

Regression analyses were also performed in which combination change was defined as making any alteration, including just dropping drugs, to the antiretroviral therapy received. With this definition, the overall rate of change of combination antiretroviral therapy after the first combination was 0.95 per follow-up year. In the univariate analysis, as with the previous analysis, prior AIDS-defining illness and CD4 count < 200 cells/μL were significantly associated with a faster rate of changing combination antiretroviral treatment. Additionally, the inclusion of an NNRTI in the treatment was associated with significantly slower rates of changing combination therapy. All three cofactors remained significantly associated with rates of change of combination antiretroviral therapy in multivariate analyses. This is in contrast with the previous analysis in which a previous AIDS-defining

Table 2 Proportion of patients on their first, second and third combination: CD4 count and viral load by treatment class

	1st combination			2nd combination			3rd combination		
	Excludes NNRTI* ($n = 334$) *n* (%)	Excludes PI† ($n = 244$) *n* (%)	NNRTI + PI ($n = 18$) *n* (%)	Excludes NNRTI ($n = 219$) *n* (%)	Excludes PI ($n = 94$) *n* (%)	NNRTI + PI ($n = 9$) *n* (%)	Excludes NNRTI ($n = 95$) *n* (%)	Excludes PI ($n = 42$) *n* (%)	NNRTI + PI ($n = 12$) *n* (%)
CD4 cells/μL									
> 350	136 (52)	121 (46)	6 (2)	90 (69)	39 (30)	1 (1)	32 (63)	18 (35)	1 (2)
200–350	63 (51)	58 (47)	2 (2)	40 (62)	24 (37)	1 (0)	15 (60)	6 (6)	4 (16)
< 200	93 (68)	39 (28)	5 (4)	54 (70)	19 (25)	4 (5)	26 (60)	11 (25)	6 (14)
NR	42	26	5 (7)	35	12	3	22	7	1
Viral load HIV-1 RNA copies/mL									
⩾ 50 000	164 (60)	101 (37)	7 (3)	100 (68)	43 (29)	3 (2)	45 (68)	14 (21)	7 (11)
< 50 000	122 (49)	123 (49)	5 (2)	81 (65)	41 (33)	2 (2)	29 (57)	19 (37)	3 (6)
NR	48	20	6	38	10	4	21	9	2

*Includes a nucleoside reverse transcriptase inhibitor and/or PI but does not include an NNRTI. †Includes at least an NNRTI but does not include a PI. NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NR = not reported.

illness was only marginally significant in multivariate analyses.

Discussion

The overall rate of combination antiretroviral treatment change among patients in AHOD who commenced antiretroviral treatment after 1 January 1997 was 0.45 combinations per year. In this study, the rate of changing combination treatments was independently associated with CD4 cell count at the initiation of treatment and with the drug class. Patients initiating combination treatment at a CD4 cell count < 200 cells/μL had a 43% faster rate of change than patients who initiated treatment at higher CD4 cell counts. In this study, however, there appeared to be little difference in the rate of combination-treatment changes between patients who initiated treatment with a CD4 cell count > 350 cells/μL and those who initiated treatment with a CD4 cell count of 200–350 cells/μL. Patients receiving combination treatment, including an NNRTI, had a 36% slower rate of change compared with patients whose combination included a PI. Patients with an AIDS-defining illness diagnosed prior to starting the combination treatment had a 31% increased rate of change, although this was not quite statistically significant. In this analysis, sex, age, viral load at the initiation of treatment and calendar year were not associated with an increased or decreased rate of change of combination antiretroviral treatment. Determining the reasons for stopping the treatment and whether they were associated with an increased or decreased rate of change was not possible in this analysis. Reasons for stopping the treatment were largely unavailable in AHOD and were only collected prospectively since July 1999.

Where a combination change was redefined to include dropping an antiretroviral from an existing regimen, the overall rate of therapy change doubled to 0.95 per follow-up year. The cofactors independently associated with the rate of change remained the same (CD4 count and treatment class). However, a previous AIDS-defining illness was statistically significantly associated with an increased rate of combination change whereas in the previous analysis this variable was only marginally significant.

Our finding that the rate of change is faster if the combination antiretroviral treatment is initiated at a CD4 count < 200 cells/μL is supported by analyses from other cohorts of HIV-infected persons. Several studies have assessed factors associated with failure of a patient's first combination antiretroviral treatment [4–6]. These studies have consistently shown that an increased rate of failure of first combination antiretroviral treatment is associated with starting treatment at a lower CD4 count. More recently, some studies have found that rates of AIDS-defining ill-

Table 3 Factors associated with the rates of combination antiretroviral treatment changes

					Univariate		Multivariate		
	n	FU	Count	Rate	RR	P value	RR	(95% CI)	*P* value
Overall	596	1349	590	0.45					
Age (years)									
< 30	125	248	99	0.40	1.0				
30–39	263	615	250	0.41	1.01	0.912	0.95	(0.71, 1.26)	0.711
40–49	139	322	158	0.49	1.24	0.148	1.19	(0.87, 1.61)	0.274
> 50	69	163	83	0.51	1.27	0.163	1.10	(0.76, 1.59)	0.606
Sex									
Male	570	1294	558	0.43	1.0				
Female	26	55	32	0.58	1.37	0.146	1.35	(0.88, 2.08)	0.163
Exposure									
MHS	459	1049	447	0.43	1.0				
Other	107	223	112	0.50	1.18	0.177	1.12	(0.86, 1.46)	0.406
NR	30								
Previous ADI									
No	533	1210	500	0.41	1.0				
Yes	63	139	90	0.65	1.54	0.002	1.31	(0.97, 1.77)	0.078
HIV-1 RNA (copies/mL)									
⩾ 50 000	272	588	266	0.45	1.0				
< 50 0000	250	569	214	0.38	0.83	0.079	0.96	(0.77, 1.2)	0.751
NR	74								
CD4 (cells/μL)									
> 350	263	587	218	0.37	1.0				
200–350	123	277	100	0.36	0.95	0.723	0.96	(0.74, 1.24)	0.750
< 200	137	290	168	0.58	1.53	< 0.001	1.43	(1.13, 1.80)	0.003
NR	73								
Drug class combination									
Excludes NNRTI	359	779	399	0.51	1.0				
Excludes PI	284	521	160	0.31	0.61	< 0.001	0.64	(0.51, 0.80)	< 0.001
NNRTI + PI	33	48	31	0.64	1.10	0.642	1.08	(0.66, 1.77)	0.758
Combination									
First	596	817	322	0.39	1.0				
Second	322	334	149	0.45	0.85	0.142	0.87	(0.69, 1.10)	0.258
Third +	149	197	119	0.60	0.87	0.301	0.93	(0.70, 1.25)	0.652
Time period									
1997	278	167	84	0.50	1.0				
1998	446	373	179	0.48	0.96	0.747	0.86	(0.67, 1.20)	0.465
1999	565	500	197	0.39	0.79	0.071	0.80	(0.60, 1.10)	0.126
2000	567	308	130	0.42	0.84	0.212	0.84	(0.61, 1.14)	0.266

Number of patients may add up to more than total for some variables as patient can contribute to more than one category.
FU = total follow-up measured as person-years; count = number of combination antiretroviral treatment changes; rate = rate of combination antiretroviral treatment changes; RR = rate ratio; CI = confidence interval; MHS = male homosexual contact; ADI = AIDS defining illness; NR = not reported; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor. Drug class combination: excludes NNRTI = a nucleoside reverse transcriptase inhibitor and/or PI; excludes PI = at least one NNRTI, without a PI.

nesses following the initiation of combination antiretroviral treatment are raised in those patients who start treatment with a CD4 count < 200 cells/μL [11–14]. Furthermore, consistent with our analyses, rates of AIDS-defining illnesses were similar in patients who started treatment with CD4 counts > 350 cells/μL and in those who started with CD4 counts between 200 and 350 cells/μL [6,15].

However, it is also possible that more rapid treatment changes in patients who started treatment with a CD4 count < 200 cells/μL are owing to clinician or patient concerns about low immunological status. In an attempt to assess this we examined the proportion of patients with undetectable viral load at 6 and 12 months following treatment initiation according to baseline CD4 count strata (Table 5). Although the viral load at baseline was higher in patients with a low baseline CD4 count, the proportion of patients with undetectable viral load at 6 and 12 months was very similar at around 65–70% in all three strata. This lends some support to the argument that the faster treatment changes observed in patients with a baseline CD4 count < 200 cells/μL reflect different prescribing patterns. This probably results from the poorer immunological status and hence the immediate risk of opportunistic infections in this group. Different prescribing patterns are also, to some extent, reflected in Table 2, where a larger proportion of patients with a baseline CD4 count < 200 cells/μL and a

Table 4 Proportion of patients whose first, second and third combination change was either an addition of a new antiretroviral or a single/multiple antiretroviral substitution

	1st combination change		2nd combination change		3rd combination change	
	Substituted antiviral ($n = 228$) *n* (%)	Added antiviral ($n = 94$) *n* (%)	Substituted antiviral ($n = 105$) *n* (%)	Added antiviral ($n = 44$) *n* (%)	Substituted antiviral ($n = 56$) *n* (%)	Added antiviral ($n = 15$) *n* (%)
Sex						
Male	219 (72)	86 (28)	101 (72)	39 (28)	52 (78)	15 (22)
Female	9 (53)	8 (47)	4 (44)	5 (56)	4 (100)	0 (–)
Age (years)						
< 30	41 (69)	18 (31)	14 (67)	7 (33)	9 (82)	2 (18)
30–39	94 (69)	42 (31)	48 (73)	18 (27)	21 (78)	6 (22)
40–49	59 (71)	24 (29)	29 (69)	13 (31)	14 (67)	7 (33)
> 50	34 (77)	10 (23)	14 (70)	6 (30)	12 (100)	0 (–)
Exposure						
MHS	174 (72)	69 (28)	80 (73)	30 (27)	44 (79)	12 (21)
Other	42 (70)	18 (30)	20 (67)	10 (33)	11 (92)	1 (8)
NR	11	7	5	4	1	2
Previous ADI						
No	204 (73)	77 (27)	87 (70)	38 (30)	45 (76)	14 (24)
Yes	24 (58)	17 (42)	18 (75)	6 (25)	11 (92)	1 (8)
CD4 cells/μL						
> 350	91 (70)	39 (30)	31 (61)	20 (39)	22 (85)	4 (15)
200–350	45 (69)	20 (31)	19 (76)	6 (24)	5 (71)	2 (29)
< 200	52 (68)	25 (32)	31 (72)	12 (28)	18 (75)	6 (25)
NR	40	10	24	6	11	3
Viral load (HIV-1 RNA copies/mL)						
⩾ 50 000	99 (68)	47 (32)	47 (71)	19 (29)	28 (88)	4 (12)
< 50 000	91 (73)	33 (27)	32 (63)	19 (37)	19 (76)	6 (24)
NR	38	14	26	6	9	5

'Substituted antiviral' refers to the substitution of at least one antiviral from the previous combination, including the addition of an antiviral.
'Added antiviral' refers to the addition of at least one new antiviral to the otherwise unchanged previous combination.
MHS = male homosexual contact; ADI = AIDS-defining illness; NR = not reported.

viral load > 50 000 copies/mL initiated combination therapy with a treatment regimen containing a PI.

In our analyses, patients receiving combination antiretroviral treatment including an NNRTI had a slower rate of change than patients receiving a PI. Whether this reflects increased effectiveness of combinations including NNRTIs, better tolerability of these compounds, fewer long-term adverse events, or a perception of fewer adverse events is not known. In Australia, there has been a perception that combination treatment including a PI is strongly associated with the development of lipodystrophy [16]. It may be that this has led to patients changing their combination treatment to include NNRTIs and exclude PIs which, in turn, would contribute to a faster rate of change of combinations including a PI. Certainly, in our data, the proportion of patients on NNRTI combinations increased from 36% in 1997 to 51% in 2000, although this increase has largely been in the patients' initial combination.

An apparent inconsistency in our analyses is that the estimated time to treatment change was longer for the first combination treatment than the second and third combinations (Fig. 1), while the formal analysis of rates of change revealed little difference in the rates according to whether a patient was receiving a first, second or third and later combination. The reason for this apparent discrepancy is that we included in the time to changing treatment following first antiretroviral treatments those patients who had not changed their treatment. These patients would not contribute to the estimated time to treatment change following a second or later antiretroviral combination. Hence, a naive comparison of the survival curves in Fig. 1 is confounded by different groups of patients contributing to the different curves. In contrast, the formal analyses of rates of combination change, which is based on a random-effects Poisson model, is essentially stratified by the patient. The comparison of rates of change of the first with the second

Table 5 Viral load (HIV-1 RNA copies/mL) at baseline, 6 months and 12 months following initiation of combination therapy by CD4 strata

	Baseline CD4 (cells/μL)		
Viral load (HIV-1 RNA copies/mL)	**< 200 ($n = 137$)**	**200–349 ($n = 123$)**	**> 350 ($n = 263$)**
Median viral load at baseline	187 700	78 950	10 900
% Undetectable (≤400)			
6 months ($n = 540$)	68.5	74.4	65.5
12 months ($n = 496$)	71.5	69.9	62.6

combination, for example, is therefore correctly based on patients who have received at least two combination treatments. The best interpretation of these results is that the rate of change of combination antiretroviral treatments is similar regardless of whether the patient is receiving a first or any subsequent combination. Patients receiving a third combination, however, are those who tend to change combinations more rapidly.

There are weaknesses and limitations to our study. Firstly, patients were recruited to AHOD from June 1999, with data on antiretroviral treatment and HIV disease natural history collected retrospectively. Thus, the analysis presented in this paper is based on both retrospective and prospective follow-up. Because the analysis of data from 1997 onwards from patients recruited in June 1999 might introduce some biases and patient heterogeneity into the results, we limited the analyses to those patients who commenced antiretroviral therapy after 1 January 1997. In these analyses we were unable to investigate the reasons for treatment change. Although this information is currently being collected in AHOD, it has been collected prospectively only since July 1999. The use of reasons for stopping would help elucidate the question of whether the increased rate of combination treatment is a result of treatment-related toxicities or virological failure. Secondly, as AHOD is a reasonably young cohort, our analyses are based on relatively small numbers of patients and modest periods of follow-up. Certainly some factors, such as female patients and patients with a previous AIDS-defining illness, had nonstatistically significantly increased rates of antiretroviral-treatment change. It is not clear whether these results reflect a lack of power in our analyses, or whether these variables are genuinely nonsignificant predictors of rates of change. Similar analyses of combination antiretroviral-treatment change rates in other, larger HIV cohorts would be useful in validating our results.

In this study, we used the rate of combination antiretroviral treatment change as the endpoint. The advantage of adopting this endpoint for analysis is that it covers the entire time period from when a patient first starts antiretroviral treatment. Many studies have looked at short-term virological or immunological endpoints after first initiating antiretroviral treatments, but this only addresses the early time period of treatment. Using rates of AIDS-defining illnesses as an endpoint has become increasingly difficult in the era of effective antiretroviral treatment as such illnesses are now rare, with most HIV-infected patients living without AIDS for long periods. Robust analyses based on AIDS-defining illnesses require very long periods of follow-up. Rates of combination antiretroviral treatment change represent an intermediate endpoint for analyses of HIV-infected cohorts that could complement the analyses of these short- and long-term endpoints. Furthermore, data on antiretroviral treatments received are now collected routinely from all HIV-infected cohorts, and thus rates of change of combination treatment could be analysed in a similar fashion.

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