Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre

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Objective: To describe the reasons for, and factors associated with, modification and discontinuation of highly active antiretroviral therapy (HAART) regimens at a single clinic.

Subjects: A total of 556 patients who started HAART at the Royal Free Hospital were included in analyses. Modification was defined as stopping or switching any antiretrovirals in the regimen, whereas discontinuation was defined as the simultaneous stopping of all antiretrovirals included in the initial regimen. Reasons were classified as immunological/virological failure (IVF) and toxicities and patient choice/poor compliance (TPC).

Results: The median CD4 count at starting HAART was 171×10^6 cells/l and viral load 5.07 log copies/ml. During a median follow-up of 14.2 months, 247 patients (44.4%) modified their HAART regimen, 72 due to IVF (29.1%) and 159 due to TPC (64.4%) and a total of 148 patients (26.6%) discontinued HAART. Older patients were less likely to modify HAART [relative hazard (RH), 0.73 per 10 years; $P = 0.0008$], as were previously treatment-naive patients (RH, 0.65; $P = 0.0050$), those in a clinical trial (RH, 0.64; $P = 0.027$) and those who started nelfinavir (RH, 0.57; $P = 0.035$). Patients who started with four or more drugs (RH, 2.21, $P < 0.0001$), who included ritonavir in the initial regimen (RH, 1.41; $P = 0.035$) or who had higher viral loads during follow-up (RH per log increase, 1.51; $P < 0.0001$) were more likely to modify HAART.

Conclusions: There was a high rate of modification and discontinuation of HAART regimens in the first 12 months, particularly due to toxicities, patient choice or poor compliance.

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Introduction

The introduction of highly active antiretroviral therapy (HAART) has been shown to be highly effective in reducing mortality and morbidity in both clinical trials and in a number of large observational studies [1–7]. A therapeutic goal of HAART includes the complete inhibition of viral replication and hence significantly

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reduce the risk of developing drug resistance [8,9]. Although results from clinical trials suggest that in excess of 90% of patients who start HAART can achieve viral loads below the limit of detection [10–12], results from observational studies suggest a much lower proportion of patients respond to HAART in this way [13–17]. The problems of toxicities and complicated treatment regimens associated with HAART are considerable [18–20] and may lead to problems with adherence, sub-optimal therapy, discontinuation of therapy, and potentially to treatment failure [21]. Clinical trials have reported the frequency and severity of toxicities associated with HAART but similar results from observational studies are less common. In a group of patients starting predominantly saquinavir regimens, 25% of patients had stopped HAART by 1 year after starting treatment [22] and in another study, 36% modified HAART over a median follow up of 45 weeks [23]. Patients with lower CD4 cell counts, higher viral loads and who had previously been treated were more likely to modify their HAART regimen. To our knowledge only one study has described the reasons for modification of HAART, and found a higher proportion of patients stopped HAART due to toxicities than to treatment failure over the 45 weeks of follow-up [23].

The aims of this study were therefore to describe discontinuation and modification of HAART regimens among all patients initiating HAART at a single treatment centre, to describe the reasons for and the factors associated with discontinuation or modification of the regimen.

Methods

Patients

Patients with HIV are seen at the Ian Charleson Centre at the Royal Free Hospital at regular intervals for clinical assessment, trial follow-up and laboratory monitoring. The patients have been previously described [24]. Information on deaths and all AIDS-defining illnesses are updated annually from patient notes by a trained research assistant and by cross checking with a HIV/AIDS clinic database. The analyses presented in this paper use all information collected to the end of 1998. Information on all AIDS-defining illnesses, including those made after an initial AIDS-defining illness, are recorded. Information on viral loads and CD4 cell counts are provided directly from the laboratory; all viral loads included in this analysis were measured using the Roche Amplicor assay (Roche, Branchberg, New Jersey, USA), with a lower limit of detection of 400 copies/ml. For all antiretrovirals, including those used in clinical trials, each reported start and stop date was collected; thus all interruptions of therapy were collected as well as continuous periods of treatment. Prescribing of antiretrovirals at the Royal Free Hospital follows national guidelines wherever possible [9]. For each time a patient stopped therapy, the reason for stopping was collected from patient notes. Reasons for stopping included increasing viral loads, decreasing CD4 cell counts, short-term side effects including nausea, malaise, headaches, allergy, diarrhoea, mouth ulcers, rash and longer-term side effects including lipodystrophy, peripheral neuropathy, anaemia, pancreatitis, diabetes and abnormal liver function tests, patient choice and poor compliance. Reasons were retrospectively classified in one of these groups; they were not assigned prospectively at the time of the treatment modification. For this analysis reasons were further grouped as immunological or virological failure (IVF) toxicities or patient choice/poor compliance (TPC), and unknown reasons.

A total of 556 patients were included in these analyses. Inclusion criteria for the current study were starting a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) for the first time as part of a HAART treatment regimen (i.e. in conjunction with at least two nucleosides) and with a CD4 cell count measurement prior to starting HAART and at least one subsequent follow-up visit. Patients starting HAART as part of a clinical trial were included in the analyses under their trial HAART regimen.

Modification of HAART was defined as the first time at least one of the antiretrovirals used as part of an initial HAART regimen was stopped. Only the first modification for each patient was included in statistical analyses of HAART modification. Discontinuation was defined as the simultaneous stopping of all antiretrovirals used as part of the initial HAART regimen. Thus patients whose first change to HAART was discontinuation were also included as a modification, but once a patient had modified HAART in some way they were no longer considered at risk for discontinuation.

Statistical methods

Comparisons of demographic characteristics at starting HAART were performed using chi-square tests, the Kruskall–Wallis test or unpaired t-test, as appropriate. A person–years analysis was used to determine the incidence of stopping specific antiretrovirals. Patient follow-up began at the date of starting HAART and ended at stopping the antiretroviral in question or at last patient follow-up. Confidence intervals for the incidence of modification were calculated from a normal approximation or from the exact Poisson distribution when there were less than 20 events.

Kaplan–Meier estimates were used to describe the time to first modification of HAART; the analysis was repeated to describe the time to discontinuation of

HAART and to describe the time to modification due to IVF and TPC separately. The reason for modification was not known for 16 patients (6.5%). Toxicity, patient choice and non-compliance were grouped together as they are likely to be strongly related to each other and it may not be easy to specifically identify if a regimen was modified or discontinued due to toxicities or patient choice/poor compliance. In analyses of time to modification of HAART due to a specific reason, patients who modified their HAART regimen due to a reason other than the one investigated were censored at the date of modification. Kaplan–Meier analyses were also used to describe the time to restarting HAART after discontinuation of HAART.

Cox proportional hazards models were used to determine the factors associated with modification of HAART. All the models were stratified by calendar quartile of starting HAART. The factors investigated included demographic variables, treatment related variables, such as the number of new drugs started, whether the patient was treatment naïve, date of starting HAART, the antiretrovirals used as part of HAART (zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine/efavirenz, saquinavir, indinavir, ritonavir and nelfinavir), clinical status, and CD4 cell count and viral load. Both laboratory markers were included as fixed variables at starting HAART and time-updated variables, using the latest available measurement of each marker. Variables that were significant in univariate analyses ($P < 0.10$) were then included in a forward selection multivariate model with a removal level of significance of $P > 0.10$. The sensitivity of results from this model were further assessed by using backward selection models and by including all variables significant in univariate analyses ($P < 0.10$) with consistent results. Cox models were repeated to investigate the factors associated with discontinuation of HAART and the factors associated with modification of HAART due to IVF or TPC and the factors related to restarting a HAART regimen among those patients who discontinued HAART. Tests of the proportional hazards assumption showed no evidence that the assumption of proportional hazards did not hold.

Analyses were performed using Statistical Analyses Software (SAS, version 6.12, Cary, North Carolina, USA). All tests of significance are two-sided and *P*-values of less than 0.05 were considered significant.

Results

The patients are described in Table 1. The median CD4 cell count at starting HAART was 171×10^6

Table 1. The characteristics of 556 patients from the Royal Free Centre for HIV Medicine starting highly active antiretroviral therapy (HAART).

	Patients	NNRTI-HAART	PI-HAART		CD4 ($\times 10^6$ cells/l)		Viral load (log copies/ml)	
	n (%)	n (%)	n (%)	*P*	Median	*P*	Median	*P*
Total	556 (100)	138 (24.8)	418 (75.2)	–	171	–	5.07	–
Gender								
Male	450 (80.9)	105 (76.1)	345 (82.5)	0.094	186	0.0040	5.08	0.099
Female	106 (19.1)	33 (23.9)	73 (17.5)		140		4.90	
Risk group								
Homosexual	363 (65.3)	86 (62.3)	277 (66.3)	0.091	207	< 0.0001	5.09	0.51
Other	45 (8.1)	7 (5.1)	38 (9.1)		116		5.17	
Heterosexual	148 (26.6)	45 (32.6)	103 (24.6)		140		4.96	
Ethnic origin								
White	385 (69.2)	93 (67.4)	292 (69.9)	0.66	190	0.0003	5.10	0.75
African	122 (21.9)	34 (24.6)	88 (21.1)		137		5.03	
Other	49 (8.8)	11 (8.0)	38 (9.1)		170		4.99	
Year of first visit								
⩽ 1993	156 (28.1)	44 (31.9)	112 (26.8)	< 0.001	160	0.26	4.91	0.014
1994–1996	245 (44.1)	72 (52.2)	173 (41.4)		180		5.03	
⩾ 1997	155 (27.9)	22 (15.9)	133 (31.8)		188		5.23	
Year started HAART								
< 2/97	139 (25.0)	42 (30.4)	97 (23.2)	< 0.001	110	< 0.0001	5.11	0.0002
→ 7/97	133 (23.9)	14 (10.1)	119 (28.5)		202		5.05	
→ 2/98	145 (26.1)	55 (39.9)	90 (21.5)		185		4.91	
⩾ 2/98	139 (25.0)	27 (19.6)	112 (26.8)		210		5.30	
AIDS at HAART								
No	339 (61.0)	87 (63.0)	252 (60.3)	0.57	250	< 0.0001	5.02	0.025
Yes	217 (39.0)	51 (37.0)	166 (39.7)		80		5.19	
ARV naive								
No	242 (43.5)	80 (58.0)	162 (38.8)	< 0.001	139	< 0.0001	4.84	< 0.0001
Yes	314 (56.5)	58 (42.0)	256 (61.2)		214		5.17	

NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ARV, antiretroviral.

cells/l [interquartile range (IQR), 73–300 $\times 10^6$ cells/l] and viral load, available for 452 patients (81.3%), was 5.07 log copies/ml (IQR, 4.37–5.55 log copies/ml). The median follow-up was 14.2 months (IQR, 0.2–18.7 months) and median age was 34.9 years (IQR, 30.5–40.1 years). Patients had first visited the Royal Free a median of 20 months prior to starting HAART (IQR, 4–44 months). The majority of patients (n = 418; 75.2%) started a PI-based HAART, as opposed to an NNRTI-based HAART. There was some heterogeneity in viral load and CD4 cell count at starting HAART between demographic groups (Table 1). Patients starting a PI-based HAART regimen had significantly higher viral loads at starting HAART compared with those starting NNRTI-HAART regimens (medians of 5.17 and 4.74 log copies/ml respectively, $P < 0.0001$), but there was no significant difference in the CD4 cell count at starting HAART (medians 170 and 184 $\times 10^6$ cells/l, respectively, $P = 0.27$). A total of 314 patients (56.5%) were treatment naive at starting HAART, and this was generally consistent across patient groups, as was the duration of previous treatment among pre-treated patients (median 8 months; IQR, 4–18 months). Patients starting an NNRTI-based HAART were significantly less likely to be antiretroviral naive ($P < 0.001$). The majority of patients (n = 428; 77.0%) were starting HAART with three or more antiretrovirals to which they were previously treatment naive and 182 patients (32.7%) started HAART as part of a clinical trial.

Figure 1 describes the incidence of stopping (modification or discontinuation) specific antiretrovirals used in HAART. The incidence of stopping nucleosides used in HAART was highest for didanosine at 22.4 per 10 person–years of follow-up [PYFU; 95% confidence interval (CI), 15.2–29.6] and lowest for zalcitabine (9.4; 95% CI, 3.6–13.0). The incidence of stopping indinavir, ritonavir and nelfinavir was quite similar at around 16 per 10 PYFU, and was slightly lower for hard-gel saquinavir (11.0 per 10 PYFU; 95% CI. 7.4–14.6). The incidence of stopping NNRTIs was 13.3 per 10 PYFU; there was not enough data to consider specific NNRTIs separately. There were no differences in the incidence of stopping specific antiretrovirals when comparing pre-treated and treatment-naive patients (data not shown). Figure 1 also describes the incidence of stopping specific antiretrovirals according to the reason for stopping. The incidence of stopping due to IVF was highest for NNRTIs (6.6 per 10 PYFU) whereas the incidence of stopping ritonavir and didanosine was highest due to TPC (12.7 and 17.6 per 10 PYFU, respectively).

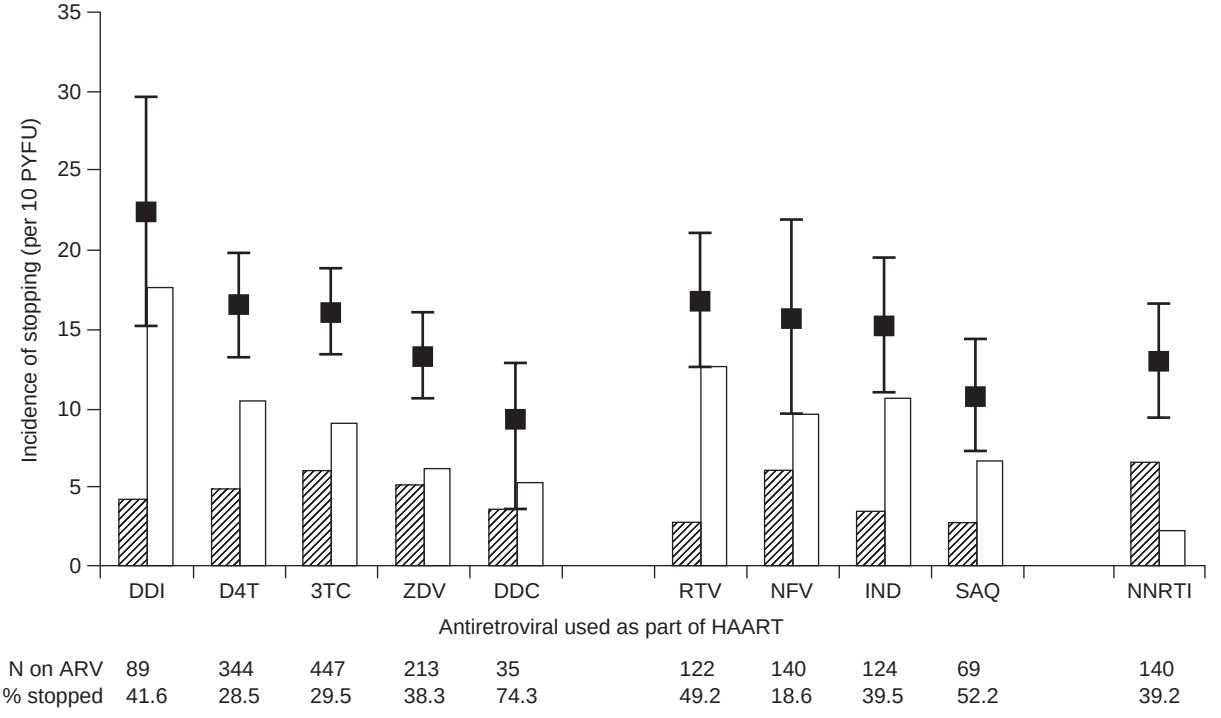

Fig. 1. Incidence of stopping individual antiretrovirals. Values are means and 95% confidence intervals. The vertical bars describe the incidence of stopping specific antiretrovirals according to reason for stopping: open bars, toxicities, patient choice/poor compliance; shaded bars, immunological/virological failure. ARV, antiretroviral; HAART, highly active antiretroviral therapy; PYFU, person–years of follow-up; DDI, didanosine; D4T, stavudine; 3TC, lamivudine, ZDV, zidovudine; DDC, zalcitabine; RTV, ritonavir; NFV, nelfinavir; IND, indinavir; SAQ, saquinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor.

In total, 247 patients (45%) modified their HAART regimen and 148 (26%) discontinued HAART as shown in Figure 2a. By 6 months after starting HAART, 25.6% of patients are estimated to have modified their HAART regimen (95% CI, 21.8–29.4%) and 14.8% are estimated to have discontinued HAART (95% CI, 11.7–17.9%). Of those that discontinued HAART, 83 patients subsequently restarted HAART (56.1%), and the time to restarting HAART is illustrated in Figure 2b. The median time to restarting HAART was 7 months (95% CI, 5.2–9.0 months) and by 6 months after discontinuation, 47.0% were estimated to have restarted HAART (95% CI, 38.4–55.6%). Among patients who discontinued HAART, there were no differences in the proportion who restarted HAART according to the reason for discontinuation of the initial HAART regimen ($P = 0.97$, χ^2 test), nor in the time to restarting HAART ($P = 0.24$, log-rank test).

The factors associated with modification, discontinuation, and restarting after discontinuation of HAART are shown in Table 2. Older patients were less likely to modify their HAART regimen [relative hazard (RH) per 10 years older, 0.73; $P = 0.0008$], as were patients who were treatment naive at starting HAART (RH, 0.65; $P = 0.0050$), those starting HAART as part of a clinical trial (RH, 0.64; $P = 0.027$), and those who included nelfinavir in HAART (RH, 0.57; $P = 0.035$). Patients who started HAART with four or more antiretrovirals (RH, 2.21; $P < 0.0001$), with ritonavir (RH, 1.41; $P = 0.035$) or whose latest viral load was higher (included as a time-dependent covariate RH, 1.51 per log higher, $P < 0.0001$) were all significantly more likely to modify HAART. Age, nelfinavir as part of HAART and latest viral load were similarly related to discontinuation of HAART. It was of interest to note that females were significantly less likely to discontinue HAART when compared with men (RH,

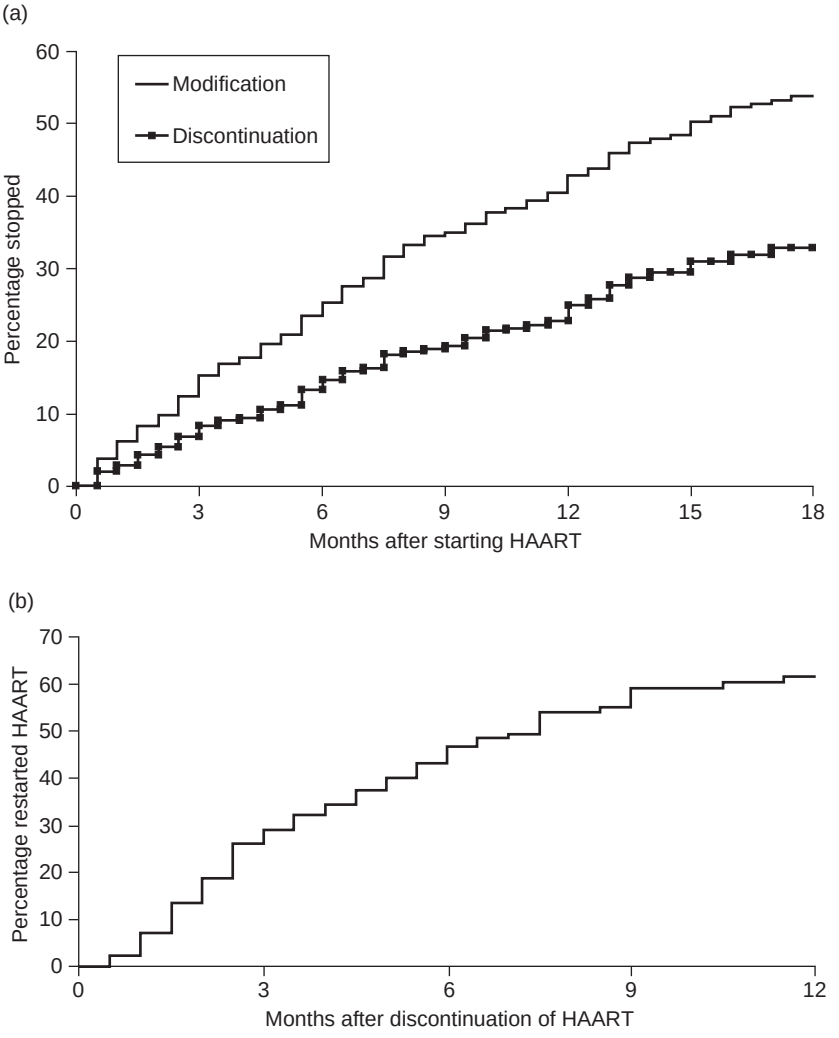

Fig. 2. (a) Kaplan–Meier time to modification and discontinuation of highly active antiretroviral therapy (HAART). (b) Time to restarting HAART after discontinuation of HAART.

Table 2. Factors associated with modification or discontinuation of highly active antiretroviral therapy (HAART) regimens.

		RH	95% CI	*P*-value
Modification of HAART				
Age	(per 10 years older)	0.73	0.60–0.88	0.0008
Treatment naïve		0.65	0.48–0.88	0.0050
Four or more ARVs in HAART [a]		2.21	1.50–3.26	< 0.0001
HAART as clinical trial		0.64	0.43–0.95	0.027
RTV in HAART		1.41	1.02–1.94	0.035
NFV in HAART		0.57	0.34–0.95	0.035
Viral load	(td, per log higher)	1.51	1.34–1.70	< 0.0001
Discontinuation of HAART				
Gender	Female	0.44	0.24–0.80	0.0072
Age	(per 10 years older)	0.69	0.53–0.89	0.0041
D4T in HAART		0.71	0.48–1.04	0.075
NFV in HAART		0.54	0.33–0.89	0.016
Viral load	(td, per log higher)	1.59	1.36–1.85	< 0.0001
Restarting HAART after discontinuation				
Gender	Female	1.96	1.00–3.89	0.050
PI-HAART		0.45	0.27–0.76	0.0024
CD4 cell count	(td, per 50% lower)	1.17	1.02–1.32	0.021
Viral load	(td, per log higher)	1.43	1.16–1.78	0.0010

All models are from forward selection multivariate analyses with factors significant at $P < 0.1$ from univariate analyses included. [a]HAART was started with four or more antiretrovirals in regimen. RH, relative hazard; CI, confidence interval; ARVs, antiretrovirals; RTV, ritonavir; NFV, nelfinavir; D4T, stavudine; td, variable included as time-updated variable.

0.44; $P = 0.0072$). Females were also significantly more likely to restart HAART after discontinuation (RH, 1.96; $P = 0.050$), whereas patients who started HAART with a PI-based HAART were less likely to restart HAART (RH, 0.45; $P = 0.0024$). Patients whose latest CD4 cell count was lower or viral load was higher during follow-up (both included as time-dependent covariates) were more likely to restart HAART (RH per 50% lower CD4 cell count, 1.17; $P = 0.021$ and per log higher viral load 1.43; $P = 0.0010$). Similar results were obtained when the analyses were repeated separately for pre-treated and treatment-naive patients, and among patients starting NNRTI- or PI-based HAART regimens (data not shown).

Figure 3 illustrates the time to modification of HAART due to IVF or TPC separately. A total of 159 patients (28.6%) modified their HAART regimen through TPC and this increased steadily throughout follow-up with 20.0% estimated to have modified their HAART regimen due to TPC by 6 months after starting HAART (95% CI, 16.5–23.5%). Seventy-two patients (12.9%) modified their HAART regimen due

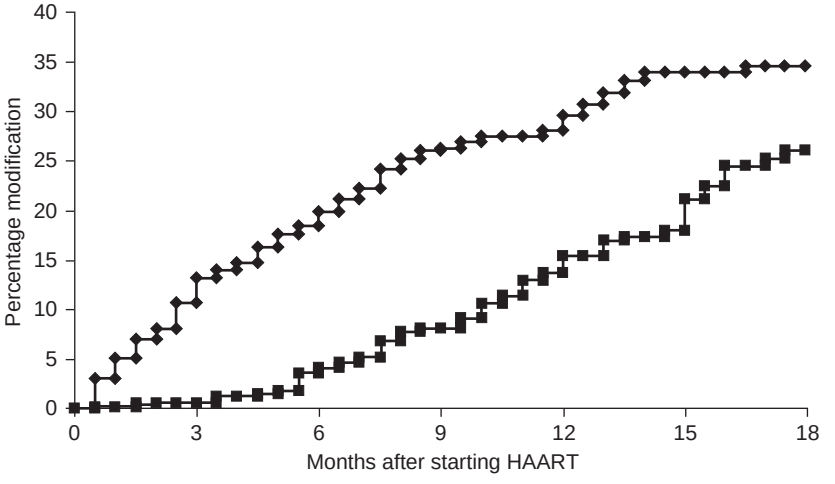

Fig. 3. Kaplan–Meier time to modification of highly active antiretroviral therapy (HAART): reasons for stopping. Diamonds, toxicities, patient choice/poor compliance; squares, immunological/virological failure.

to IVF, and as would be expected, there was an initially low rate of modification due to IVF which increased steadily as time on HAART increased. By 6 months after starting HAART 4.2% had modified HAART due to IVF (95% CI, 2.2–6.2%). Table 3 describes the factors associated with modification of HAART due to IVF or TPC. Patients who started HAART with four or more antiretrovirals were significantly more likely to modify their HAART regimen due to TPC (RH, 2.74; $P < 0.0001$), as were those who included ritonavir in their regimen (RH, 1.66; $P = 0.0072$). Older patients were significantly less likely to modify HAART due to TPC (RH, 0.73, $P = 0.0053$), as were those who started HAART as part of a clinical trial (RH, 0.54; $P = 0.0024$). A higher viral load was only associated with modification of HAART due to IVF (RH, 3.16; $P < 0.0001$). Patients who were treatment naive at starting HAART or who started HAART with three or more new antiretrovirals were less likely to modify HAART due to IVF (RH, 0.35 and 0.47; $P = 0.012$ and 0.029, respectively), as were patients who started nelfinavir (RH, 0.44; $P = 0.063$), although this result was of marginal statistical significance.

Discussion

This study has provided an important insight into the reasons and factors associated with modification and discontinuation of HAART treatment regimens among over 550 patients who started HAART as part of routine clinical care and were seen in a single centre where treatment policies and access to HAART are relatively uniform. This work adds to the multicentre observational study of Monforte *et al.* (23), where no distinction was made between modification or discontinuation of HAART, restarting HAART regimens or participation in clinical trials were not considered, and the incidence of stopping specific antiretrovirals was not studied. The median follow-up of patients at the Royal Free is longer than that reported by Monforte *et al.* and the cohort presented here included both pre-treated and treatment-naive patients.

In general, there were no large differences between the incidence of stopping specific antiretroviral, although in some cases the person–years of follow-up were quite limited and the analyses may have lacked power to identify differences; for example, efavirenz and nevirapine were combined to create a single NNRTI group. It was interesting to note that patients who started an NNRTI-based HAART stopped the NNRTI primarily due to IVF rather than TPC, although a higher proportion of patients starting an NNRTI-based HAART regimen were pre-treated. NNRTIs have been reported to have a more favourable side-effect profile when compared with PIs [9,25]. A large proportion of patients stopped ritonavir due to TPC, in agreement with a large clinical trial where almost 20% of patients stopped ritonavir treatment due to toxicities [1], which are reported to be worst in the first few days of treatment [18].

The frequency of discontinuation found in this study is consistent with that of Monforte *et al.* [23] and a previous report from the Royal Free [26] and extends earlier results on modification of therapy from the Royal Free [27]. A total of 45% of patients modified their HAART regimen and 26% discontinued HAART completely. These proportions were considerably higher than that reported from clinical trials, where typically 5–10% of patients stop their randomized treatment due to toxicities or problems with adherence [3,10]. The higher rate of modification and discontinuation within observational studies may partly

Table 3. Factors associated with modification of HAART for specific reasons.

		RH	95% CI	*P*-value
Drug-related toxicities or patient choice/poor compliance (TPC)				
Age	(per 10 years older)	0.73	0.59–0.91	0.0053
Four or more ARVs in HAART[a]		2.74	1.83–4.10	< 0.0001
HAART as clinical trial		0.54	0.37–0.81	0.0024
RTV in HAART		1.66	1.15–2.40	0.0072
Immunological/virological failure (IVF)				
Treatment naïve			0.15–0.79	0.012
Three or more new ARVs[b]		0.47	0.24–0.93	0.029
NFV in HAART		0.44	0.19–1.05	0.063
Viral load	(td, per log higher)	3.16	2.40–4.16	< 0.0001

All models are from forward selection multivariate analyses with factors significant at $p < 0.1$ from univariate analyses included. [a]HAART was started with four or more antiretrovirals in regimen. [b]Patient started HAART with three or more antiretrovirals to which they were previously treatment naive. RH, relative hazard; CI, confidence interval; ARVs, antiretrovirals; RTV, ritonavir; NFV, nelfinavir; td, variable included as time-updated variable.

explain the poorer virological and immunological outcomes reported from observational studies, compared to clinical trials [14–17].

TPC was the most common reason for modification of HAART regimens at the Royal Free, as in the ICONA (Italian Cohort of those Naïve to Antiretrovirals) study [23]. Patients tended to modify HAART regimens quite rapidly due to TPC, and further follow-up of large cohorts of patients are needed to identify long-term toxicities associated with HAART therapy, such as lipodystrophy and a possible increased risk of cardiovascular events and diabetes [28,29]. As expected, modification due to IVF was initially very low and only started to increase after an initial 6 months of HAART. In this study we combined together modification due to toxicities or patient choice/poor compliance as these reasons are unlikely to be independent and because only one reason for stopping each antiretroviral was collected. Compliance was not directly measured by a standardized questionnaire, pill-use monitoring devices or some other reported measure of compliance with HAART [30–33]. Poor compliance may be under-reported by the patient to the treating clinician and thus not recorded in the notes, or it may be related to other underlying reasons, such as toxicities.

We found that older patients were less likely to modify or discontinue HAART. Older patients may tend to have a more settled lifestyle into which complicated treatment regimens can be more easily incorporated. In addition, women were significantly less likely to discontinue HAART, and significantly more likely to restart HAART after discontinuation. The Royal Free has a dedicated clinic for women which is open on one day every week and this may have helped with compliance and initial management of toxicities leading to a lower rate of discontinuation. It is unclear however why women were more likely to restart HAART after discontinuation. One potential explanation is that women planned a small treatment break to fit in with family commitments and always planned to restart HAART after a short break. Neither exposure group or ethnic origin was related to modification or discontinuation of HAART. This may be due to a lack of power for exposure groups, where only a small number of intravenous drug users have started HAART. It is encouraging however that there was no evidence that those intravenous drug users who started HAART were more likely to modify or discontinue a HAART regimen, which supports evidence of a similar response to HAART among exposure groups reported from the EuroSIDA study [34], although no data was available on current injecting use.

There was a significantly lower rate of modification of HAART among patients starting HAART as part of a clinical trial, suggesting that there are some differences in the characteristics of patients who participate in a clinical trial and those that do not [35]. Further, patients who started HAART in a clinical trial were less likely to modify HAART due to TPC, reinforcing that patients who take part in clinical trials are often well-motivated and somewhat different from other patients who start HAART as part of their routine clinical care. Patients starting nelfinavir were less likely to modify or discontinue HAART, which is consistent with reports of a favourable side-effect profile [36,37]. Although we have adjusted for latest viral load and participation in a clinical trial, it may be that nelfinavir was given to a selected group of patients who were less likely to modify or discontinue HAART.

As would be expected, patients whose latest viral load was higher were significantly more likely to modify and discontinue their HAART regimen. Achieving low levels of viral replication is one of the key aims of antiretroviral therapy [8,9] and clinicians would consider modifying or discontinuing a HAART regimen after 16–24 weeks of treatment if a low viral load had not been achieved, a finding emphasized by the low rate of modification due to immunological/virological failure during the first 6 months of HAART therapy. Numerous observational studies have reported that patients with higher viral loads at initiating HAART were less likely to achieve viral loads below the limit of detection and more likely to experience a rebound in viral load [13–17], which may ultimately lead to modification or discontinuation of HAART. In agreement with Monforte *et al.* [23], the CD4 cell count was not related to modification or discontinuation of HAART, suggesting that everyday clinical decisions are made mostly on the basis of viral load measurements. However, the prognostic value of the CD4 cell count for clinical progression is well known [38,39], and the immediate risk of clinical progression may depend more on the CD4 cell count than viral load [40,41]. Patients whose latest CD4 cell count was lower were more likely to restart HAART, however, a lower more recent CD4 cell count was not an important factor for modifying or discontinuing a HAART regimen.

There are several limitations to this study which deserve attention. Firstly, reasons for stopping antiretrovirals were not classified prospectively, but retrospectively assessed from inspection of patient case notes. In some cases, this could result in an innacurate classification. Further, only one reason was recorded. There may be several contributory factors to stopping antiretrovirals, which are likely to be related and additionally may or may not be reported to the clinician and subsequently recorded in medical notes. We have tried to address this problem by combining reasons for modification which were unlikely to be independent, such as patient compliance and toxicities.

A second limitation is that our patient population is predominantly white homosexual men, which may limit the extent to which the results can be generalized to other groups of patients. However, the strengths of these data and analysis were that each and every episode of stopping antiretrovirals and the reason for doing so were collected by a single trained research assistant and this should help to minimize errors in collecting data from medical records. In addition, all patients starting HAART, including those in clinical trials were included in our analyses.

To conclude, we found a high rate of modification and discontinuation of HAART regimens at the Royal Free. Over half of the patients who discontinued HAART subsequently restarted. Patients in clinical trials were less likely to modify HAART. A higher viral load was strongly related to both modification and discontinuation of HAART. Patients starting more intensive HAART regimens were more likely to modify HAART due to TPC but less likely to modify HAART due to IVF. Further follow-up of large cohorts of patients is required to determine the long-term adherence to and toxicities of HAART, and ultimately the long-term clinical outcome of patients treated with HAART.

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