Experience with the use of a first-line regimen of stavudine, lamivudine and nevirapine in patients in the TREAT Asia HIV Observational Database

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Abstract

Background—The antiretroviral treatment (ART) combination of stavudine, lamivudine and nevirapine (d4T/3TC/NVP) is the most frequently used initial regimen in many Asian countries. There are few data on the outcome of this treatment in clinic cohorts in this region.

Methods—We selected patients from the TREAT Asia HIV Observational Database (TAHOD) who started their first ART regimen with d4T/3TC/NVP. Treatment change was defined as cessation of therapy or the addition or change of one or more drugs. Clinical failure was defined as diagnosis with an AIDS defining illness, or death while on d4T/3TC/NVP treatment.

Results—The rate of treatment change among TAHOD patients starting d4T/3TC/NVP as their first antiretroviral treatment was 22.3 per 100 person-years, with lower baseline haemoglobin (i.e. anaemia) associated with slower rate of treatment change. The rate of clinical failure while on d4T/3TC/NVP treatment was 7.3 per 100 person-years, with baseline CD4 cell count significantly associated with clinical failure. After d4T/3TC/NVP was stopped, nearly 40% of patients did not restart any treatment and, of those who changed to other treatment, the majority changed to zidovudine (ZDV)/3TC/NVP and less than 3% of patients changed to a protease inhibitor (PI)-containing regimen. The rates of disease progression on the second-line regimen were similar to those on the first-line regimen.

Conclusions—These real-life data provide an insight into clinical practice in Asia and the Pacific region. d4T/3TC/NVP is maintained longer than other first-line regimens and change is mainly as a result of adverse effects rather than clinical failure. There is a need to develop affordable second-line antiretroviral treatment options for patients with HIV infection in developing countries.

Keywords

adverse effects; antiretroviral treatment; Asia-Pacific region; stavudine / lamivudine / nevirapine; treatment change

Introduction

The combination of stavudine, lamivudine and nevirapine (d4T/3TC/NVP) is the most popular combination currently in use in many Asian countries because the individual drugs are available as generics and also in a convenient fixed-dose combination [1,2]. Although increasingly widely used, the regimen has some theoretical disadvantages. d4T and NVP do not have the optimal toxicity profile of drugs within their class [3]. Furthermore, 3TC and NVP have a low genetic barrier to resistance and failure may involve and compromise further treatment with two of the major classes of drugs [nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs)]. The third class of drugs, protease inhibitors (PIs), are expensive, and hence the management of patients who fail this regimen may be especially challenging in resourcepoor settings.

In spite of the widespread adoption of this regimen in antiretroviral therapy (ART) scale-up programmes, there is a paucity of published data on the use and outcome of this regimen in real-life clinical settings outside that of randomized controlled trials. Information about how well the regimen is tolerated and sustained in clinical practice is essential for evaluating the likely success of large-scale treatment programmes, and for understanding the magnitude of the need for second-line therapy or alternative drugs. The TREAT Asia HIV Observational Database (TAHOD) is a collaborative study by the TREAT Asia network, a co-operative network of clinicians throughout Asia and the Pacific, funded by the American Foundation of AIDS Research (amfAR) [4]. In this study, we describe the rate of treatment change among patients taking d4T/3TC/NVP in TAHOD and determine factors associated with d4T/3TC/NVP treatment change. We also describe the spectrum of first regimen changes selected after d4T/3TC/NVP change and examine the outcome with the second-line regimen.

Methods

TAHOD is a collaborative observational cohort study involving 12 sites in the Asia and Pacific region (see the Appendix). Detailed methods are published elsewhere [4], but briefly, each site recruited 200 patients, both treated and untreated with antiretroviral (ARV) drugs. Recruitment was based on a consecutive series of patients regularly attending a given site from a particular start-up time.

The following data were collected: (1) patient demographics: date of the clinical visit, age, gender, ethnicity, exposure category, date of first positive HIV test, HIV-1 subtype, and date and result of hepatitis B virus, hepatitis C virus and syphilis serology; (2) stage of disease: CD4 and CD8 cell count, HIV viral load estimation, prior AIDSdefining illness, and date and cause of death; (3) treatment history: prior and current prescribed antiretroviral treatments, reason for treatment changes (e.g. treatment failure, clinical failure and adverse events) and prophylactic treatments for opportunistic infection.

A modified version of the 1993 Centers for Disease Control and Prevention (CDC) AIDS case definition [5] was adopted, in which a presumptive diagnosis was available for most illnesses. All data were entirely observational, with test or intervention performed only according to the clinical guideline at each site. It was also noted that the laboratory methods varied across the sites. For example, HIV viral load estimations were obtained using a Roche Amplicor monitor (Roche Molecular Systems Inc., Branchburg, NJ, USA) or Quantiplex bDNA assay (Chiron Diagnostics, East Walpole, MA, USA).

Patients who started their first ARV combination with d4T/3TC/NVP were included in the study. Because of the limited number of patients who initiated treatment with d4T/3TC/NVP after recruitment to TAHOD, analysis was carried out on both retrospective and prospective data. Endpoints were defined as follows:

> Treatment change: either stopping the d4T/3TC/NVP combination, or any addition or change of at least one drug. Follow-up was censored at the time of treatment change or death, or at the date of most recent data transfer (October 2004). Clinical failure: diagnosis with an AIDS-defining illness, or death while on d4T/3TC/NVP treatment. Follow-up was censored at the time of clinical failure while on treatment, or at the time of treatment change. Virological failure: while on d4T/3TC/NVP treatment, an HIV viral load measurement of 4 400 HIV-1 RNA copies/mL, obtained at least 6 months after treatment was started. Follow-up was censored at virological failure, or at the time of treatment change. Immunological failure: while on d4T/3TC/NVP treatment, three successive decreasing CD4 cell counts (the first obtained at least 6 months after treatment was started). Follow-up was censored at immunological failure or at the time of treatment change. Clinical failure after first treatment change: diagnosis with an AIDS-defining illness or death after d4T/3TC/ NVP was stopped. Follow-up was censored at the time of AIDS or death, or at the date of most recent data transfer (October 2004).

Rate of treatment change, and clinical, virological and immunological failures were measured using the persontime method. Factors associated with treatment change and

clinical failure were assessed by univariate and multivariate analyses using Cox proportional hazard models. Covariates included in the analysis were demographics, time since HIV diagnosis, clinical disease at time of ART start, CD4 cell count and viral load prior to initiation of ART, nutritional status (body mass index), hepatitis B and C virus infection status, and haemoglobin level. Multivariate models were built using forward stepwise techniques. Statistical significance was taken as Po0.05.

Results

From September 2003 to 15 October 2004, 2088 patients were recruited to TAHOD. A total of 1702 patients were treated with ARV drugs (Table 1). The proportion of treated patients receiving monotherapy or double therapy decreased from 72% before 2000 to around 10% in recent years. From 2000 onwards, the majority of treated patients started with a NNRTI-based treatment combination, with three or more drugs containing at least one NNRTI and at least one NRTI, but without a PI. A total of 404 patients (23.7% of all patients starting their first treatment) started ARV treatment with d4T/3TC/NVP, which has been the major NNRTI-based treatment since 2002, with nearly half of all patients receiving the treatment. Treatment change and reasons: Among the 404 patients who started d4T/3TC/NVP as their first antiretroviral treatment, there were 131 patients who stopped the combination over a total of 586.9 person-years, a rate of 22.3 [95% confidence interval (CI) 18.8–26.5] per 100 person-years. The median duration of d4T/3TC/NVP treatment among the patients who stopped was 262 days (range 2–1519 days). The rate of treatment change of d4T/3TC/NVP was compared with that of other initial ARV regimens (Table 2, Fig. 1). Monotherapy and double therapy had the highest rate of treatment change, with almost all patients stopping within a year. The rate of change was lower in treatment with NNRTI-based triple or more combination therapy than in treatment with PI-based treatment, or in treatment containing three or more NRTIs. Treatment with d4T/3TC/NVP showed a lower rate of change than treatment with most other NNRTI-based regimens (Table 2). Baseline haemoglobin was the only significant risk factor associated with treatment change, with patients who were anaemic when d4T/3TC/NVP was started having a longer duration on this treatment (Table 3).

Table 4 summarizes the reasons for d4T/3TC/NVP treatment change and duration of treatment. Adverse effects (62.6% of patients stopped d4T/3TC; 20.3% of the 404 patients included in the study) were the major reason for treatment change, among which lipodystrophy was the most common, followed by hepatitis, rash and peripheral neuropathy. Drug interaction was not reported as a reason for treatment change. There were large variations of duration on treatment before the treatment change. Clinical failure: Among the 404 patients who started d4T/3TC/NVP as their first antiretroviral treatment, two patients died and 38 patients developed AIDS during treatment over 547.7 person-years of follow-up, giving a rate of clinical failure of 7.3 per 100 person-years (95% CI 5.4–10.0). The majority of newly diagnosed AIDS cases after treatment were a result of tuberculosis (39.5%), followed by cytomegalovirus retinitis (15.8%), extrapulmonary cryptococcosis (10.5%) and toxoplasmosis (10.5%). Baseline CD4 cell count was significantly associated with disease progression (data not shown).

Among the 38 patients who had an AIDS diagnosis, 13 stopped d4T/3TC/NVP at various stages, but none of these 13 patients stopped d4T/3TC/NVP because of the AIDS diagnosis, which was defined as an endpoint in the analysis. Reported reasons for stopping varied from the patient's decision to adverse effects or clinical failure at a later stage (nearly 1 year after the AIDS diagnosis).

Virological and immunological failure (among patients with a viral load or CD4 cell measurement after starting d4T/3TC/NVP)

There were 57 patients who had at least one HIV viral load assessment 6 months after starting d4T/3TC/NVP. Five patients had an HIV viral load of more than 400 copies/mL while on treatment (over 132.3 person-years), giving a rate of 3.7 per 100 person-years (95% CI 1.6–9.1). There were 56 patients who had at least three CD4 cell counts 6 months after starting d4T/3TC/NVP. During the period of d4T/3TC/NVP treatment (over 148.5 person-years), 10 patients had three consecutive decreasing CD4 cell counts, giving a rate of 6.7 per 100 person-years (95% CI 3.6–12.5).

Most of these patients either did not stop d4T/3TC/NVP treatment because of the virological or immunological failure, or stopped long after the failure, with the reasons for treatment change mainly not related to virological failure (data not shown). Adverse effects (mainly lipodystrophy) were again the major reason for treatment change.

Treatment change and outcome

Table 5 summarizes the ARV treatment used after d4T/3TC/NVP was stopped and the duration on d4T/3TC/NVP before stopping. Nearly 40% of the 131 patients stopped taking any treatment, at least for some period of time. Among those who changed to other treatment, the majority changed to zidovudine (ZDV)/3TC/NVP. Only three patients (< 3%) changed to a combination containing a PI.

The major reason for treatment change among those patients who changed to ZDV/3TC/NVP was adverse effects (86%, P<0.001), over half of which were lipodystrophy (52%), followed by peripheral neuropathy (20%) and lactic acidosis (14%). Patients who changed to ZDV/3TCNVP had remained on d4T/3TC/NVP for a significantly longer time (median 469 days; range 5–1398 days) than had the patients who changed to treatment other than ZDV/3TC/NVP after stopping d4T/3TC/NVP (median 79 days; range 2–1297 days; P<0.001).

A total of 20 patients developed AIDS and three died (one patient died with an AIDS diagnosis on the same day) after stopping d4T/3TC/NVP, over a total of 152.0 person-years of follow up, giving a rate of clinical failure of 14.5 per 100 person-years (95% CI 9.5–22.0). Patients receiving ZDV/3TC/NVP after stopping d4T/3TC/NVP had a lower rate of clinical failure than patients receiving no treatment (3.8 vs 27.3 per 100 person-years; P=0.004).

Discussion

Initial treatment with two NRTIs and one NNRTI is recommended by the World Health Organization (WHO) [6], as part of the '3 by 5' strategy against HIV and AIDS [7]. Nearly one in four of the TAHOD patients started their ARV treatment with d4T/3TC/NVP. Data on whether the drug was generic or proprietary was not collected. However, in Asian countries such as India [1,2] and Thailand [8], the generic d4T/3TC/NVP combination, or GPO-VIR in Thailand, is the most popular combination currently in use.

In this study, the rate of treatment change among TAHOD patients starting d4T/3TC/NVP as the first ARV treatment was found to be 22.3 per 100 person-years. The rate of d4T/3TC/NVP treatment change was comparable to that seen in other studies. Using data from the Australia HIV Observational Database (AHOD), Petoumenos et al. [9] reported a rate of treatment change of 31% among patients who started their first NNRTI-based HAART combination. In the OzCombo 2 Study [10], 27% of the patients on d4T/3TC/NVP did not complete treatment over a 52-week clinical trial. In a study in India [1], among patients receiving a generic NVP-based HAART regimen (55% of them receiving NVP in combination with d4T/3TC), 16% stopped treatment. The substantial rate of change is of concern given the very limited options available in some settings in TAHOD, as many people who stop actually do not have a viable alternative treatment regimen. This also shows that a one-combination-fits-all policy is potentially going to deprive a substantial number of patients of effective long-term therapy. In AHOD, patients with a baseline CD4 count of<200 cells/μL had an earlier treatment change, while in this study a lower baseline haemoglobin level (i.e. anaemia) was associated with a later treatment change. This association with anaemia may be explained by the fact that the common alternative drug, ZDV, is contraindicated in patients with anaemia. Hence there might be greater reluctance to change d4T/3TC/NVP therapy in anaemic patients because there are few effective and affordable options.

The rate of treatment change was lower among patients starting d4T/3TC/NVP than among patients initiating most other NNRTI-based triple or more combination therapies, a PI-based regimen or a triple combination containing only NRTI. Similar to AHOD, patients receiving NNRTI-based HAART treatment had a slower change rate than patients receiving PI-based treatment. Because of the small number of patients who were receiving PI-based treatment, further comparison was not performed. The reason for a higher change rate for PI-based regimens might be toxicity [9] or the unsustainable expense for some patients.

In this study, the main reported reason for d4T/3TC/NVP treatment change was adverse effects, this reason being recorded for 20% of the 404 patients initiating d4T/3TC/NVP and 62.6% of the 131 patients who stopped d4T/3TC/NVP. In a study with a relatively short follow-up time of 24 weeks in treatment-naïve patients receiving a fixed-dosed combination of d4T/3TC/NVP in Thailand [8], 20% experienced adverse events and 15% withdrew from the study because of the adverse events. Side effects were also the major reason for discontinuing HAART treatment in Indian patients (64% of patients who discontinued a generic HAART regimen) [1]. Although lactic acidosis and lipodystrophy were not observed during this 24-week study, this is consistent with our observation that these are late events:

the median duration on treatment for patients who stopped because of lactic acidosis was 416 (range 204–951) days and that for lipodystrophy was 546 (30–1519) days. Given the relatively short period of follow up in TAHOD, the true prevalence of adverse effects leading to long-term treatment change, such as lipodystrophy, lactic acidosis and peripheral neuropathy, may have been underestimated in this study, whereas early toxicities, such as hepatitis, rash and pancreatitis, may mainly have been captured. The prevalence of treatment-related hepatitis (2.5% of all patients receiving d4T/3TC/NVP) was similar to that found in a clinical trial setting in Thailand (5.8%) [11] and in observational studies in India (3.2%) [2] and Thailand (7%) [8]. However, without liver enzyme monitoring for all patients receiving treatment, this prevalence may be underestimated. The prevalence of lipodystrophy was low compared with prevalences for Western cohorts (38–50% [3,12,13]) but similar to those for other Asian patient populations [14,15]. This may reflect the fact that lipodystrophy is less common among nonwhite patients, and also the small proportion of patients receiving PI-based treatment in our cohort [15].

The rate of clinical failure while on d4T/3TC/NVP treatment and the relationship between baseline CD4 cell count and disease progression are similar to findings obtained in other studies [1,8,16,17]. It is possible that some of the events may have represented immune reconstitution syndrome. In a cohort of patients receiving fixed-dose combination therapy in India, 67% of clinical events were defined as immune reconstitution syndrome [2].

The rate of virological and immunological failure after 6 months of treatment was consistent with the findings of previous studies [8,16], although relatively few patients had measurements taken. It is interesting that neither disease progression nor virological or immunological failure was a major reason for treatment change, as patients generally continued their treatment after failure. When they finally stopped the regimen, it was mainly because of adverse effects. Another point worth noting is the relative paucity of data for HIV viral load and CD4 cell count change among patients receiving treatment, although TAHOD participating sites are by and large the better academic centres in the region. It is clear that many patients are managed without regular viral load and CD4 cell count monitoring, and yet seem to have similar rates of survival and response to treatment to patients who do receive such monitoring [4,17]. This shows that limitations in laboratory monitoring should not necessarily impede implementation of ART. However, the fact that early failure is not being detected in these patients by laboratory monitoring and the fact that treatment is maintained even in the patients in whom such failure is being detected suggest that many of these patients are likely to develop extensive resistance by the time a treatment change finally occurs.

After d4T/3TC/NVP was stopped, nearly 40% of patients ceased ART entirely. Among those who changed to other treatment, the majority changed to ZDV/3TC/NVP. This change is unlikely to be a result of early toxicity and is more likely to reflect a concern to avoid future lipodystrophy. When a cheap fixed-dose combination containing ZDV/3TC/NVP becomes more widely available, it is likely that this will be frequently used as the initial regimen because of this concern to avoid lipodystrophy. Only three patients changed to a combination containing PI. This may also reflect the limited choice of treatment among patients in the Asia and Pacific region. The rates of progression on the second-line regimen

were similar to those on the first-line regimen, further confirming that patients who changed were probably not failing the first-line regimen, but changed mainly because of toxicity concerns.

Several limitations should be taken into consideration when interpreting the results. Firstly, the analysis was performed on both prospective and retrospective data. With data transfer each year, increasing amounts of prospective data will be available for better understanding of the efficacy and side effects of the d4T/3TC/NVP regimen and other treatment combinations. Secondly, the TAHOD patients, who are recruited if they have 'good' follow-up based on clinicians' judgement, cannot be seen as entirely representative of HIV-infected patients in the Asia–Pacific region. However, studies on the natural history of HIV disease and responses to ARV treatment can still be derived from a cohort of TAHOD patients with good follow up, albeit with some limitations on the generalizability of the findings. Thirdly, although the overall follow-up rate is satisfactory (up to 90%), loss to follow-up must be considered when interpreting the results. AIDS or adverse effects might be underreported if a patient does not regularly visit the clinics or if a patient dies. Efforts have been made to maximize follow-up, with each site developing its own mechanism to contact patients whenever possible.

In summary, our study presents real-life data providing an insight into clinical practice in Asia and the Pacific region. It confirms the findings of earlier studies in African and Asian countries that have shown treatment with the simple fixed-dose combination of d4T/3TC/NVP to be safe and effective, with good adherence and tolerability [1,2,8,16]. It is of concern that there is a lack of systematic laboratory monitoring, together with very limited options for treatment changes, other than those implemented for side effects. It is also notable that adverse events are the most common reported reason for treatment change. As toxicity is likely to remain a problem, there is a need to develop affordable second-line ART options for patients with HIV infection in developing countries. Although d4T/3TC/NVP appears to be relatively well tolerated by the majority of patients, the current practice of treatment may well create extensive problems with resistance in the future.

Acknowledgements

Appendix

Appendix: the TREAT Asia HIV Observational Database

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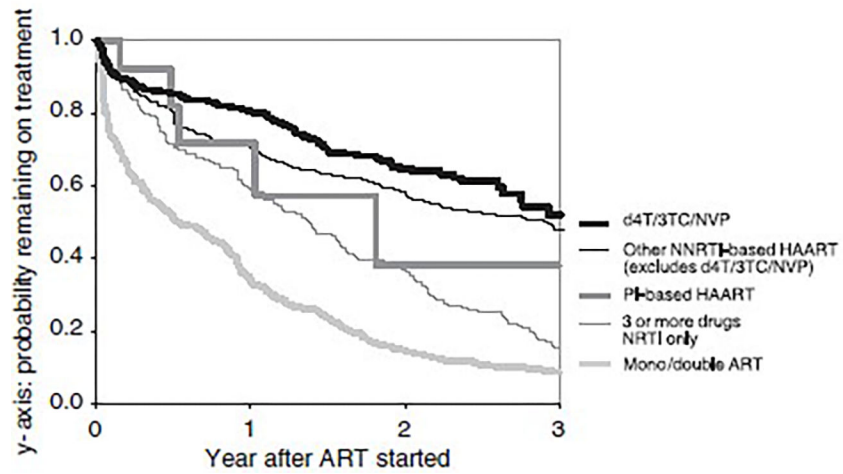
Fig. 1.
Duration of first antiretroviral treatment. d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; HAART, highly active antiretroviral therapy; PI, protease inhibitor; ART, antiretroviral therapy.

Table 1.

Type of first antiretroviral treatment, by year in which treatment started

Year started	Mono/double antiretroviral	3+ (NRTI ± PI – NNRTI)[*]	3+ (NRTI+NNRTI – PI)[†]			3+(NNRTI+PI ± NRTI)[‡]
			d4T/3TC/NVP	3TC/ZDV/NVP	Others	
1999	281 (72%)	101 (26%)		6 (2%)		0 (0%)
			1 (17%)	1 (17%)	4 (66%)	
2000	48 (29%)	27 (16%)		89 (54%)		0 (0%)
			22 (25%)	8 (9%)	59 (66%)	
2001	38 (17%)	39 (18%)		140 (64%)		3 (1%)
			33 (24%)	19 (14%)	88 (63%)	
2002	31 (8%)	36 (10%)		297 (81%)		3 (1%)
			140 (47%)	30 (10%)	127 (43%)	
2003	30 (7%)	21 (4%)		403 (88%)		4 (1%)
			174 (43%)	50 (12%)	179 (45%)	
2004	15 (14%)	6 (6%)		81 (77%)		3 (3%)
			34 (42%)	12 (15%)	35 (43%)	

[*] 3+ (NRTI ± PI – NNRTI), three or more drugs including at least one nucleoside reverse transcriptase inhibitor (NRTI) and/or a protease inhibitor (PI), but without a nonnucleoside reverse transcriptase inhibitor (NNRTI).

[†] 3+ (NRTI + NNRTI – PI), three or more drugs including at least one NNRTI, but without a PI.

[‡] 3+ (NNRTI + PI ± NRTI), three or more drugs including at least one NNRTI and one PI, with or without an NRTI.

d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; ZDV, zidovudine.

Table 2.

Rate of change of first antiretroviral treatment

First antiretroviral combination	Number of patients	Number stopped	Follow up (years)	Rate (per 100 person-years)	95% CI (per 100 person-years)
NNRTI-based	1016	395	1504.6	26.3	23.8–29.0
d4T/3TC/NVP	404	131	586.9	22.3	18.8–26.5
Other NNRTI-based [*]	612	264	917.7	28.8	25.5–32.5
3TC/ZDV/EFV	201	67	309.9	21.6	17.0–27.5
3TC/ZDV/NVP	120	51	160.6	31.8	24.1–41.8
3TC/d4T/EFV	112	38	180.7	21.0	15.3–28.9
ddI/d4T/EFV	76	48	151.8	31.6	23.8–42.0
ddI/d4T/NVP	56	35	47.9	73.1	52.5–101.8
Other	47	25	66.8	37.4	25.3–55.4
PI-based	13	5	13.5	36.9	15.4–88.7
Three or more, NRTI only	230	181	334.9	54.1	46.7–62.5
Mono/double therapy	443	422	424.4	99.4	90.4–109.4
Total	1702	1003	2277.4	44.0	41.4–46.9

[*] Excluding d4T/3TC/NVP.

CI, confidence interval; d4T, stavudine; 3TC, lamivudine; NVP, nevirapine; ZDV, zidovudine; EFV, efavirenz; ddI, didanosine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 3.

Predictors of treatment change among patients starting stavudine/lamivudine/nevirapine (d4T/3TC/NVP) as their first antiretroviral treatment

	Number of patients	Follow up (years)	Number of events	Rate*	Univariate		Multivariate	
					HR	*P*-value	HR (95% CI)	*P*-value
Total	404	586.9	131	22.3				
Gender								
Male	299	434.6	98	22.5	1.00		1.00	
Female	105	152.3	33	21.7	0.96	0.822	0.92 (0.62–1.37)	0.677
Age when treatment started (years)								
30	129	206.8	40	19.3	1.00		1.00	
31–40	202	275.8	67	24.3	1.22	0.322	1.26 (0.84–1.87)	0.260
41	73	104.4	24	23.0	1.16	0.571	1.18 (0.71–1.96)	0.517
Ethnicity								
Thai	222	345.2	79	22.9	1.00		1.00	
Indian	128	188.4	34	18.0	0.78	0.223	0.69 (0.45–1.06)	0.089
Other	54	53.3	18	33.8	1.33	0.272	1.12 (0.65–1.95)	0.682
Exposure category								
Heterosexual contact	363	534.7	118	22.1	1.00		1.00	
Other	41	52.2	13	24.9	1.07	0.823	1.01 (0.56–1.82)	0.983
Time between HIV treatment and treatment initiation (years)								
<1	239	360.7	77	21.3	1.00		1.00	
1–3	119	154.1	39	25.3	1.14	0.497	1.10 (0.74–1.62)	0.638
4	43	69.4	14	20.2	0.94	0.843	0.95 (0.54–1.68)	0.854
Test missing	3	2.7	1	36.4	1.60	0.640	1.76 (0.24–12.8)	0.577
Prior AIDS when treatment started								
No	215	334.1	72	21.6	1.00		1.00	
Yes	189	252.8	59	23.3	1.08	0.667	1.21 (0.84–1.73)	0.308
CD4 count prior to treatment (cells/μL) [†]								
<50	81	104.1	23	22.1	1.00		1.00	
50–99	43	63.3	11	17.4				
100–199	69	93.2	22	23.6				
200	42	56.6	19	33.6				
50	154	213.1	52	24.4	1.12	0.650	1.00 (0.61–1.66)	0.973
Not tested	169	269.8	56	20.8	0.98	0.936	0.90 (0.51–1.59)	0.706
HIV viral load prior to treatment (copies/mL) [†]								
150 000	25	36.0	8	22.2	1.00		1.00	
150 001	27	28.1	12	42.7	1.81	0.193	2.20 (0.88–5.45)	0.090
Not tested	352	522.8	111	21.2	0.93	0.842	1.05 (0.50–2.20)	0.901
BMI[‡] prior to treatment								
Underweight	57	82.2	15	18.2	1.00		1.00	

	Number of patients	Follow up (years)	Number of events	Rate*	Univariate		Multivariate	
					HR	*P*-value	HR (95% CI)	*P*-value
Normal	61	84.0	17	20.2	1.09	0.806	0.93 (0.46–1.91)	0.853
Overweight	13	9.8	3	30.8	1.40	0.597	0.97 (0.27–3.51)	0.961
Not tested	273	410.9	96	23.3	1.27	0.397	1.24 (0.67–2.30)	0.501
Hepatitis B virus infection§								
Negative	140	167.4	50	29.9	1.00		1.00	
Positive	11	21.8	4	18.3	0.62	0.363	0.64 (0.23–1.79)	0.395
Not tested	253	297.7	77	19.4	0.67	0.035	0.73 (0.50–1.07)	0.107
Hepatitis C virus infection§								
Negative	98	115.8	31	26.8	1.00		1.00	
Positive	12	15.3	5	32.7	1.18	0.731	1.13 (0.43–2.95)	0.801
Not tested	294	455.8	95	20.8	0.81	0.320	0.85 (0.57–1.28)	0.442
Haemoglobin¶ prior to treatment								
Normal	61	68.7	21	37.8	1.00		1.00	
Anaemia	155	215.9	41	19.0	0.53	0.013	0.53 (0.32–0.87)	0.013
Not tested	188	302.3	64	21.2	0.61	0.034	0.61 (0.38–0.96)	0.034

*
Rate per 100 person-years.

†
CD4 count measured within 180 days before treatment started; HIV viral load measured within 365 days before treatment started.

‡
Body mass index (BMI)=weight (kg)/[height (m)]2: Underweight, BMI < 18.5; normal, BMI 18.5–24.9; overweight, BMI>25.0.

§
Hepatitis B virus infection: a positive hepatitis B surface antigen (HBsAg) test; hepatitis C virus infection: a positive anti-hepatitis C virus antibody test.

¶
Haemoglobin tested within 180 days before treatment started. Definition of anaemia: normal, haemoglobin>13 g/dL for male and 12 g/dL for female subjects; anaemia, 8–13 g/dL for male and 8–12 g/dL for female subjects; severe anaemia, <8 g/dL for both male and female subjects.

CI, confidence interval; HR, hazard ratio.

Table 4.

Reasons for stavudine/lamivudine/nevirapine (d4T/3TC/NVP) treatment change and duration of treatment

Reason for treatment change	No. (%)	Days on treatment [median (range)]	No. (%) who stopped treatment permanently[*]
Total	131 (100)	262 (2–1519)	15 (11.5)
Adverse effects	82 (62.6)	295 (2–1519)	2 (2.4)
Lipodystrophy	26 (31.7)	546 (30–1519)	0 (0.0)
Hepatitis	10 (12.2)	27.5 (14–1297)	0 (0.0)
Rash	12 (14.6)	14 (10–108)	0 (0.0)
Peripheral neuropathy	9 (11.0)	407 (117–532)	0 (0.0)
Lactic acidosis	6 (7.3)	416 (204–951)	0 (0.0)
Pancreatitis	5 (6.1)	55 (5–343)	1 (20.0)
Nausea and vomiting	4 (4.9)	17.5 (2–49)	0 (0.0)
Fever	2 (2.4)	19 (11–27)	0 (0.0)
Allergy	1 (1.2)	61	0 (0.0)
Insomnia	1 (1.2)	42	0 (0.0)
Missing	6 (7.3)	67.5 (21–491)	1 (16.7)
Patient's decision/request	18 (13.7)	195.5 (6–1005)	7 (38.9)
Treatment failure	5 (3.8)	457 (138–672)	0 (0.0)
Clinical progression/hospitalization	3 (2.3)	85 (34–322)	1 (33.3)
Compliance difficulties	2 (1.5)	135.5 (9–262)	0 (0.0)
Other	18 (13.7)	250 (13–1071)	4 (22.2)
Financial problem	3 (16.7)	467 (264–549)	1 (33.3)
Doctor's decision	2 (11.1)	809 (547–1071)	0 (0.0)
Pregnancy	2 (11.1)	646.5 (286–1007)	0 (0.0)
Lost to follow up	1 (5.6)	29	0 (0.0)
Patient died	1 (5.6)	236	1 (100)
Not specified	9 (50.0)	155 (13–415)	2 (22.2)
Not reported	3 (2.3)	211 (88–545)	1 (33.3)

[*] As a percentage of the total number of patients who changed treatment for a specific reason (in the second column).

Table 5

Antiretroviral treatment after stavudine/lamivudine/nevirapine (d4T/3TC/NVP) stopped and duration on d4T/3TC/MVP before treatment changed

Antiretroviral treatment after d4T/3TC/NVP stopped	No. of patients	% of patients	Duration on d4T/3TC/NVF before Stopping [median (range)]
Not treated	49	37.4	83 (2–549)
Stopped treatment permanently	15	11.4	343 (23–545)
Changed to other treatment	34	26.0	27.5 (2–549)
after some time			
d4T/3TC/NVP	11	8.4	
d4T/3TC/EFV	11	8.4	
3TC/ZDV/EFV	4	3.1	
d4T/3TC	3	2.3	
ddI/3TC/NVP	1	0.8	
ddI/d4T/SQV/RTV	1	0.8	
d4T/3TC/IDV/RTV	1	0.8	
3TC/ZDV/NVP	1	0.8	
3TC/NVP	1	0.8	
3TC/ZDV/NVP	51	38.9	469 (5–1519)
Stopped d4T/3TC/NVP	44	33.4	470.5 (5–1519)
because of adverse effects			
Lipodvstrophy	23	17.6	618 (406-1S19)
Peripheral neuropathy	9	6.9	407 (117–532)
Lactic acidosis	6	4.6	416 (204–951)
d4T/3TC	12	9.2	32.5 (11–95)
d4T/3TC/EFV	6	4.6	60.5 (14–1297)
3TC/ZDV/EFV	5	3.8	418 (138–672)
3TC/NVP	3	2.3	547 (14–1007)
ABC/3TC/NVP	1	0.8	552
d4T/3TC/NVP/IDV	1	0.8	202
d4T/3TC/NVP/RTV	1	0.8	88
d4T/3TC/NVP/5QV/RTV	1	0.8	211
d4T/NVP	1	0.8	42

ABC, abacavir; ddI, didanosine; EFV, efavirenz; IDV, indinavir; RTV, ritonavir; SQV, saquinavir; ZDV, zidovudine.