Time to triple drug class antiretroviral treatment failure after initiation of HAART : Results from the EuroSIDA study group

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Abstract

Objectives: To determine the prevalence, incidence of and time to triple class failure (TCF) and the factors related to it after initiation of HAART.

Design and Methods: Observational longitudinal study of 3538 patients starting HAART from the pan-European study, EuroSIDA. Patients were followed from the date of starting HAART (baseline) until TCF. The incidence of TCF after starting HAART among both treatment experienced (TE) and treatment naïve (TN) patients according to calendar year and years of exposure to HAART were determined, as were factors associated with TCF in both patient groups, using Cox proportional hazards models.

Results: 469 patients (13.3%) failed 3 drug classes; of these, 400/2430 (16.5%) were TE and 69/1108 were TN (6.2%). At 6 years after baseline, 24.1% of TE patients were estimated to have TCF (95% confidence interval (CI) 21.6 – 26.6) compared to 11.9% of TN patients (95% CI 8.6 – 15.2) while the prevalence of TCF among patients under follow-up at/after 2002 was 16.1% in TE patients and 5.5% in TN patients. Among TN patients, there was an increase in the incidence of TCF with increasing time from baseline from 1.2 per 100 PYFU (95% CI 0.7 – 1.7) in the first 2 years after baseline to 4.7 per 100 PYFU (95% CI 2.1 – 8.9) at or after 5 years from baseline (33% increase per year, 95% CI 12 – 58%, p = 0.030), similar to the rate seen in TE patients treated for the same period of time (5.4 per 100 PYFU, 95% CI 3.5 – 7.3). TE patients who also started 2 new nucleosides at baseline had a 49% reduced risk of TCF (95% CI 23 – 66%, p = 0.0012), while each additional 12 months cumulative exposure to nucleosides prior to baseline was associated with a 6% increased risk of TCF (95% CI 2 – 11%, p = 0.0016).

Conclusion: We found a low rate of TCF among patients starting HAART, particularly among TN naïve patients, although the rate has increased progressively over time since starting HAART. Despite the influx of new patients, the prevalence of TCF is increasing significantly over calendar time. The long term consequences of TCF on the durability of HAART and how best to manage this situation deserves further focus.

Introduction

One of the goals of highly active antiretroviral therapy (HAART) is to reduce the viral load to below the limit of detection to reduce the chances of further viral evolution under therapeutic selection pressures. Despite an initial good response to HAART the viral load may rebound in some patients. This might be related to the potentially serious adverse events, the emergence of drug resistant viruses, and the difficulties of maintaining long-term adherence (1-2). Patients with rebounding viral load are typically switched to a second-line or salvage regimen, where the response is usually poorer than when patients first start HAART (3-6). Such salvage regimens often contain a different class of antiretrovirals, so an initial protease-inhibitor (PI) containing HAART regimen may be switched to a non-nucleoside reverse transcriptase inhibitor (NNRTI) containing HAART regimen or vice versa. Once patients have been exposed to the three main classes of antiretrovirals their treatment options are limited because of cross resistance; it is usually not possible to keep the viral load in such patients at sufficiently low levels and eventually this may lead to decreasing CD4 lymphocyte counts and clinical disease progression (7-8). While there is considerable evidence from both observational studies and clinical trials of the response to both first-line and second-line HAART regimens (9-11), there is relatively little known about the time to triple drug class failure (TCF) or the factors related to it.

The aims of this study were therefore to describe the time to triple drug class drug exposure, the incidence of virologic TCF among 3538 patients from across Europe starting HAART and to describe the factors associated with TCF.

Methods

Patients

The EuroSIDA study is a prospective, European study of patients with HIV-1 infection in 72 centres across Europe (including Israel - see appendix) and now including Argentina. Details of the study have been published (12). In brief, Centres provided data on consecutive patients seen in the outpatient clinic from 2 May 1994 until a predefined number of patients was enrolled from each centre. This cohort of 3118 patients was defined as the EuroSIDA I cohort. Enrolment of a second cohort of 1365 patients began in December 1995. In April 1997 a further 2839 patients were recruited and was defined as the EuroSIDA III cohort. Cohort IV, 1225 patients, was enrolled from April 1999, and a fifth cohort, Cohort V, 1256 patients, was recruited from September 2001. At recruitment, in addition to demographic and clinical information, a complete antiretroviral history is collected, together with the 4 most recent CD4 counts and viral load measurements. At each follow-up visit, details on all CD4 lymphocyte counts measured since last follow-up and viral load measurements were collected, as was the date of starting and stopping each antiretroviral drug and the use of drugs for prophylaxis against opportunistic infections. Dates of diagnosis of all AIDS defining illnesses have also been recorded using the 1993 clinical definition of AIDS from the Centers for Disease Control. Members of the coordinating office visited all centres to ensure correct patient selection and that accurate data was provided by checking the information provided against case-notes for a proportion of patients.

HAART was defined as a minimum of 3 antiretroviral drugs, of which at least one was a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or abacavir. All patients starting HAART for the first time were eligible for inclusion. Patients who had previously taken a PI or NNRTI which was not included in a HAART regimen were excluded. The baseline date was taken as the date of starting HAART. Patients without a CD4 count or viral load measured in the 6 months before baseline were excluded, as were patients with no prospective follow-up. Patients who started HAART prior to recruitment to EuroSIDA were only included if they had a minimum of 2 viral loads measured in each year prior to recruitment to try to ensure that patients had not failed three drug classes prior to the start of prospective follow-up.

Virological failure of a drug class was defined in the same way as for the PLATO (**P**ursuing **LA**ter **T**reatment **O**ptions) collaborative study (7) . In brief, virological failure of a drug class was defined as a viral load > 1000 copies/ml for a total of at least 4 months after starting the drug class whilst still being on the same drug class. Failure of any class could occur when it was used alone as monotherapy or as a component of dual, triple or more intensive regimen, providing viral load measures were available. Patients were classified as a TCF on the first date they had failed nucleosides, PI's and NNRTI's. For example, a patient starting HAART with 2 nucleosides and a PI and with a viral load > 1000 copies/ml for at least 4 months would be defined at that time as failing both nucleosides and PI's.

Statistical methods

The prevalence of TCF at each time point was defined as the proportion of patients with TCF divided by the total number at risk. Patients were removed from this analysis at the date of their last viral load measurement. The incidence of TCF was defined as the number of triple-class failures divided by the person-years of follow-up (PYFU) and was stratified according to time since starting HAART, calendar year and use of antiretrovirals prior to starting HAART (i.e., treatment experienced (TE) compared to treatment naive patients). Patient follow-up was measured from the date of starting HAART until the date of TCF. Patients who did not have TCF were censored at the date of their last viral load measurement. Trends over time were tested using Poisson regression.

Time from starting HAART to exposure to three drug classes and to TCF was analysed using Kaplan-Meier survival curves. The factors associated with TCF were determined using Cox proportional hazards models. All Cox models were stratified by centre and performed separately for TN and TE patients. Factors that were significant in univariate analyses ($p < 0.1$) were included in multivariate analyses. Variables in univariate analyses included gender, exposure group, race, hepatitis B and C status, prior AIDS diagnosis, age, date of starting antiretroviral therapy, CD4 and viral load. Treatment variables included whether patients were TN at baseline, HAART regimen started and the number of antiretrovirals patients were taking at baseline. CD4 and viral load were included both as continuous and categorical variables. In TE patients the additional variables considered included time since starting antiretrovirals, total exposure time to nucleosides (i.e., the sum of exposure to each of the individual nucleosides), the cumulative number of nucleosides ever taken, the number of new (i.e., never previously taken) nucleosides started at HAART and what prior treatment strategy patients had taken (monotherapy, dual therapy or both).

A further Cox model was constructed which redefined the baseline date to be 1 January 1987, and patient follow-up was left-censored until the date of starting HAART. This analysis allowed changes in the rate of TCF over time since starting HAART to be formally tested after adjustment for the other factors related to TCF.

Poisson regression was performed using STATA (version 7) and all other analyses were performed using SAS (version 8.2, Cary NC, USA). All tests of significance were 2-sided.

Results

Characteristics of the patients

Of 9803 patients enrolled in EuroSIDA, 3873 had not started HAART and 2209 had no CD4 or viral load measured in the 6 months prior to starting HAART. A further 183 patients were excluded because they had less than 2 viral loads measured per year prior to recruitment to EuroSIDA; thus 3538 patients satisfied the inclusion criterion, and are described in Table 1. The majority of the patients were male (2747, 77.6%), belonged to the homosexual exposure group (1644, 46.5%) and were of White ethnic origin (2978, 84.2%). 832 patients (23.5%) had a diagnosis of AIDS at or before the date of starting HAART. 1192 patients (33.7%) started HAART prior to recruitment in EuroSIDA, a median time of 5 months before recruitment (IQR 3 – 10 months). The median CD4 count at starting HAART was 221/mm^3 (IQR 110 – 343/mm^3) and median viral load was 4.43 $\log_{10}$copies/ml (IQR 3.62 – 5.08 $\log_{10}$copies/ml). There was a median of 15 viral loads per patient measured during follow-up (IQR 9 – 21) at a median time apart of 3 months (IQR 2 – 4 months). Median follow-up after starting HAART was 50 months (IQR 29 – 64 months), with a total of 13,614 person-years of follow-up (PYFU).

2430 patients (68.7%) had prior antiretroviral treatment at baseline. Patients first started antiretrovirals a median time of 34 months before starting HAART (IQR 15 – 60 months). A large proportion of the TE patients had taken both monotherapy and dual therapy (1417, 58.3%), 787 patients had taken dual therapy alone (32.4%) and 226 had only taken monotherapy (8.3%). The median number of antiretrovirals patients had been exposed to prior to baseline was 3 (IQR 2 –4). The median cumulative exposure time (i.e., the sum of exposure to each of the nucleosides taken) to nucleosides prior to starting HAART was 48 months (IQR 23 – 81 months). Almost half the patients starting HAART did not start any new nucleosides (i.e., nucleosides to which they had never previously been exposed) at the date of starting HAART (1115, 45.9%), while 811 patients started 1 (33.4%) and 504 started two new nucleosides (20.7%).

The Kaplan-Meier estimate of the median time to exposure to 3 classes of antiretrovirals was 47 months (95% confidence interval (CI) 45 – 50 months), and was significantly shorter among patients who were TE (41 months, 95% CI 39 – 43 months) compared to TN patients (61 months, 95% CI 56 – 66 months, $p < 0.0001$, log-rank test).

Prevalence and incidence of TCF and calendar time

469 patients (13.3%) experienced TCF after starting HAART; of these, 400/2430 (16.5%) were TE and 69/1108 were TN (6.2%). Figure 1 shows the prevalence of TCF over calendar time. The prevalence at/after 2002 was 16.1% in TE patients and 5.5% among TN patients. The majority of patients in this study started HAART prior to 1999, as shown in Figure 2. There was a low incidence of TCF during 2001, particularly in TN patients. Using Poisson regression, over time the incidence of TCF has increased, at an estimated 29% per year in TN patients (95% CI 9 – 53%, $p = 0.003$). The change over time was not linear for TE patients; there was a significantly decreased incidence of TCF during 1999 (rate ratio (RR) 0.42, 95% CI 0.32 – 0.57, $p < 0.0001$) and during 2001 (RR 0.57, 95% CI 0.41-0,73, $p = 0.001$) compared to 1999, but no significant differences in the rates in other calendar years ($p > 0.05$).

Time to TCF and incidence of TCF

Figure 3 shows the time from start of HAART to TCF, stratified by prior antiretroviral treatment. At 6 years after starting HAART, 24.1% of TE patients were estimated to have failed three classes of antiretrovirals (95% CI 21. 6 – 26.6) compared to 11.9% of TN patients (95% CI 8.6 – 15.2, $p < 0.0001$, log-rank test). During follow-up, just over half of the patients who started HAART were exposed to three classes of antiretrovirals (1816 patients, 51.3%). At 3 years after starting the third class, 32.3% of TE patients were estimated to have TCF (95% CI 29.5 – 35.1) compared to 17.2% of TN patients (95% CI 13.2 – 21.2, $p < 0.0001$, log-rank test).

Among TN patients, the overall incidence of TCF was 1.7 per 100 PYFU (95% CI 1.3 – 2.1), compared to 4.2 per 100 PYFU (95% CI 3.8 – 4.6) among TE patients, a rate 2.4 times higher (95% CI 1.88 – 3.13, $p < 0.0001$, Poisson regression). Figure 4 shows the incidence of triple-class failure according to time since starting HAART, separately for TN and TE patients. Among TN patients, there was an increase in the incidence of failure with increasing time from baseline from 1.2 per 100 PYFU (95% CI 0.7 – 1.7) in the first 2 years after baseline to 4.7 per 100 PYFU (95% CI 2.1 – 8.9) at or after 5 years from baseline (33% increase per year, 95% CI 12 – 58%, $p = 0.030$), similar to the rate seen in TE patients treated for the same period of time (5.4 per 100 PYFU, 95% CI 3.5 – 7.3).

Is the rate of triple-class failure increasing over time since starting HAART?

Given the pattern of TCF seen in Figure 2 and 4, for TN patients a continuous variable was used for time since starting HAART while for TE patients a categorical variable was fitted with between 2-3 years as the reference category. Among TN patients, after adjustment for CD4 and viral load at starting HAART there was a 41% increased risk of TCF with each extra year since starting HAART (relative hazard (RH) 1.41, 95% CI 1.06 – 1.88, $p = 0.018$). In TE patients, after adjustment for CD4 and viral load at starting HAART, number of new nucleosides started and the total cumulative exposure to nucleosides prior to HAART patients were at a significantly decreased risk of TCF in the first 2 years after starting HAART (RH 0.42; 95% CI 0.31 – 0.57, $p < 0.0001$) compared to patients 2-3 years after starting HAART. After this time, there were no significant differences in the risk of TCF with increasing time from starting HAART. Similar results were seen when the first 2 years of follow-up after starting HAART (where there were few TCFs) were excluded from the analysis.

Factors associated with TCF in TN patients

Table 2 shows the univariate and multivariate factors associated with TCF among TN patients. In the first multivariate model, both CD4 and viral load were included as continuous variables. There was no statistically significant relationship between year of starting HAART and risk of TCF in multivariate analyses. Patients with a higher CD4 count at starting HAART were at a decreased risk of TCF, while patients with a higher viral load at starting HAART were at an increased risk. For example, patients with a CD4 of below 200/mm^3 at starting HAART had a 55% increased risk of TCF compared to patients with a CD4 of 350/mm^3 or higher (RH 1.55; 95% CI 0.74 – 3.22, $p = 0.24$), although this was not statistically significant and patients with an intermediate CD4 count of 200 – 349/mm^3 had no increase in risk.

Factors associated with TCF in TE patients

Among TE patients, the total number of ARV's taken prior to starting HAART, number of new drugs started and the cumulative exposure to ARV's prior to HAART were significantly associated with TCF in univariate analyses and were therefore included in multivariate analyses. The results are shown in Table 3.

There was no statistically significant relationship between year of starting HAART and risk of TCF in multivariate analyses. After adjustment, patients with a higher viral load at starting HAART were at an increased risk of failing three drug classes (RH 1.51; 95% CI 1.34 – 1.70, $p < 0.0001$), while patients with a higher CD4 count at starting HAART were at a reduced risk of TCF (RH 0.94; 95% CI 0.88 – 1.00, $p = 0.067$) although this did not quite reach statistical significance. Patients who started 2 new nucleosides at the date of starting HAART had almost a 50% reduced risk of TCF (RH 0.51, 95% CI 0.34 – 0.77, $p = 0.0012$), while each additional 12 months cumulative exposure to nucleosides prior to starting HAART was associated with a 6% increased risk of TCF (95% CI 2 – 11%, $p = 0.0016$). Similar results were seen when categorical variables were used for CD4 and viral load. Compared to patients with a CD4 at starting HAART of 350/mm^3 or higher, patients with a CD4 count of less than 200/mm^3 at starting HAART had a significantly increased risk of TCF (RH 1.59; 95% CI 1,14 – 2.20, $p = 0.0060$), while those with a CD4 count of 200-349/mm^3 had an increased risk of TCF, which was marginally statistically significant (RH 1.31; 95% CI 0.94 – 1.83, $p = 0.11$). For viral load, there was no clear line where the risk of TCF changed but a steadily increasing risk of TCF as the viral load categories increased.

Discussion

In 2002, 1 in 20 patients who were treatment naïve and 1 in 6 who were treatment experienced had triple drug class failure after starting HAART. The incidence of TCF was considerably lower among TN patients but was significantly increasing with increasing time since starting HAART, whereas the incidence among TE patients was stable after an initially low incidence in the first 2 years after starting HAART. The World Health Organisation projects that 3 million people with HIV in the developing world will be on treatment by the end of 2005 (13). As the rate of TCF will be comparable in the developing world to that reported here, and as the population with extended exposure to HAART in the developed world increases, the number of patients with TCF worldwide will continue to increase in the coming years.

At 6 years after starting HAART just over 24% of TE patients and 12% of TN patients were estimated to have TCF. In some small but detailed studies with more extended follow-up, around 30% of patients who were initially TN have virologic failure of their first HAART regimen at 2-3 years after starting HAART (14-15) while from larger observational studies between 20-40% of patients are estimated to have virologic failure of their first HAART regimen, with, on average, 2-3 years follow-up (16-17). The definition of virologic failure differs between studies, as do the patients included (TN, TE or a mix of both), but those patients who fail their initial HAART regimen usually change to a regimen containing a different class of drug and are therefore at immediate risk of TCF. Our estimates of TCF in TN and TE patients at 6 years after starting HAART appear consistent with the above estimates, coupled with those suggesting that a further 20-50% of patients fail subsequent second-line regimens (3-6), and the fact that there is a substantial number of patients who interrupt treatment (Olsen, manuscript in preparation).

Several studies have shown that TE patients have a poorer virologic response to HAART (18-20). The time between TCF and subsequent clinical progression is currently unknown, and in general, to date, there has been no difference in risk of clinical progression between TE and TN patients (21-23). However, it may take several years from TCF to subsequent clinical progression and with extended follow-up of patients with exposure to HAART and TCF differences in clinical progression may become apparent. To date, cross-resistance to antiretroviral classes is irreversible, thus the prevalence of patients living with TCF will increase over time both within a study population such as EuroSIDA and within the population of patients with HIV as more patients are exposed to more drug classes. For the individual, this may lead to a poorer prognosis over time, and the potential for transmission of resistant virus to others (24). For the clinics, it may lead to increased costs due to more intensive diagnostic tests, the use of more expensive regimens such as enfuvirtude (25), and the use of more drugs in each regimen.

The incidence of TCF was increasing with more extended exposure to HAART among TN patients, but remained fairly steady among TE patients, after an initially low rate. The low rate of TCF among TN patients during 2001 may be partly explained by the comparatively high number of TN patients starting HAART in this time period, as patients recently starting HAART were comparatively over-represented. By 5 years after starting HAART the incidence of TCF in TN patients was approaching the rate seen in TE patients, although the confidence intervals around the estimate were comparatively wide. The initially low and then steady rate of TCF in TE patients may simply reflect that, in the first years after starting HAART, patients with rapid TCF had more resistance, were least able to adhere to the new regimens, or differences in early treatment

guidelines (26). Once such patients have TCF, the remaining TE patients may fail at a rate similar to that seen in TN patients and the curves will increase with extended exposure to HAART at the same rate.

The factors related to failing three drug classes in this study were similar to those related to failing either an initial or second-line HAART regimen. Thus in both TN and experienced patients, a higher viral load at starting HAART was associated with a higher risk of TCF, as seen for patients starting HAART or a second-line HAART regimen (5, 27). Among TE patients adding new nucleosides to the initial HAART regimen resulted in a lower risk of TCF, as reported from studies looking at other aspects of treatment failure (4-5, 7, 18, 21, 27-31). In addition, a higher cumulative exposure to nucleosides prior to starting HAART rather than the number of nucleosides taken was associated with TCF, suggesting resistance may be accumulating over time. Although a number of studies have shown a significant correlation between drug resistance and virologic response (32-33), the role of resistance testing remains unclear (2). In patients with extensive prior treatment and multiple treatment failures, the interpretation of resistance tests is difficult and other factors, such as treatment history, adherence and toxicities need to be taken into account (34-36).

Results from other studies of the virologic, immunologic or clinical benefits of starting HAART at higher CD4 counts vary (37-41). In this study, when CD4 was included as a continuous variable, patients with higher CD4 counts at starting HAART had a reduced risk of TCF in both TN and TE patients, and the increased risk of TCF at lower CD4 counts was comparable to that of TE patients. However, the results were not so clear when the CD4 count was categorised. In general, TN or TE patients starting HAART with a CD4 of below 200/mm^3 were at an increased risk of TCF compared to patients with a CD4 count of 350/mm^3 or above. This was not statistically significant in TN patients, as found in a larger study of treatment naïve patients (39), and this highlights that the decision to start therapy is a complicated one which depends on many different factors. The CD4 count at starting HAART may reflect previous adherence in TE patients, and thus may be acting as a marker for future adherence after patients start HAART.

Patients starting HAART with 4 or more drugs had a similar risk of TCF as those starting HAART with 3 drugs. Patients starting HAART with a boosted PI regimen would be categorised as starting 4 drugs, but a further analysis which included specific regimen started showed similar results. In addition, calendar date of starting HAART was not associated with the risk of TCF, and this was explained by the increasing CD4 count and decreasing viral load over time at the date of starting HAART. Some patients in this analysis started HAART back in 1997, and there have been considerable changes over time in the regimens used, the way HAART is started and in managing toxicities. It is possible that further improvements over the next five years make TCF less likely than that reported here. However, given that patients have up to 6 years follow-up, those who started HAART earlier in the study will have swapped regimens over time, thus these results represent an estimate of TCF among a heterogeneous clinic population where there are many factors involved in which regimen to start, and the virologic threshold required for treatment failure.

There are several limitations of this study which should be noted. We used a definition of TCF based on the PLATO definition with a viral load above 1000 copies/ml for at least 4 months on each class of drug (7). Most randomised clinical trials define virologic failure on the basis of a viral load above 50 copies/ml, however, we believe that the PLATO definition represents a more conservative approach to virologic failure,

and one that may be used in the more routine clinic setting, with less frequent monitoring of patients, and in some cases, maintaing treatment on a regimen with low level viremia. The results were highly consistent when we changed the criterion to at least 6 months above 1000 copies/ml, when we left censored the data until prospective follow-up in the EuroSIDA study began, or included only patients who started HAART during prospective follow-up to exclude the possibility that patients may have satisfied the criterion for failure before prospective follow-up began (data not shown). In addition, although nevirapine became available in mid 1996, efavirenz was not widely used among EuroSIDA patients until 1998 (42). A further sensitivity analysis which included only patients starting HAART in 1998 or later showed similar results. The results from both clinical trials and observational studies have shown that adherence plays a role in virological failure (15, 35, 43-44), but we are unable to estimate the effect of adherence on the risk of TCF, as we do not currently have this data. It is likely that since patients may have TCF due to poor adherence and such patients would not have resistance. Similarly, we do not have data on virologic resistance which may play an important role in failing three drug classes, but further work is ongoing to collect resistance data within the study. The future responses to therapy for such patients are different to those for patients with TCF and resistance; sustained virologic suppression should be achievable if good adherence can be achieved and maintained on future regimens.

In summary, further treatment options, such as mega-HAART regimens, treatment interruptions or other innovative treatment design (45-47) will be needed as the number of patients with TCF increases. The recent introduction of fusion inhibitors, where around 20% of patients had virologic suppression after 48 weeks (48), is unlikely to significantly diminish the proportion of patients with virologic failure to all classes of antiretrovirals (i.e., 4 classes). The long term consequences of triple drug class virologic failure on the durability of HAART and how best to manage this situation deserves further focus.

Table 1

Characteristics of 3538 patients at risk of triple drug class failure

		N	%
All		3538	100
Gender	Male	2747	77.6
	Female	791	22.4
Exposure group	Homosexual	1644	46.5
	IDU	750	21.2
	Heterosexual	891	25.2
	Other	253	7.1
Region	South	986	27.9
	Central	1017	28.7
	North	1283	36.3
	East	236	6.7
	Argentina	16	0.4
Ethnic origin	White	2978	84.2
	Other	560	15.8
HAART regimen	Single PI	2533	71.6
	Dual PI	261	7.4
	Single NNRTI	443	12.5
	Triple nuc	49	1.4
	Other	252	7.1
Prior AIDS		832	23.5
Treatment naïve		1108	31.3
CD4	(Median, IQR)	221	110 – 343
CD4 nadir		155	69 – 254
Viral load		4.43	3.62 – 5.08
Peak viral load		4.74	4.13 – 5.29
Age		37.1	32.3 – 44.2
Time started HAART		7/97	1/97 – 9/98

Baseline CD4 was measured a median of 0.5 months prior to starting HAART (IQR 0 – 1.9 months) and viral load a median of 0 months before starting HAART (IQR 0 – 1 month). The CD4 nadir was measured a median of 5 months before starting HAART (IQR 1 – 18 months).

Table 2 - Factors associated with triple drug class failure among TN patients

		RH	95% CI	P
Univariate				
Prior AIDS	Yes[1]	1.60	0.92 – 2.70	0.095
Drugs in HAART	>=4[2]	1.81	0.95 – 3.18	0.067
Date HAART	12 months later	0.84	0.62 – 1.10	0.075
CD4 at HAART	50% higher	0.79	0.69 – 0.90	0.0004
VL at HAART	Log higher	1.65	1.20 – 2.26	0.0019
Multivariate – continuous variables				
Prior AIDS	Yes[1]	1.15	0.62 – 2.12	0.66
Drugs in HAART	>=4[2]	0.77	0.27 – 2.21	0.63
Date HAART	12 months later	1.19	0.86 – 1.58	0.29
CD4 at HAART	50% higher	0.84	0.71 – 0.99	0.034
VL at HAART	Log higher	1.47	1.05 – 2.05	0.023
Multivariate – categorical variables				
Prior AIDS	Yes[1]	1.32	0.71 – 2.43	0.38
Drugs in HAART	>=4[2]	0.76	0.27 – 2.16	0.61
Date HAART	12 months later	1.11	0.81 – 1.53	0.51
CD4 at HAART	<200	1.55	0.74 – 3.22	0.24
	200 – 349	0.97	0.45 – 2.10	0.93
	>=350	1.00	-	-
VL at HAART	< 10,000	1.00	-	-
	>=10,000	1.29	0.61 – 2.72	0.51

69/1108 patients with TCF. Multivariate models were also adjusted for exposure group, Hepatitis B status and hepatitis C status at starting HAART. [1]Compared to patients without AIDS; [2] compared to patients on 3 drugs.

Table 3 - Factors associated with triple drug class failure in TE patients

		RH	95% CI	P
Univariate				
Number new nucleosides	0	1.00	-	-
started at HAART	1	0.91	0.72 – 1.14	0.40
	>=2	0.60	0.44 – 0.82	0.0011
Number nucs ever taken	Per extra one	1.20	1.08 – 1.34	0.0012
Cumulative time on nucs	Per 12 months	1.04	1.01 – 1.08	0.020
Prior AIDS	Yes[1]	1.54	1.23 – 1.93	<0.0001
Drugs in HAART	>=4[2]	1.00	0.91 – 1.23	0.98
Date HAART	12 months later	0.73	0.63 – 0.85	<0.0001
CD4 at HAART	50% higher	0.85	0.80 – 0.90	<0.0001
VL at HAART	Log higher	1.55	1.39 – 1.73	<0.0001
Multivariate – continuous variables				
Number new nucleosides	0	1.00	-	-
started at HAART	1	0.76	0.56 – 1.02	0.071
	>=2	0.51	0.34 – 0.77	0.0012
Number nucs ever taken	Per extra one	0.99	0.86 – 1.15	0.92
Cumulative time on nucs	Per 12 months	1.06	1.02 – 1.11	0.0016
Prior AIDS	Yes[1]	1.25	0.98 – 1.59	0.074
Drugs in HAART	>=4[2]	1.25	0.96 – 1.63	0.11
Date HAART	12 months later	0.90	0.77 – 1.05	0.18
CD4 at HAART	50% higher	0.94	0.88 – 1.00	0.067
VL at HAART	Log higher	1.51	1.34 – 1.70	<0.0001
Multivariate – categorical variables				
Number new nucleosides	0	1.00	-	-
started at HAART	1	0.78	0.58 – 1.06	0.11
	>=2	0.53	0.35 – 0.79	0.0017
Number nucs ever taken	Per extra one	1.00	0.86 – 1.15	0.97
Cumulative time on nucs	Per 12 months	1.06	1.02 – 1.10	0.0045
Prior AIDS	Yes[1]	1.27	1.01 – 1.61	0.044
Drugs in HAART	>=4[2]	1.24	0.95 – 1.63	0.11
Date HAART	12 months later	0.91	0.78 – 1.06	0.23
CD4 at HAART	<200	1.59	1.14 – 2.20	0.0060
	200 – 349	1.31	0.94 – 1.83	0.11
	>=350	1.00	-	-
VL at HAART	< 1,000	1.00	-	-
	1,000 – 9,999	1.64	1.07 – 2.50	0.023
	10,000 – 99,999	2.54	1.72 – 3.76	<0.0001
	>=100,000	3.43	2.27 – 5.18	<0.0001

400/2430 patients with TCF. Multivariate models were also adjusted for exposure group, Hepatitis B status and hepatitis C status at starting HAART. [1]Compared to patients without AIDS; [2] compared to patients on 3 drugs.

Sponsorship

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Appendix

The multicentre study group on EuroSIDA (national coordinators in parenthesis).

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Coordinating centre staff
J Lundgren (project leader), I Gjørup, O Kirk, N Friis-Moeller, A Mocroft, A Cozzi-Lepri, W Bannister, D Mollerup, M Nielsen, A Hansen, D Kristensen, L Kolte, L Hansen, J Kjær.

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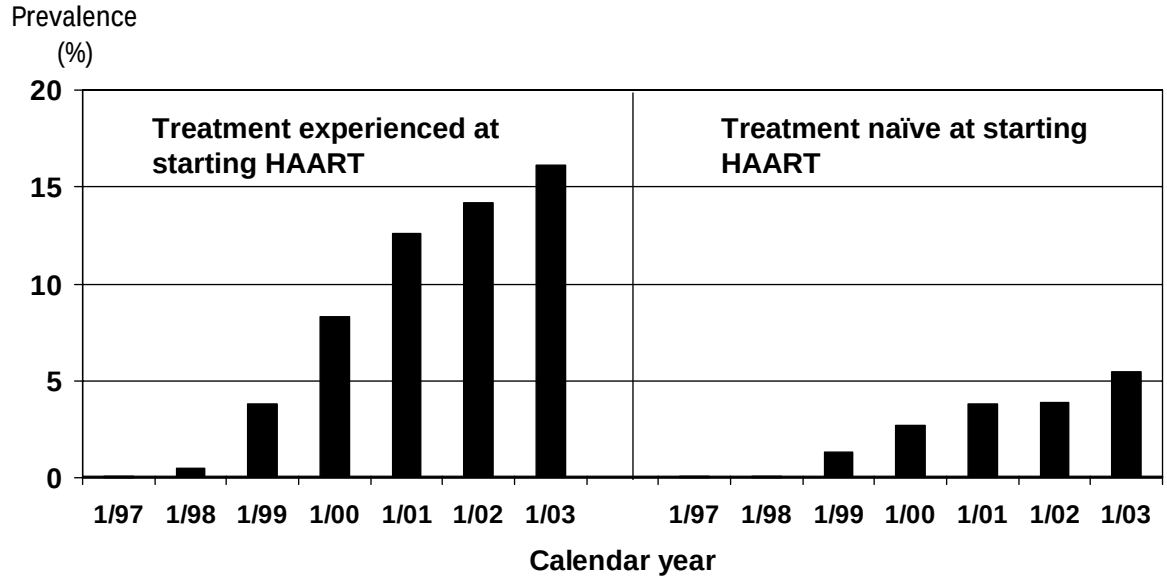
Figure 1
Prevalence of triple-drug class failure over calendar time

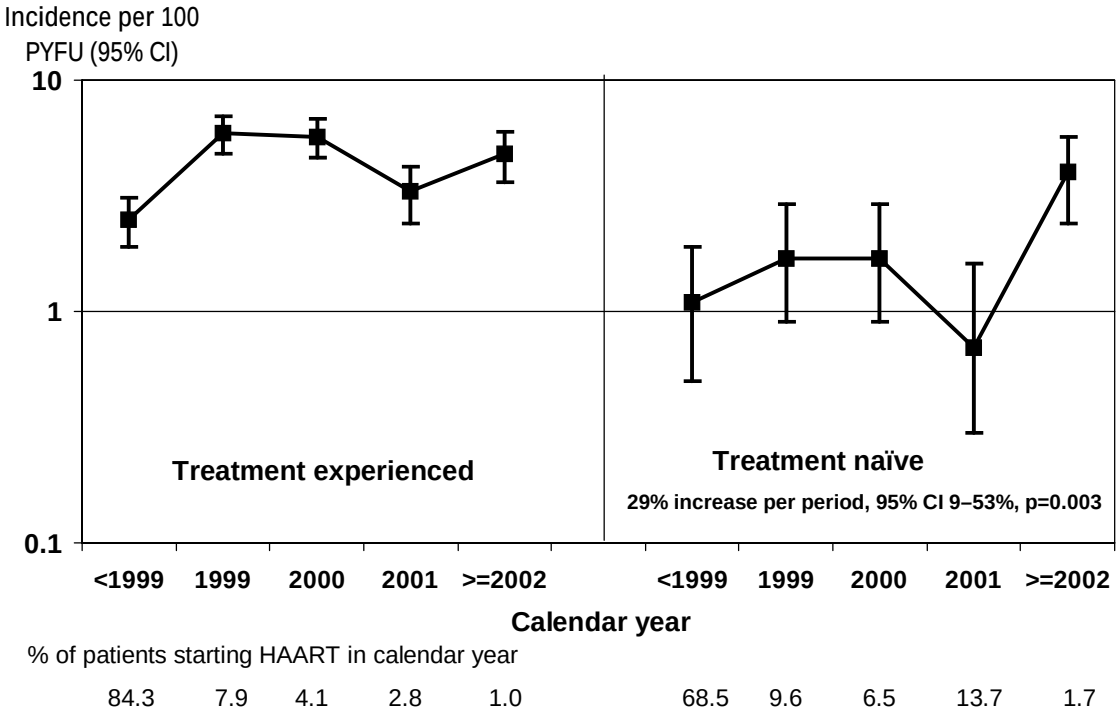


Number under follow-up

589	1592	1923	1985	1958	1821	280	143	533	715	786	809	870	128
0	8	73	165	247	258	45	0	0	9	21	31	34	7

Triple-class treatment failure

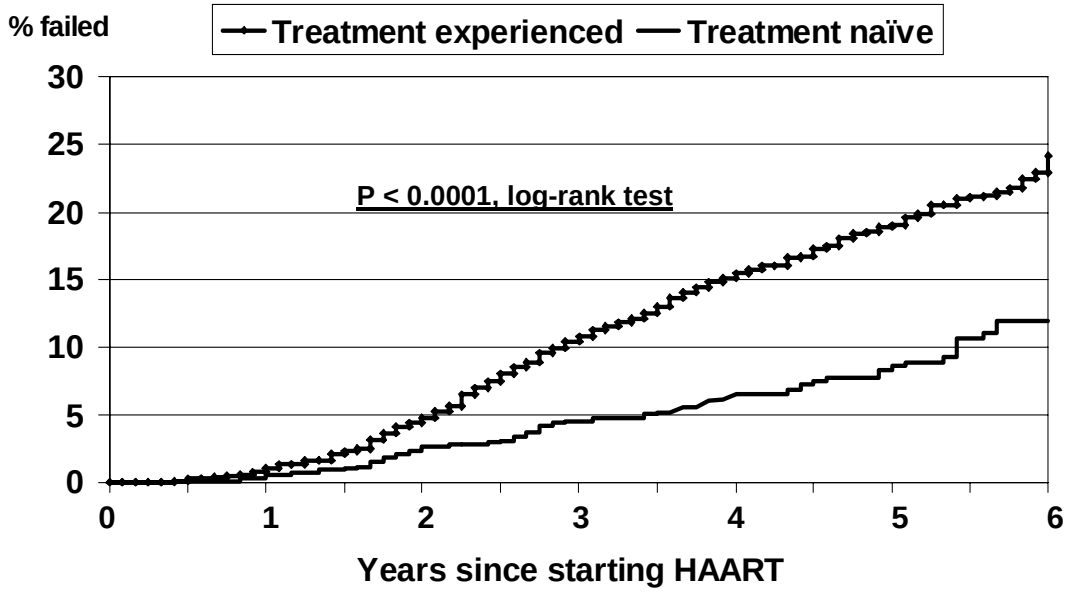
Figure 2
Triple-drug class failure over calendar time



% of patients starting HAART in calendar year

<1999	1999	2000	2001	>=2002	<1999	1999	2000	2001	>=2002
84.3	7.9	4.1	2.8	1.0	68.5	9.6	6.5	13.7	1.7

Figure 3
Time to triple-drug class failure



N under follow-up

Experienced	2430	2381	2261	2163	2007	1849	1694	1521	1339	1134	868	600	155
Naïve	1108	1082	1019	919	820	760	700	639	533	448	314	190	44

Figure 4
Incidence of triple-drug class failure and time on HAART