Time to Virological Failure of 3 Classes of Antiretrovirals after Initiation of Highly Active Antiretroviral Therapy: Results from the EuroSIDA Study Group

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Objective. The purpose of the present study was to determine the prevalence and incidence of virological triple drug–class failure (TCF) and to summarize the clinical outcome for patients who started receiving highly active antiretroviral therapy (HAART).

Methods. The present study is an observational longitudinal study of 3496 treatment-experienced (TE) and treatment-naive (TN) patients monitored from the time they started receiving HAART (baseline) until TCF occurred (as determined on the basis of viral loads), until AIDS was newly diagnosed, or until death.

Results. Four hundred forty-five patients (12.7%) had TCF; 370 (16.6%) of 2230 patients were TE, and 75 (5.9%) of 1266 patients were TN. At 6 years after starting HAART, 21.4% of TE and 11.2% of TN patients had TCF ($P < .0001$). The prevalence of TCF at or after 2002 was 15.5% in TE patients and 4.8% in TN patients. TN patients had a 32% annual increase in the incidence of TCF (95% confidence interval [CI], 14%–54%; $P < .0001$); at 5 years after starting HAART, the rate was comparable for TE and TN patients (3.3 and 3.4 cases/100 person-years of follow-up [PYFU], respectively). The incidence of new cases of AIDS or death was 2.7 cases/100 PYFU in patients who did not experience TCF and 5.0 cases/100 PYFU in patients who did experience TCF, an estimated 36% increase with each category of TCF (95% CI, 19%–56%; $P < .0001$).

Conclusion. The prevalence of TCF was low after patients started receiving HAART, particularly among TN patients. Despite the influx of patients who had started receiving HAART more recently, the prevalence of TCF increased over calendar time. Patients with TCF had a higher incidence of newly diagnosed AIDS or death. Treatment of patients with TCF deserves further investigation.

One of the goals of highly active antiretroviral therapy (HAART) is to reduce the viral load to below the limit of detection, which reduces the chances of further viral evolution in response to therapeutic selection pressures. Despite an initial good response to HAART, the viral load may rebound in some patients. This phenomenon might be related to 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, in which the response is usually poorer than that elicited when patients first start HAART [3–6]. Such salvage regimens often

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contain a different class of antiretrovirals, so an initial protease inhibitor (PI)–containing HAART regimen may be switched to a nonnucleoside reverse-transcriptase inhibitor (NNRTI)–containing HAART regimen or vice versa. Once patients have experienced virological failure of the 3 main classes of antiretrovirals (i.e., triple drug–class failure [TCF]), their treatment options are limited because of cross-resistance; for such patients, it is usually not possible to keep the viral load at sufficiently low levels, and this may lead to decreasing CD4 cell counts and clinical disease progression [7, 8]. Although 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], relatively little is known about the time to or incidence of TCF. The aims of the present study were, therefore, to describe the time to and prevalence and incidence of TCF among 3496 patients from across Europe who started receiving HAART and to summarize the clinical outcome in these patients.

PATIENTS AND METHODS

Patients. The EuroSIDA study is a prospective, European-based study of patients with HIV-1 infection in 72 centers in Europe, Israel, and Argentina. Details of the study have been published elsewhere [12]. In brief, centers provided data on consecutive patients who were seen in the outpatient clinic, from 2 May 1994 until a predefined number of patients was enrolled from each center. This cohort of 3115 patients was defined as the EuroSIDA I cohort. A second cohort (EuroSIDA II cohort; 1365 patients) was enrolled beginning in December 1995, a third cohort (EuroSIDA III cohort; 2839 patients) was enrolled beginning in April 1997, a fourth cohort (EuroSIDA IV cohort; 1225 patients) was enrolled beginning in April 1999, and a fifth cohort (EuroSIDA V cohort; 1258 patients) was enrolled beginning in September 2001. At recruitment, in addition to demographic and clinical information, a complete antiretroviral history was obtained, together with the 4 most recent CD4 cell counts and viral load measurements. At each follow-up visit, details on all CD4 cell counts measured since the last follow-up visit and viral load measurements were collected, as was the date of starting and stopping each antiretroviral drug and information on the use of drugs for prophylaxis against opportunistic infections. The latest follow-up visit was in December 2003. Members of the coordinating office visited all centers to ensure that patient selection was performed correctly and that accurate data were 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 1 was a PI, an NNRTI, or abacavir. All patients receiving HAART for the first time were eligible for inclusion. Patients who had previously taken a PI or an NNRTI that was not included in a HAART regimen were excluded. The baseline date was taken as the date of starting HAART. Patients for whom a CD4 cell count or viral load was not measured during the 6 months before baseline were excluded, as were patients with no prospective follow-up. Patients who started receiving HAART before recruitment to EuroSIDA were included only if they had a minimum of 2 viral loads measured in each year before recruitment, to ensure that patients had not experienced TCF before prospective follow-up began.

Virological failure of a drug class was defined as it was for the Pursuing Later Treatment Options (PLATO) collaborative study [7]. In brief, virological failure of a drug class was defined as having occurred when all recorded viral loads were >1000 HIV RNA copies/mL for a total of >4 months after starting the drug class while still receiving the same drug class. Failure of any drug class could occur when it was used as monotherapy or as a component of dual therapy, triple therapy, or a more intensive regimen, if viral loads were >1000 copies/mL for ≥7 months while receiving the drug. Patients were classified as having experienced TCF on the first date that therapy with nucleosides, PIs, and NNRTIs failed. An alternative definition of TCF was also analyzed ("other"), defined as failure of any drug class after >4 months of receiving the drug class and on the basis of a single viral load >1000 HIV RNA copies/mL.

Statistical methods. The prevalence of TCF at each time point was defined as the proportion of patients with TCF up to that date divided by the total number of patients being followed up at that date. Patients were followed-up to the date of their last viral load measurement. The incidence of TCF was defined as the number of patients with TCF divided by the person-years of follow-up (PYFU) and was stratified according to the time since starting HAART and according to whether patients were treatment experienced (TE) or treatment naive (TN). Patient follow-up was measured from the date of starting HAART (baseline) until the date of TCF. Patients who had not experienced TCF were censored at the date of their last viral load measurement. Trends over time were tested by use of Poisson regression.

The time from starting HAART to TCF was analyzed by use of Kaplan-Meier survival curves. The factors associated with TCF were determined by use of Cox proportional hazards models. All Cox models were stratified by center and were performed separately for TN and TE patients. Variables in univariate analyses included sex, exposure group, race, hepatitis B and C status, prior AIDS diagnosis, age, CD4 cell count, viral load, and the availability of a resistance test before starting HAART. A resistance test may have been obtained by the clinic and reported to the coordinating center, or it may have been performed by one of the central laboratories on a stored serum sample as part of any one of a number of ongoing resistance studies. Treatment variables included HAART regimen started, date of starting antiretroviral therapy, and the number of an-

Table 1. Characteristics of 3496 patients at risk of triple drug–class failure.

Characteristic	TE patients	TN patients	P^a
Sex			
Male	1724 (77.3)	999 (78.9)	.27
Female	506 (22.7)	267 (21.1)	
Exposure group			
Homosexual	1015 (45.5)	594 (46.9)	.15
IDU	497 (22.3)	242 (19.1)	
Heterosexual	556 (24.9)	326 (25.8)	
Other	162 (7.3)	104 (8.2)	
Region			
South/Argentina	682 (30.6)	265 (20.9)	<.0001
Central	673 (30.2)	321 (25.4)	
North	805 (36.1)	446 (35.2)	
East	70 (3.1)	234 (18.5)	
Ethnic origin			
White	1866 (83.7)	1092 (86.3)	.042
Other	364 (16.3)	174 (13.7)	
HAART regimen			
Single PI	1710 (76.7)	782 (61.8)	<.0001
Boosted PI	124 (5.6)	117 (9.2)	
Single NNRTI	328 (14.7)	312 (24.6)	
Triple nucleoside	46 (2.1)	34 (2.7)	
Other	22 (1.0)	21 (1.7)	
Prior AIDS	546 (24.5)	257 (20.3)	.0047
Resistance test			
Before HAART	231 (10.4)	289 (22.8)	<.0001
CD4 cell count, median (IQR), cells/mm^3	220 (115–341)	231 (103–346)	.0066
CD4 cell count nadir, median (IQR), cells/mm^3	150 (63–230)	197 (92–304)	<.0001
Viral load, median (IQR), HIV RNA copies/mL	4.18 (3.38–4.86)	4.92 (4.36–5.40)	<.0001
Peak viral load, median (IQR), HIV RNA copies/mL	4.58 (3.97–5.15)	5.04 (4.56–5.49)	<.0001
Age, median (IQR), years	37.6 (33.3–45.0)	36.0 (30.8–43.3)	<.0001
Time started receiving HAART, median (IQR)	Jun 1997 (Jan 1997–May 1998)	Jun 1998 (May 1997–Aug 2000)	<.0001
Total	2230 (63.8)	1266 (36.2)	…

NOTE. Data are no. (%) of patients, except where noted. HAART, highly active antiretroviral therapy; IDU, injection drug use; IQR, interquartile range, NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TE, treatment experienced; TN, treatment naive.

[a] P values were calculated by use of the χ^2 test, for categorical variables, and the Wilcoxon test, for continuous variables.

tiretrovirals patients were taking at baseline. CD4 cell count and viral load were included as continuous variables. In TE patients, the additional variables considered included time since starting antiretrovirals, the cumulative number of nucleosides ever taken, the number of new (i.e., never previously taken) nucleosides started with HAART, and what prior treatment strategy patients had taken (monotherapy, dual therapy, or both). A further Cox model that redefined the baseline date to be 1 January 1987 was constructed, and patient follow-up was left-truncated 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. All analyses were repeated using the alternative definition of TCF.

The incidence of new AIDS cases and death was calculated after stratification by the number of drug classes that failed and CD4 cell count ($\leq$50, 51–200, and >200 cells/mm^3). Current (or time-updated) values for both CD4 cell count and number of drug classes failed were used. Failure of 1 or 2 classes of drugs were combined because of the small number of PYFU or events that occurred among patients for whom a single class of drugs failed. Follow-up was from baseline to a new clinical AIDS-defining illness or death (recurrence of an AIDS diagnosis or a CD4 cell count <200 cells/mm^3 were not counted as events).

All analyses were performed by use of SAS (version 8.2; SAS Institute). All tests of significance were 2-sided.

RESULTS

Characteristics of the patients. Of 9802 patients enrolled in EuroSIDA, 3939 had not started receiving HAART, and 2187 had no CD4 cell count or viral load data available for the 6 months before baseline. One hundred eighty patients were excluded because they had <2 viral loads/year measured before
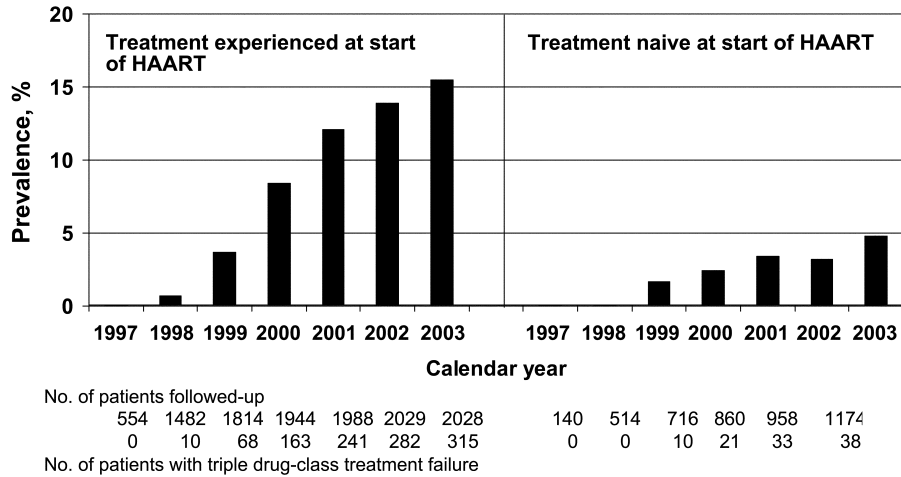
Figure 1. Prevalence of triple drug–class failure at 1 January over calendar time. HAART, highly active antiretroviral therapy.

recruitment to EuroSIDA; thus, 3496 patients satisfied the inclusion criteria (table 1). The majority of patients were TE ($n = 2230$; 63.8%). TE patients had lower median CD4 cell counts at the start of HAART ($P = .0066$), lower viral loads ($P < .0001$), and tended to have started receiving HAART at an earlier time point ($P < .0001$). For both TE and TN patients, CD4 cell count and viral load at baseline was measured a median of 0 months before baseline (interquartile range [IQR], 0–1 months). During follow-up, there were a median of 16 viral load measurements/TE patient (IQR, 9–22 viral load measurements) and 13 viral load measurements/TN patient (IQR, 8–20 viral load measurements), at a median interval of 3 months for both groups (IQR, 2–4 months). There were 9542 PYFU for TE patients and 4726 PYFU for TN patients.

TE patients started receiving antiretrovirals a median of 34 months before HAART (IQR, 15–59 months). A large proportion of TE patients (58.0%; 1294 patients) had received both monotherapy and dual therapy. The median number of antiretrovirals to which patients had been exposed before baseline was 3 (IQR, 2–3 antiretrovirals). Almost half the patients starting HAART did not start any new nucleosides (i.e., nucleosides to which they had never previously been exposed) at baseline (1059 patients; 47.5%), whereas 695 patients (31.2%) started receiving 1 new nucleoside, and 476 patients (21.3%) started receiving 2 new nucleosides.

Prevalence and incidence of TCF over time. During follow-up, more than half of the patients who started receiving HAART were exposed to 3 classes of antiretrovirals (1816 pa-
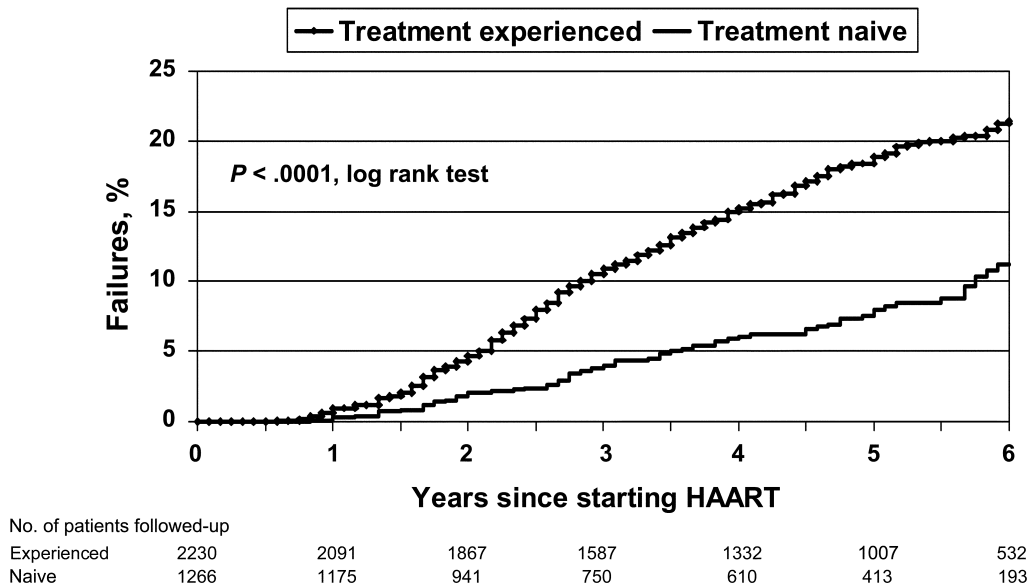

Figure 2. Time to triple drug–class failure. HAART, highly active antiretroviral therapy.
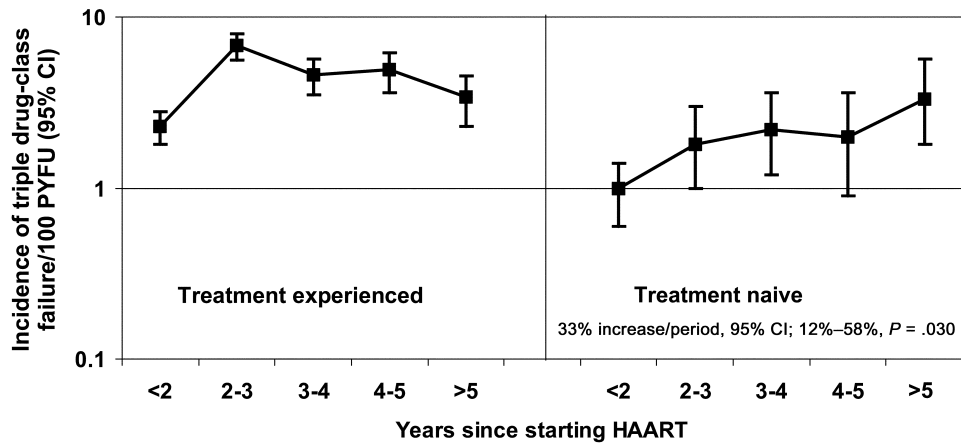
Figure 3. Incidence of triple drug–class failure and time receiving highly active antiretroviral therapy (HAART). PYFU, person-years of follow-up.

tients; 51.9%). In total, 445 patients (12.7%) experienced TCF after baseline; of these, 370 (16.6%) of 2230 were TE, and 75 (5.9%) of 1266 were TN. Figure 1 shows the prevalence of TCF over time among patients who continued to be followed up. During 1997, the prevalence of TCF was 0 for both TE and TN patients; by 1999, the prevalence had increased to 3.4% for TE patients and 1.7% for TN patients; and, at or after 2002, the prevalence had increased to 16.1% for TE patients and 5.5% for TN patients.

Time to and incidence of TCF. Figure 2 shows the time from baseline to TCF. At 6 years after baseline, 21.4% (95% confidence interval [CI], 19.3%–23.5%) of TE patients and 11.2% (95% CI, 8.4%–14.0%) of TN patients ($P < .0001$, log-rank test) were estimated to have TCF. The overall incidence of TCF was 1.6 cases/100 PYFU (95% CI, 1.2–2.0 cases/100 PYFU) and 3.9 cases/100 PYFU (95% CI, 3.5–4.3 cases/100 PYFU) in TN and TE patients, respectively. Figure 3 shows the incidence of TCF according to time since baseline. Among TN patients, there was an increase in the incidence of TCF with increasing time from baseline, from 1.0 cases/100 PYFU (95% CI, 0.6–1.4 cases/100 PYFU) during the first 2 years after baseline to 3.3 cases/100 PYFU (95% CI, 1.8–5.7 cases/100 PYFU) at or after 5 years from baseline (32% increase/year; 95% CI, 14%–54% increase/year; $P < .0001$, Poisson regression), approaching the rate seen in TE patients treated for the same period of time (3.4 cases/100 PYFU; 95% CI, 2.3–4.5 cases/100 PYFU).

Is the rate of TCF increasing over time since starting HAART? Given the pattern of TCF seen in figure 3, a continuous variable was used to model the time since baseline for TN patients, whereas a categorical variable was fitted for TE patients, with 2–3 years as the reference category. Among TN patients, after adjustment for CD4 cell count and viral load at baseline, there was a 43% increased risk of TCF with each extra year since baseline (95% CI, 27%–62%; $P < .0001$). In TE patients, after adjustment for CD4 cell count and viral load at

baseline, the number of new nucleosides started, and the total cumulative exposure to nucleosides before HAART, patients had a 71% decreased risk of TCF during the first 2 years after baseline (95% CI, 58%–80%; $P < .0001$), compared with the risk at 2–3 years after baseline. After this time, there were no significant differences in the risk of TCF with increasing time from baseline. Similar results were seen when the first 2 years of follow-up after baseline (when there were few TCFs) were excluded from the analysis.

Factors associated with TCF. Table 2 shows the univariate and multivariate factors associated with TCF in TN and TE patients. Both CD4 cell count and viral load were included as continuous variables. For TN patients, there was no statistically significant relationship between the year that HAART was started, exposure group, hepatitis B or C status, CD4 cell count at baseline, availability of a resistance test before baseline, and risk of TCF in multivariate analyses. The only factor associated with TCF was a higher viral load, with a 55% increased risk of TCF per log increase in viral load. For TE patients, the total number of antiretrovirals taken before baseline, the number of new drugs started, and regimens taken before baseline were also included in multivariate analyses. There was no statistically significant relationship between the year that HAART was started, the number of nucleosides received before HAART, prior drug regimen, the availability of a resistance test before baseline, and risk of TCF in multivariate analyses. After adjustment, patients with a higher viral load at baseline had a 41% increased risk of TCF per log increase in viral load, whereas patients with a higher CD4 cell count at baseline had an 8% reduced risk of TCF per 50% higher CD4 cell count. In addition, injection drug users had a 46% increased risk of TCF, and patients who started receiving 2 new nucleosides at baseline had a 32% reduced risk of TCF.

Changing the definition of TCF. The analyses were repeated using the alternative definition of TCF, which, among

Table 2. Factors associated with triple drug–class failure.

	Univariate analysis		Multivariate analysis	
Group of patients, factor	RH (95% CI)	P	RH (95% CI)	P
Treatment naive				
Prior AIDS	2.11 (1.25–3.58)	.0055	1.47 (0.82–2.65)	.20
IDU	1.12 (0.54–2.53)	.76	1.24 (0.52–2.98)	.63
Hepatitis B positive	0.80 (0.24–2.69)	.72	1.00 (0.29–3.50)	.99
Hepatitis C positive	0.98 (0.55–1.77)	.95	0.48 (0.14–1.63)	.24
Date started receiving HAART per calendar year later	0.72 (0.53–0.99)	.041	0.80 (0.59–1.09)	.16
CD4 cell count at start of HAART 50% higher	0.80 (0.70–0.91)	.0006	0.89 (0.76–1.03)	.12
Viral load at start of HAART log higher	1.81 (1.31–2.51)	.0003	1.55 (1.10–2.16)	.011
Resistance test before HAART	0.64 (0.29–1.39)	.26	0.87 (0.39–1.98)	.75
Treatment experienced				
No. of new nucleosides started at HAART[a]				
1	0.88 (0.69–1.12)	.30	0.95 (0.73–1.24)	.70
≥2	0.58 (0.42–0.80)	.0008	0.68 (0.4–0.98)	.040[a]
No. of nucleosides ever taken per extra 1	1.24 (1.11–1.39)	.0002	1.12 (0.97–1.29)	.12
Prior regimens taken[b]				
Dual therapy	1.01 (0.62–1.63)	.98	0.96 (0.58–1.59)	.86
Monotherapy and dual therapy	1.50 (0.96–2.34)	.079	1.18 (0.72–1.94)	.50
Prior AIDS	1.58 (1.25–1.98)	<.0001	1.17 (0.91–1.51)	.21
IDU	1.57 (1.17–2.12)	.0030	1.46 (1.00–2.12)	.048
Hepatitis B positive	1.11 (0.73–1.69)	.63	1.07 (0.70–1.65)	.75
Hepatitis C positive	0.68 (0.50–0.93)	.016	0.88 (0.60–1.30)	.52
Date started receiving HAART per calendar year later	0.68 (0.58–0.79)	<.0001	0.89 (0.76–1.05)	.17
CD4 cell count at start of HAART 50% higher	0.83 (0.78–0.88)	<.0001	0.92 (0.86–0.9)	.019
Viral load at start of HAART log higher	1.51 (1.35–1.69)	<.0001	1.41 (1.25–1.59)	<.0001
Resistance test before HAART	0.79 (0.51–1.22)	.28	0.99 (0.63–1.54)	.96

NOTE. CI, confidence interval; HAART, highly active antiretroviral therapy; IDU, injection drug use; RH, relative hazard.
[a] Compared with no new nucleosides.
[b] Compared with monotherapy.

TE patients, resulted in a prevalence of TCF that was consistently higher than that calculated according to the PLATO definition, reaching 29.1% at or after 2003. There was little difference in the prevalence of TCF in TN patients, which reached 6.4% at or after 2003. At 6 years after starting HAART, 35.5% of TE patients were estimated to have TCF (95% CI, 36.1%–40.9%), higher than the level found using the PLATO definition, whereas a very similar proportion of TE patients had TCF (9.8% at 6 years; 95% CI, 7.4%–12.2%). The incidence of TCF with time receiving HAART showed a similar pattern to that shown in figure 3 for both TE and TN patients, but, once again, the incidence of TCF was higher for TE patients when the alternative definition of TCF was used than when the PLATO definition was used. The factors related to TCF were highly consistent when the other definition was used (data not shown).

Clinical outcome. There was an increase in the incidence of new cases of AIDS and death with increasing numbers of drug classes failed. The incidence of new AIDS cases and death was 2.7 cases/100 PYFU (95% CI, 2.3–3.1 cases/100 PYFU) in patients with no drug-class failure, 3.7 cases/100 PYFU in patients with 1–2 drug-class failures (95% CI, 3.3–4.1 cases/100 PYFU), and 5.0 cases/100 PYFU in patients with TCF (95%

CI, 3.7–6.3 cases/100 PYFU). There was an estimated 36% increased incidence of new AIDS cases and death with each category of drug-class failure (95% CI, 19%–56% increased incidence; $P<.0001$, Poisson regression). The increased incidence was particularly marked among patients with a current CD4 cell count ≤50 cells/mm³ (figure 4), for whom there was an estimated 47% increased incidence of new AIDS cases and death with category of drug-class failure (95% CI, 12%–93% increased incidence; $P = .006$, Poisson regression). There was no significant change among patients with current CD4 cell counts of 51–200 cells/mm³ ($P = .70$), and an estimated 20% increase per category of drug-class failure (95% CI, 0.99%–1.48% increase; $P = .056$, Poisson regression) among those with CD4 cell counts >200 cells/mm³.

DISCUSSION

By 2003, 1 of 20 TN patients and 1 of 6 TE patients from the EuroSIDA study who started receiving HAART experienced TCF. The incidence of TCF was considerably lower among TN patients but increased with increasing time since starting HAART. The incidence of TCF among TE patients was stable
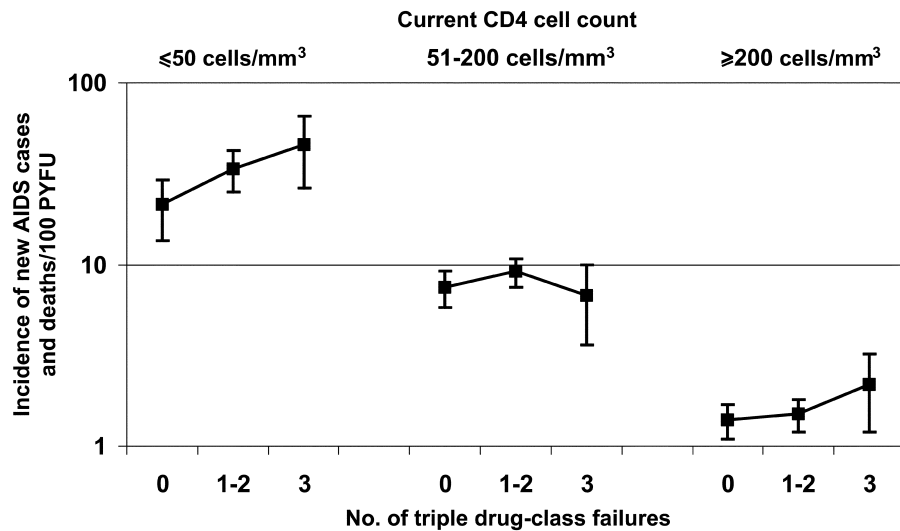
Figure 4. No. of triple drug–class failures and incidence of AIDS or deaths after starting highly active antiretroviral therapy (HAART). PYFU, person-years of follow-up.

after an initially low incidence during the first 2 years after starting HAART. The World Health Organization projects that 3 million people with HIV in the developing world will be receiving treatment by the end of 2005 [13]. Because the rate of TCF in the developing world will probably be comparable to that reported here, the number of patients with TCF worldwide will continue to increase during the coming years, as the population with extended exposure to HAART in the developed world increases.

Six years after starting HAART, ∼20% of TE patients and 10% of TN patients were estimated to have TCF. In small, detailed studies with extended follow-up, ∼30% of patients who were initially TN experienced virological failure during their first HAART regimen, 2–3 years after starting HAART [14, 15]. In larger observational studies, 20%–40% of patients experienced virological failure during their first HAART regimen, on the basis of an average of 2–3 years of follow-up [16, 17]. The definition of virological failure differs between studies, as do the patients included, but patients whose initial HAART regimen failed usually change to a regimen containing a different class of drug and are, therefore, at immediate risk of TCF, according to the PLATO definition. Our estimates of TCF in TN and TE patients 6 years after starting HAART appear to be consistent with the above estimates, coupled with estimates suggesting that a further 20%–50% of patients experience failure of second-line regimens [3–6].

Several studies have shown that TE patients have a poorer virological response to HAART than do TN patients [18–20], but, in general, there has been no difference in the risk of clinical progression between TE and TN patients [21–23]. However, it may take years from TCF to clinical progression, and, with extended follow-up, differences in clinical progression may

become apparent. To date, cross-resistance to antiretroviral classes has been 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 and to potential 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 drugs such as enfurvirtide [25], and the use of more drugs in each regimen.

The incidence of TCF increased 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 explained, in part, by the comparatively high number of TN patients who started receiving HAART during this time period, because patients who recently started receiving HAART were comparatively overrepresented. By 5 years after starting HAART, the incidence of TCF in TN patients was similar to that in TE patients, although the CIs around the estimate were wide. The initially low and then steady rate of TCF in TE patients may reflect that, during the first years after starting HAART, patients with rapid TCF had more resistance and were least able to adhere to the new regimens, or it may reflect differences in early treatment guidelines [26]. Once such patients have TCF, the remaining TE patients may experience TCF at a rate similar to that seen in TN patients, and the curves will increase at the same rate, with extended exposure to HAART.

The factors related to TCF in the present study were similar to those related to failure of a first- or second-line regimen [5, 27–31]. TE patients and those who had a high viral load or low CD4 cell count had an increased risk of TCF. Although a

number of studies have shown a significant correlation between drug resistance and virological response [32, 33], the role of resistance testing remains unclear. We found no relationship between the availability of a pre-HAART resistance test and TCF. In patients with extensive prior treatment and multiple treatment failures, the interpretation of resistance tests is difficult, and other factors, such as adherence, treatment history, and toxicities, need to be taken into account [34–36].

We used a definition of TCF based on the PLATO definition, which classifies failure as viral loads >1000 HIV RNA copies/mL for >4 months while receiving each class of drug [7]. In the present study, viral loads were measured, on average, every 3 months. We repeated our analysis using an alternative definition of TCF, and the results showed consistently higher rates of TCF in TE patients. In general, however, the differences between TN and TE patients remained the same, and similar factors were related to TCF. Most randomized clinical trials define virological failure on the basis of a viral load >50 HIV RNA copies/mL. We believe that the PLATO definition represents a more conservative approach to virological failure, one that may be used in the routine clinic setting, where there may be less-frequent monitoring of patients, and maintenance on a regimen with that keeps viremia at low levels. The PLATO definition has been shown to have clinical relevance [7] and is a measure of extensive drug exposure and virological failure during therapy. It should be recognized that some failures may be due to poor adherence and that a patient with TCF may still respond to another drug within these classes.

We found a significant increase in the incidence of new cases of AIDS and death with an increasing number of drug-class failures. This trend was most pronounced among patients with a current CD4 cell count of ≤50 cells/mm^3. Although patients with TCF have significantly higher rates of clinical disease, the PLATO study demonstrated that, even among patients for whom it was not possible to completely suppress viremia, the risk of clinical progression remained low as long as the CD4 cell count was maintained at >200 cells/mm^3 [7]. Further, the incidence of clinical progression was ~5/100 PYFU, significantly lower than the rate of disease progression seen in EuroSIDA before 1998 [12].

There are several limitations of the present study that should be noted. The results from clinical trials and observational studies have shown that adherence plays a role in virological failure [15, 35, 37, 38], data we do not currently have. It is likely that some patients may have TCF because of poor adherence and thus would not have resistance. The future responses to therapy for nonadherent patients could be different from those for patients with TCF and resistance; sustained virological suppression should be achievable if good adherence can be achieved and maintained on future regimens. We had only a small selected patient group with available resistance tests before start-

ing HAART, and further work is ongoing to collect resistance data at baseline and at TCF. We used a definition of TCF based on the PLATO study, but we performed several additional sensitivity analyses. The results were highly consistent when we changed the criteria for failure to 6 months with a viral load >1000 HIV RNA copies/mL, when we left-truncated the data until prospective follow-up in the EuroSIDA study began, or when we excluded patients who started receiving HAART before prospective follow-up. In addition, although nevirapine became available in the middle of 1996, efavirenz was not widely used by EuroSIDA patients until 1998 [39]. A further sensitivity analysis that included only patients who started receiving HAART in 1998 or later showed similar results.

Further treatment options, such as mega-HAART regimens or treatment interruptions [40–42], will be needed as the number of patients with TCF increases. The recent introduction of fusion inhibitors, with which 20% of patients experienced viral suppression after 48 weeks [43], is unlikely to significantly diminish the proportion of patients with virological failure of all classes of antiretrovirals (i.e., 4 classes). Other treatment options, such as conserving drugs for future treatment options, are currently being investigated in clinical trials. In the Strategies for Management of Anti-Retroviral Therapy study, HAART is used both periodically, to maintain the CD4 cell count at >200 cells/mm^3 in the drug-conservation arm, and at all time points, to maximize viral suppression in the virological suppression arm (http://www.smart-trial.org/).

In summary, although it is possible that further treatment improvements over the next 5 years will make TCF less likely than reported here, these results estimate TCF among a heterogeneous pan-European population where there are many factors involved in decisions about which regimen to start and the virological threshold required for treatment failure. Given that patients with TCF experience higher rates of clinical progression, it seems important to optimize the first-line HAART regimen to avoid virological failure. The long-term consequences of TCF on the durability of HAART and on the reduction in clinical progression of disease and how best to manage this situation deserve further focus.

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