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ORIGINAL RESEARCH

Changing utilization of Stavudine (d4T) in HIV-positive people in 2006–2013 in the EuroSIDA study*

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Objectives

The long-term side effects of stavudine (d4T) led to recommendations in 2009 to phase out use of this drug. We aimed to describe temporal patterns of d4T use across Europe.

Methods

Patients taking combination antiretroviral therapy (cART) in EuroSIDA with follow-up after 1 January 2006 were included in the study. cART was defined as d4T-containing [d4T plus at least two other antiretrovirals (ARVs) from any class] or non-d4T-containing (at least three ARVs from any class, excluding d4T). Poisson regression was used to describe temporal changes in the prevalence of d4T use and factors associated with initiating d4T.

Results

A total of 5850 patients receiving cART on 1 January 2006 were included in the current analysis, rising to 7768 patients on January 1 2013. During this time, the prevalence of d4T use fell from 11.2% to 0.7%, with an overall decline of 19% per 6 months [95% confidence interval (CI) 19–20%]. d4T use declined fastest in Northern Europe [26% (95% CI 23–29%) per 6 months], and slowest in Eastern Europe [17% (95% CI 16–19%) per 6 months]. In multivariable Poisson regression models, new d4T initiations decreased by 14% per 6 months [adjusted incidence rate ratio (aIRR) 0.86; 95% CI 0.80–0.91]. Factors associated with initiating d4T were residence in Eastern Europe (aIRR 4.31; 95% CI 2.17–9.98) versus other European regions and HIV RNA > 400 copies/mL (aIRR 3.11; 95% CI 1.60–6.02) versus HIV RNA < 400 copies/mL.

Conclusions

d4T use has declined sharply since 2006 to low levels in most regions; however, a low but persistent level of d4T use remains in Eastern Europe, where new d4T initiations post 2006 are also more common. The reasons for the regional differences may be multifactorial, but it is important to ensure that all clinicians treating HIV-positive patients are aware of the potential harmful effects associated with d4T.

Keywords: combination antiretroviral therapy, Europe, EuroSIDA, HIV, stavudine utilization

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†See Appendix for the EuroSIDA Study Group.

Introduction

Stavudine (d4T; trade name Zerit) is one of the early antiretroviral drugs from the class of nucleoside reverse transcriptase inhibitors (NRTIs). It was approved for treatment of HIV-positive people in Europe in 1996. Since then, it has been widely used as part of initial combination antiretroviral therapy (cART). Although short-term tolerability of d4T was reported to be good, the drug turned out to be associated with serious long-term side effects [1–5]. Of major concern is mitochondrial toxicity, resulting primarily in lactic acidosis, polyneuropathy and lipodystrophy [5–8]. The first concerns regarding the safety of d4T were reported in the late 1990s [9,10]. Strong evidence of greater d4T toxicity compared with other NRTIs has since been documented in several cohorts and randomized studies [11–15]. From 2004, treatment guidelines began to remove d4T from the list of preferred first-line antiretroviral drugs [16]. In 2007, the World Health Organization (WHO) recommended reduction of standard d4T dosage from 40 to 30 mg for all adults receiving cART [17]. In 2009, WHO recommended that the drug be phased out of first-line antiretroviral therapy programmes [18]. In 2011, the European Medicines Agency (EMA) warned that d4T should be used for as short a time as possible and only when there are no appropriate alternatives [19,20]. According to the EMA estimation, over a million HIV-positive patients in Europe have been exposed to d4T since its approval, although the number of patients being treated with d4T has declined from over 65 000 in 2005–2006 to nearly 9000 in 2009–2010 [19]. However, utilization of d4T in Europe has not been studied in detail, and it is not known whether prescription patterns are in line with the restricted indication of the drug. EuroSIDA represents a unique opportunity for assessing temporal trends in the uptake of d4T across Europe.

This study aimed to assess the level of d4T use in HIV-positive patients on cART across Europe between 2006 and 2013, and to identify reasons for discontinuation of d4T and factors associated with the initiation of the drug during the study period.

Methods

The EuroSIDA cohort

EuroSIDA is a prospective observational cohort study of 18 786 HIV-1-infected patients from 107 clinics in 37 countries (Europe, Israel and Argentina). The details of the cohort have been presented elsewhere [21,22]. The cohort study aims to include a representative sample of the HIV-positive patients followed in the participating clinics. Clinical and laboratory information is collected on a standardized adjustable data collection form at enrolment and every 6 months thereafter (http://www.cphiv.dk), including mode of HIV transmission, all CD4 counts and HIV RNA measurements, and dates of initiation and discontinuation of all antiretroviral drugs (ARVs) as well as drugs used for treatment and chemoprophylaxis against opportunistic infections. Dates of diagnosis of all AIDS-defining illnesses are also recorded using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention [23]. A comprehensive quality assurance programme has been established to ensure correct patient selection and to verify that accurate data are supplied.

The study was approved by the Ethics Committees of participating clinics, as per local and national regulations. All patients' data were obtained from patients' medical records or via database exchange using the HIV Cohorts Data Exchange Protocol (HICDEP; see www.hicdep.org for more details) format. Informed consent was obtained according to local legislation.

Statistical analysis

The current analysis evaluated the use of d4T from January 2006 until January 2013. All patients enrolled in EuroSIDA with at least one follow-up visit after 1 January 2006 were eligible for inclusion in the study. Cross-sectional analysis was used to determine the proportion of patients taking d4T-containing cART regimens on 1 January 2006 and at 6-monthly intervals thereafter among patients under follow-up on these dates. Univariable Poisson regression was used to describe temporal changes in the prevalence of d4T use. d4T-based cART regimens were defined as d4T plus at least two other ARVs of any class, and non-d4T-based cART regimens were defined as three or more ARVs of any class (excluding d4T). Characteristics of patients taking d4T-based regimens and non-d4T-based regimens were described at the beginning and the end of the study period: 1 January 2006 and 1 January 2013.

A subgroup analysis was performed on data for 3857 patients who were receiving cART on 1 January 2006 and 1 January 2013 in order to determine the extent of switching to and from d4T-based cART. Follow-up was counted from 1 January 2006 until the first switch to or from d4T. Among those on non-d4T-based cART at 1 January 2006, the number and percentage who switched to d4T-based cART were determined. Among those on d4T-based cART at 1 January 2006, the number and percentage who switched to non-d4T-based cART were calculated. The

reasons for discontinuing d4T were described (i.e. treatment failure, toxicities, patient/physician choice, other or unknown).

Multivariate Poisson regression was used to identify factors associated with initiating d4T-based regimens after 1 January 2006 and to determine whether the rate of uptake changed over time. Initiating a d4T-based cART regimen was defined as the first time a patient started d4T after 1 January 2006 while receiving at least two other ARVs. Patients initiating d4T without two other ARVs were censored at the date of d4T initiation. Baseline for this analysis was defined as 1 January 2006, the date of starting cART or the date of recruitment to EuroSIDA, whichever occurred later. Follow-up was counted to initiation of a d4T-containing regimen, death or last available follow-up.

The following covariates were considered in multivariable analysis: region of residence, gender, age, race, risk factors for HIV exposure, hepatitis B/C virus (HBV/HCV) status, presence of AIDS, smoking status, previous history of diabetes and hypertension, estimated glomerular filtration rate (eGFR), previous exposure to nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) at baseline, baseline nadir CD4 cell count, maximal HIV RNA, calendar time, time since cART initiation and time enrolled in EuroSIDA. Factors that were significant in univariable models ($P < 0.1$) were then included in multivariable models.

To compare d4T utilization across EuroSIDA, six regions were established according to the country of residence of the patient, as in previous EuroSIDA studies [22]: Southern Europe (South): Greece, Italy, Israel, Portugal and Spain; West Central Europe (West Central): Austria, Belgium, France, south Germany, Luxembourg and Switzerland; Northern Europe (North): Denmark, Finland, north Germany, Ireland, the Netherlands, Norway, Sweden and the UK; East Central Europe (East Central): Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, Serbia and Slovakia; Eastern Europe (East): Belarus, Estonia, Latvia, Lithuania, the Russian Federation and the Ukraine; and Argentina.

All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC).

Results

Overall, 963 of 13 246 (7.3%) EuroSIDA patients under follow-up during the study period 2006–2013 received a d4T-based cART regimen. Table 1 describes the characteristics of patients on d4T-based cART compared with those on non-d4T-based cART at 1 January 2006 and 1 January 2013. There were substantial differences between d4T and non-d4T cART users in both time periods. Generally, d4T users were younger and a higher proportion resided in South Europe, East Europe and Argentina, while fewer d4T users resided in West Central and North Europe ($P < 0.0001$). In both time periods, d4T users were more likely to have acquired HIV via injecting drug use (IDU) or heterosexual contact, to be HCV coinfected, and to have a prior AIDS diagnoses. They also had been exposed to fewer ARVs, while a lower proportion had undetectable HIV RNA.

Overall, the proportion of patients on d4T-based cART fell from 11.2% to 0.7% over the study period, a 19% decrease [95% confidence interval (CI) 19–20%; $P < 0.0001$] per 6 months. Highly significant univariable decreases in d4T use were also observed in each region of EuroSIDA (Fig. 1). Of note, although the proportion of patients taking d4T fell significantly from 26.2 to 2.3% in East Europe and from 22.0 to 2.3% in Argentina, there remained a low but persistent level of d4T use in these regions. The interaction between calendar time and region of Europe was highly significant ($P < 0.0001$), meaning that the rate at which d4T use has reduced over time varies by region of Europe. In multivariable models adjusting for age, gender, HIV transmission risk group, CD4 cell count and HIV RNA, faster declines in d4T use were seen in North [26% (95% CI 23 – 29%) decline per 6 months], West Central [23% (95% CI 21 – 25%)] and East Central Europe [23% (95% CI 21–25%)] compared with 21% (95% CI 20 – 23%), 17% (95% CI 16 – 19%) and 18% (95% CI 16 – 21%) in South Europe, East Europe and Argentina, respectively. Significant decreases in the proportion of d4T users over time were seen in all CD4 count ($\leq$ 200, 201–350 and $\geq$ 351 cells/μL) and HIV RNA strata ($\leq$ 400, 401–10 000 and > 10 000 copies/mL). Interactions between calendar time and CD4 cell count category, and calendar time and HIV RNA category were nonsignificant ($P = 0.58$ and $P = 0.70$, respectively), indicating that there was no difference in the rate of decline in d4T use according to the CD4 cell count and HIV RNA categories.

Multivariable Poisson regression was used to identify factors associated with initiating d4T-based cART after 1 January 2006 (Table 2). There were 62 d4T initiations in 20 463 person-years of follow-up (PYFU) in 5020 patients [crude incidence 3.0 (95% CI 2.3–3.8) per 1000 PYFU]. Figure 2 displays the incidence of d4T initiation by calendar year. After adjustment, there was a 14% decrease in initiation of d4T per 6-month period [incidence rate ratio (IRR) 0.86; 95% CI 0.80–0.91; $P < 0.0001$]. Forty-two of 62 (67.7%) of the patients initiating d4T were from East Europe and patients from East Europe had a 4-fold increased incidence of initiating d4T compared with patients from all other regions (IRR 4.31; 95% CI 2.17–8.56; $P < 0.0001$). Each doubling of current CD4 cell count was associated with a 26% reduction in initiation of d4T (IRR

Table 1 Characteristics of stavudine (d4T) users and nonusers in Europe at 1 January 2006 and 1 January 2013

Characteristic	1 January 2006			1 January 2013		
	d4T users ($n = 654$)	Non-d4T cART users ($n = 5196$)	*P*-value*	d4T users ($n = 56$)	Non-d4T cART users ($n = 7712$)	*P*-value*
Age (years) [median (IQR)]	43.0 (38.0–49.0)	44.0 (39.0–51.0)	0.0069	43.0 (35.0–51.0)	47.0 (39.0–54.0)	0.0200
Gender [*n* (%)]						
Female	147 (10.7)	1222 (89.3)	0.5534	21 (1.0)	2098 (99.0)	0.0848
Male	507 (11.3)	3974 (88.7)		35 (0.6)	5614 (99.4)	
Region of Europe [*n* (%)]						
South	261 (14.4)	1552 (85.6)	<0.0001	9 (0.5)	1753 (99.5)	<0.0001
West Central	110 (7.9)	1290 (92.1)		6 (0.4)	1413 (99.6)	
North	81 (4.9)	1556 (95.1)		3 (0.2)	1881 (99.8)	
East Central	118 (18.0)	539 (82.0)		7 (0.5)	1335 (99.5)	
East	53 (26.2)	149 (73.8)		24 (2.3)	1030 (97.7)	
Argentina	31 (22.0)	110 (78.0)		7 (2.3)	300 (97.7)	
HIV transmission route [*n* (%)]						
MSM	246 (9.4)	2380 (90.6)	<0.0001	11 (0.3)	3190 (99.7)	0.0028
IDU	175 (15.3)	967 (84.7)		15 (1.1)	1354 (98.9)	
Heterosexual	191 (11.3)	1500 (88.7)		28 (1.1)	2628 (98.9)	
Other	42 (10.7)	349 (89.3)		2 (0.4)	540 (99.6)	
Prior AIDS diagnoses [*n* (%)]						
No	395 (10.5)	3377 (89.5)	0.0207	33 (0.6)	5343 (99.4)	0.0945
Yes	259 (12.5)	1819 (87.5)		23 (1.0)	2369 (99.0)	
Total number of ARVs exposed to [median (IQR)]	8.0 (6.0–12.0)	10.0 (7.0–15.0)	<0.0001	6.0 (3.5–12.0)	11.0 (6.0–17.0)	<0.0001
Prior exposure to NUCS† [*n* (%)]						
No	2 (40.0)	3 (60.0)	0.0408	0	2 (100.0)	0.9041
Yes	652 (11.2)	5193 (88.8)		56 (0.7)	7710 (99.3)	
HCV antibody status [*n* (%)]						
Negative	413 (9.9)	3769 (90.1)	<0.0001	34 (0.6)	5588 (99.4)	0.0654
Positive	205 (15.8)	1090 (84.2)		20 (1.1)	1745 (98.9)	
Unknown	36 (9.7)	337 (90.3)		2 (0.5)	379 (99.5)	
HBsAg status [*n* (%)]						
Negative	558 (11.1)	4462 (88.9)	0.4644	53 (0.8)	6916 (99.2)	0.2102
Positive	40 (10.2)	352 (89.8)		3 (0.8)	389 (99.2)	
Unknown	56 (12.8)	382 (87.2)		0	407 (100.0)	
CD4 count (cells/μL) [median (IQR)]§	479.0 (299.0–691.0)	485.0 (326.0–676.0)	0.5838	537.0 (364.0–788.0)	562.0 (395.0–760.0)	0.8575
CD4 count nadir (cells/μL) [median (IQR)]§	111.0 (42.0–224.0)	129.0 (45.0–220.0)	0.3807	120.5 (35.5–236.5)	150.0 (60.0–244.0)	0.2813
HIV RNA ($\log_{10}$ copies/mL) [median (IQR)]§	1.7 (1.7–2.7)	1.7 (1.7–2.0)	<0.0001	1.6 (1.3–1.7)	1.6 (1.3–1.7)	0.8740
HIV RNA < 400 copies/mL [*n* (%)]						
No	153 (17.4)	728 (82.6)	<0.0001	4 (0.9)	430 (99.1)	0.3708
Yes	431 (9.5)	4117 (90.5)		37 (0.6)	6357 (99.4)	

*P-value for comparison of population medians using the Kruskal – Wallis test or comparison of proportions using the χ^2 test.
†Other than d4T.
§Closest measurement to date within the window of 3 months before and after.
IQR, interquartile range; MSM, men who have sex with men; IDU, injecting drug user; HBsAg, hepatitis B virus surface antigen; eGFR, estimated glomerular filtration rate.

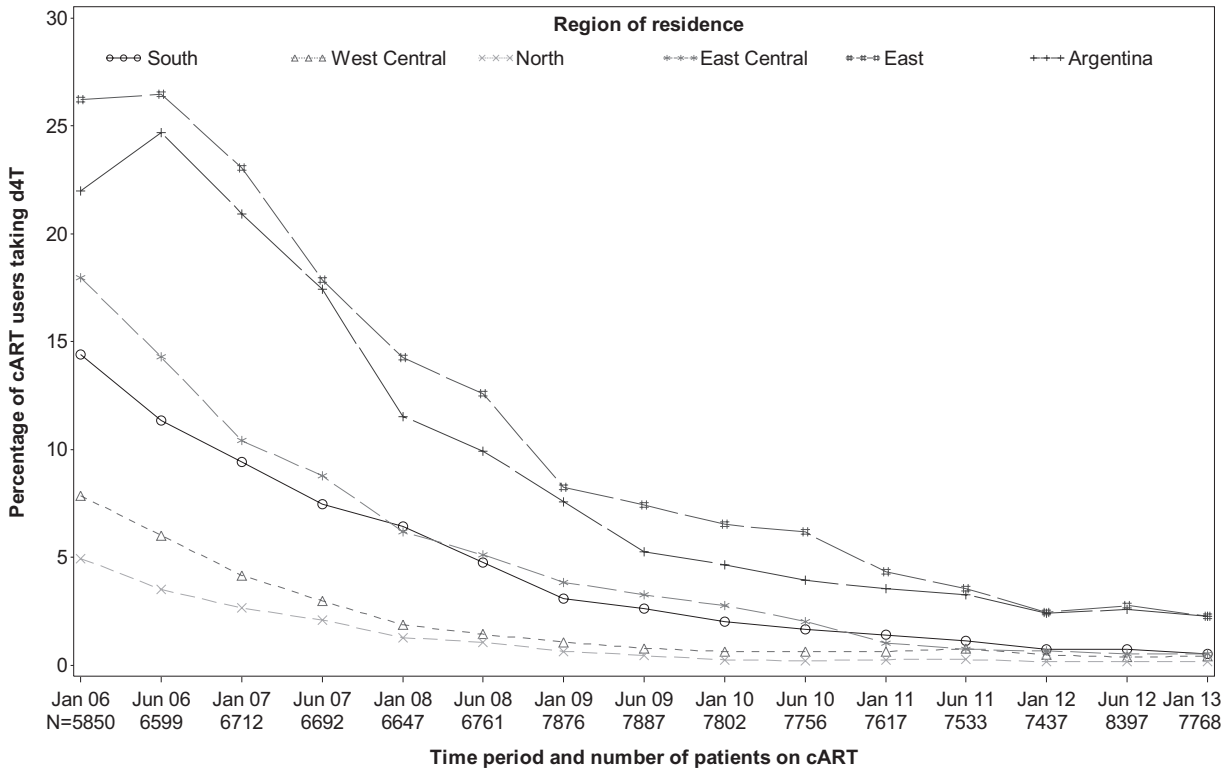

Fig. 1 In use of stavudine (d4T) stratified by region. Southern Europe (South): Greece, Italy, Israel, Spain; West Central Europe (West Central): Austria, Belgium, France, south Germany, Switzerland; Northern Europe (North): Denmark, Finland, north Germany, Ireland, the Netherlands, Norway, the UK; East Central Europe (East Central): Bulgaria, Croatia, the Czech Republic, Hungary, Poland, Romania, Slovakia; Eastern Europe (East): Belarus, Estonia, Latvia, Lithuania, the Russian the Ukraine; and Argentina. cART, combination antiretroviral therapy.

Table 2 Poisson regression estimates of factors associated with initiating stavudine (d4T) after 1 January 2006

	Univariable estimates		Multivariable estimates†	
Factor	**Estimate (95% CI)**	***P*-value***	**Estimate (95% CI)**	***P*-value***
Time/age/sex/ethnicity				
Calendar time (per 6 months later)	0.88 (0.82–0.93)	<0.0001	0.86 (0.80–0.91)	<0.0001
Age (per 5 years older)	0.63 (0.55–0.73)	<0.0001	0.86 (0.73–1.01)	0.0748
Male (versus female)	0.61 (0.36–1.01)	0.0564	1.49 (0.84–2.64)	0.1724
White (versus nonwhite)	3.96 (0.97–16.2)	0.0557	2.29 (0.52–9.98)	0.2716
Region of Europe/Argentina				
East (versus other)	14.0 (8.25–23.9)	<0.0001	4.31 (2.17–8.56)	<0.0001
HIV transmission group				
IDU (versus other)	2.87 (1.72–4.78)	<0.0001	2.46 (0.87–6.96)	0.0908
AIDS				
AIDS during follow-up‡	4.12 (1.65–10.3)	0.0024	2.32 (0.91–5.94)	0.0788
CD4 count/viral load‡				
CD4 count [per doubling (per $\log_2$ cells/μL higher)]	0.51 (0.46–0.57)	<0.0001	0.74 (0.60–0.91)	0.0045
HIV RNA > 400copies/mL (versus ≤ 400 copies/mL)	10.7 (6.38–18.0)	<0.0001	3.11 (1.60–6.02)	0.0008
HIV RNA unknown (versus ≤ 400 copies/mL)	1.22 (1.09–1.37)	0.0005	1.02 (0.89–1.17)	0.7753

The analysis was based on 62 new initiations of d4T treatment in 20 463 person-years of follow-up (PYFU) in 5020 d4T-naïve individuals.
**P*-value from Poisson regression model.
†Time updating variable/set of variables.
‡The multivariable model also adjusted for CD4 cell count nadir and time enrolled in EuroSIDA. Hepatitis C virus antibody (HCVAb) was excluded from the multivariable model because of a correlation with IDU ($R = 0.71$; $p < 0.0001$).
CI, confidence interval; IDU, injecting drug user.

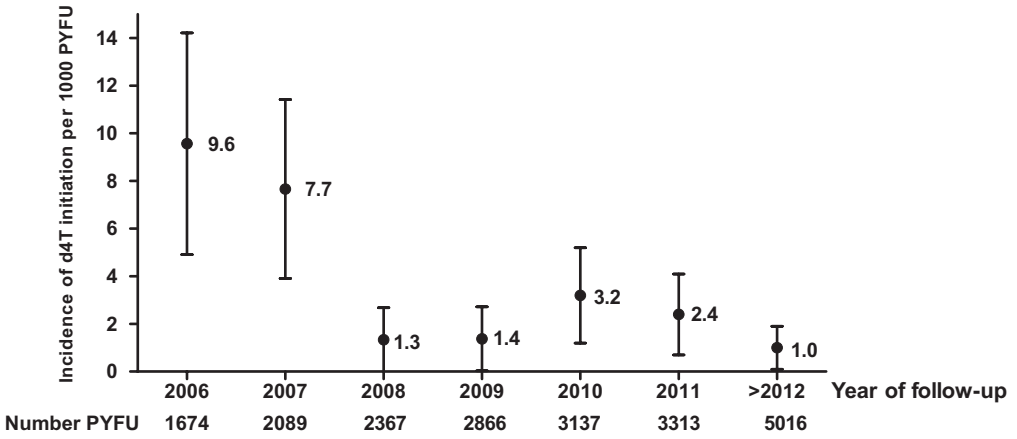

Fig. 2 Temporal trend in initiation of stavudine (d4T) in HIV-positive people after 1 January 2006. Univariable test for trend 0.88 per 6 months [95% confidence interval (CI) 0.82–0.93; $P < 0.0001$]. Multivariable test for trend 0.86 per 6 months (95% CI 0.80–0.91; $P < 0.0001$), adjusted for factors in Table 2. PYFU, person-years of follow-up.

0.74; 95% CI 0.60–0.91; $P = 0.0045$), while HIV RNA > 400 copies/mL was associated with a 3-fold increase in d4T initiation (IRR 3.11; 95% CI 1.60–6.02; $P = 0.0008$).

To determine the extent of switching to and from d4T-based cART over the study period, we performed a subgroup analysis of the 3487 patients who were on cART at both 1 January 2006 and 1 January 2013. There were 392 patients taking d4T at 1 January 2006, of whom 381 (97.2%) discontinued before 1 January 2013. The majority of patients, 288 (75.6%), discontinued d4T together with at least one other ARV drug. The most frequent reason for discontinuation was indicated as physician's choice (26.5%), followed by unknown reasons (17.6%), abnormal fat distribution (15.8%), treatment failure (virological, immunological and/or clinical) (15.0%), other reasons (9.2%), patient's wish (6.0%) and toxicity (5.5%). Among those who discontinued d4T alone ($n = 93$; 24.4%), d4T-related toxicities such as abnormal fat distribution, dyslipidaemia and nerveous system toxicity were frequently indicated (24.7, 4.3 and 3.2%, respectively) However, the proportions of d4T discontinuations where the reason was given as physician's decision, unknown and treatment failure were still high (23.7, 19.4 and 7.5% respectively). The majority of discontinuations in all regions were based on physician's decision, except in East Europe, where treatment failure together with other reasons was more common (data not shown). Statistically, there were no regional differences in the proportion of patients discontinuing d4T and all regions reported > 95% rates of d4T discontinuation. Of the 3095 patients receiving cART not taking d4T at 1 January 2006, 27 (0.9%) patients started d4T before 1 January 2013, these patients originating mainly from the East (40.7%) and South (25.9%) regions, while seven of 27 (29.2%) had CD4 cell counts < 200 cells/μL at the time of starting d4T.

Discussion

This study demonstrates that there was a significant decrease in d4T utilization in the period 2006–2013 across all regions of Europe and Argentina. However, 2.3% of the patients being treated with cART in Eastern Europe and Argentina in January 2013 were on d4T and patients receiving cART in Eastern Europe were at a 4-fold higher risk of being treated with d4T compared with patients in the other regions. Although there were a few patients who initiated d4T after 1 January 2006, the majority of them discontinued the drug again within the study period. Since 2006, regulatory bodies and clinical guidelines have recommended phasing out of d4T in the treatment of HIV infection because of its toxic long-term side effects. Instead, better tolerated and less toxic drugs should be used in first-line cART regimens (i.e. tenofovir, emtricitabine, abacavir or lamivudine) [24,25]. To the best of our knowledge, the present study is the first multinational study specifically evaluating trends in the use of d4T in clinics across Europe following the change in treatment guidelines. Our results are consistent with EMA reports showing decreases in the number of HIV-positive patients exposed to d4T over time [19]. Studies from Western European countries demonstrated that the proportion of patients on d4T peaked in 1998-99 (at around 40%) and then decreased to < 1% by 2007, indicating that d4T was quickly phased out [26,27]. The most common reason for d4T discontinuation in our study was 'physician's choice/decision', suggesting that physicians in general adhere to changes in the

treatment guidelines. However, this finding should be carefully interpreted, as physician's decision might imply a broad spectrum of reasons, for example treatment failure, toxicities or availability of the drug.

Despite well-documented d4T toxicity and recommendations to avoid the drug, we still observed a small proportion of patients remaining on d4T-containing cART in January 2013, primarily in Eastern Europe and Argentina. Declines in d4T use over time were similar and significantly lower in these regions, when compared with the other regions. Of note, the results from Argentina should be interpreted with caution as they are based on a relatively low number of patients.

Within Eastern Europe, d4T was in use in seven of 14 (50%) of the countries as of January 2013, with prevalence ranging from 1.3 to 6.4%, but numbers did not allow for meaningful analysis of country- or centre-specific data. The scale-up of antiretroviral therapy occurred only recently in many post-Soviet countries, and many patients in this region started first-line therapy with the cheapest available drugs [28]. Similar trends were reported from several cohort studies in Africa, where increase in d4T utilization was associated with scale-up of antiretroviral treatment (from approximately 2002) followed by a rapid decrease after 2006–2007 [29–31]. This scale-up of d4T use occurred in spite of the well-documented toxicity profile of the drug.

Some of the patients remaining on d4T in all regions in 2013 may represent those who tolerate the drug without any obvious severe adverse effects and do not wish to change their treatment. The continued use of d4T in Eastern Europe is concerning, as patients in this region may be at even higher risk of developing adverse events in the context of a high prevalence of tuberculosis and HCV coinfection in the HIV-infected population in this region [32]. Patients receiving concomitant d4T and isoniazid have a greatly increased risk of peripheral neuropathy, compared with those receiving only d4T [33]. Recent findings from the D:A:D study suggest avoiding use of d4T in patients with a high risk of end-stage liver disease, which is relevant in the context of a high prevalence of HCV coinfection and alcohol consumption [22,34]. However, evidence from Eastern Europe is scarce. It is worth keeping in mind that Eastern Europe is a very heterogeneous region, where adoption and implementation of international guidelines varies in time and depends on local economical and political settings. EuroSIDA previously showed that cART utilization in Eastern Europe was significantly lower compared with the other European regions, and that patients receiving cART were less likely to achieve virological suppression [35–37]. More research on the use of d4T as well as on cART utilization in general in this region is urgently needed, and it remains important to continue close monitoring of patients on d4T in order to prevent and manage toxicities.

While a limited number of patients may continue receiving d4T, it remains important that initiation of the drug, particularly as part of first-line therapy, should be avoided. Although many resource-limited countries have developed plans to phase out d4T, this will take a while to implement in practice, while prices for other first-line NRTIs (e.g. tenofovir and abacavir) remain high and these drugs are not widely available. To speed up this process, authorities might consider completely removing d4T from the list of licensed drugs without any significant impact on HIV care.

The main limitation of this analysis is that observational data should be interpreted with caution, and, while there is extensive data quality assurance in place within EuroSIDA, it still remains an observation of routine clinical practice across Europe. As a consequence, whatever statistical methods are used, we will not be able to exclude confounding by indication. It is worth mentioning that EuroSIDA clinics in Eastern Europe are major HIV clinics with well-developed infrastructure and facilities to participate in clinical research, primarily located in big cities, and thus represent centres of excellence in this region. The situation beyond these clinics, particularly in rural areas, has not been investigated and might be even worse. As a consequence of power limitations we were not able to analyse intraregional variation in d4T utilization. Unfortunately, EuroSIDA does not collect data on drug doses, which would be important to investigate in the case of d4T, as studies have shown that the 30 mg dose has a favourable safety profile when compared with the 40 mg dose [38]. Further, it would be of interest to investigate in more detail the role of the duration of being on d4T and concomitant use of other ARVs, as well as whether d4T was administrated as part of first- or second-line cART. A more extensive analysis of cART utilization with a special focus on Eastern Europe is currently under development within EuroSIDA.

In conclusion, although d4T use has sharply decreased since 2006 to very low levels in most regions and the incidence of new d4T initiations remains very low, there is still a low but persistent proportion of EuroSIDA patients in Eastern Europe receiving d4T. The reasons for continued use of d4T and regional differences may be multifactorial, but it is important to implement systems to monitor and manage toxicities for all ongoing use of d4T-containing cART regimens. The situation in Eastern Europe beyond the EuroSIDA study needs to be further investigated and well-established pharmacovigilance surveillance in this region is urgently needed. All HIV clinicians should be aware of

the potential harmful effects associated with d4T treatment and avoid the drug as far as possible.

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