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Is Stavudine (D4T) still being used in EuroSIDA despite its association with toxicity and a higher frequency of severe adverse events?

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BACKGROUND AND OBJECTIVES

Since its authorisation in 1996, post-marketing reports and published literature regarding the side effects of Stavudine (D4T) led the WHO to recommend in 2009 that countries phase out its use due to its long term irreversible side-effects[1,2]. Prescription labelling information has since been amended to state that D4T should be used for as short a time as possible and only when other antiretroviral (ARV) medicines cannot be used[3]. The aims of this study were to determine the prevalence of D4T use and describe temporal changes and factors associated with initiating D4T over time in EuroSIDA according to region of residence.

METHODS

All EuroSIDA patients taking combination antiretroviral therapy (cART) with at least 1 follow-up visit after 1/1/2006 were included in this study. A D4T-containing regimen was defined as D4T plus at least 2 other ARVs from any class, non-D4T-containing regimens were defined as at least 3 ARVs from any class. Poisson regression models were used to describe temporal changes in the prevalence of D4T use among cART users in EuroSIDA between January 2006 and June 2011, and to identify factors associated with initiation of D4T-based cART adjusting for region of residence.

RESULTS

- 5851 cART-users were included in January 2006 rising to 6879 in June 2011. Patients characteristics are shown in **Table 1**.
- The overall prevalence of D4T use among cART users fell from 11.3% in January 2006 to 1.2% in June 2011, a 16% fall per year in univariable Poisson regression (IRR: 0.84 (95% CI 0.83 – 0.85; p<0.0001)).
- D4T use declined to negligible levels in North, South, East Central and Western Europe over the study period (5.1% to 0.2%, 14.5% to 1.3%, 18.0% to 0.9% and 7.8% to 0.9%, respectively) (**Figure 1**).
- Large declines in D4T use were also seen in East Europe and Argentina, however, there remains a significant level of D4T use in these regions in 2011 (26.1% to 3.8% and 22.0% to 3.1%, respectively) (**Figure 1**).
- The incidence of D4T initiation fell sharply over the study period from 9.6 (95% CI 4.9 – 14.3) per 1000 person years follow-up (PYFU) in 2006 to 2.2 (0.4 – 3.9) per 1000 PYFU beyond 2010 (**Figure 2**). In multivariable Poisson regression, initiations of D4T were 6-fold higher (aIRR: 6.06 (95% CI 0.07 – 0.36; p<0.0001)) in 2006/07 compared to 2008/09, with no significant difference for 2010/11 (aIRR: 2.08 (95% CI 0.86 – 5.05; p=0.10)) compared to 2008/09 (**Figure 3**).
- Other factors associated with D4T initiation were residence in East Europe (aIRR: 4.82 (95% CI 1.26-18.3; p=0.021) vs. West Europe), baseline AIDS diagnosis (aIRR: 1.93 (95% CI 1.05-3.56; p=0.034)) and HIV-RNA (aIRR: 1.35 (95% CI 1.07-1.69; p=0.010) per $\log_{10}$ higher) (**Figure 3**).

CONCLUSIONS

D4T use has fallen sharply since 2006 to low levels in most regions, however, a significant level of D4T use remains in East Europe and Argentina. The incidence of new D4T initiations post 2006 remains low, but is more common in East Europe and in those with higher HIV-RNA levels. Reasons for 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 treatment.

Table 1

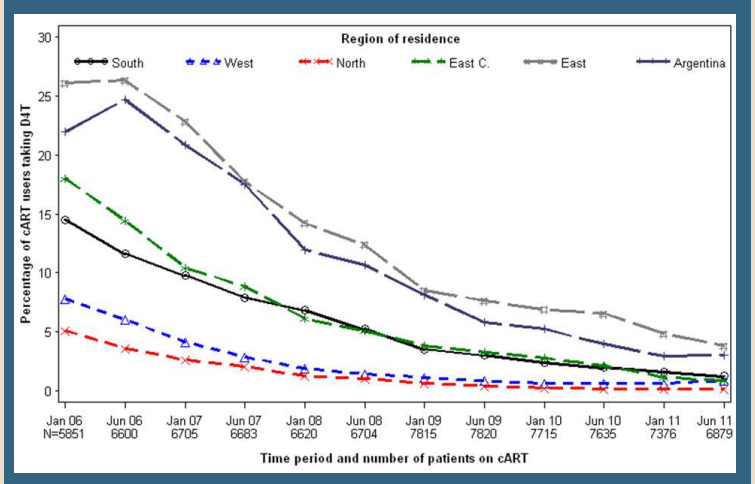
Patient characteristics

Characteristic	1st January 2006 D4T users (N=660)	1st January 2006 Non-D4T cART users (N=5191)	P-value[1]	1st June 2011 D4T users (N=84)	1st June 2011 Non-D4T cART users (N=6795)	P-value[1]
Region of Europe						
South	265 (40.2%)	1560 (30.1%)	<.0001	20 (23.8%)	1548 (22.8%)	<.0001
West	108 (16.4%)	1273 (24.5%)		13 (15.5%)	1481 (21.8%)	
North	84 (12.7%)	1556 (30.0%)		3 (3.6%)	1709 (25.2%)	
East central	119 (18.0%)	542 (10.4%)		9 (10.7%)	1019 (15.0%)	
East	53 (8.0%)	150 (2.9%)		30 (35.7%)	754 (11.1%)	
Argentina	31 (4.7%)	110 (2.1%)		9 (10.7%)	284 (4.2%)	
HIV transmission route						
MSM	251 (38.0%)	2362 (45.5%)	<.0001	18 (21.4%)	2784 (41.0%)	0.0065
IDU	173 (26.2%)	974 (18.8%)		18 (21.4%)	1247 (18.4%)	
Heterosexual	191 (28.9%)	1498 (28.9%)		39 (46.4%)	2229 (32.8%)	
Other	45 (6.8%)	357 (6.9%)		9 (10.7%)	535 (7.8%)	
HCV antibody status						
Negative	417 (63.2%)	3734 (71.9%)	<.0001	50 (59.5%)	4931 (72.6%)	0.0264
Positive	206 (31.2%)	1118 (21.5%)		30 (35.7%)	1603 (23.6%)	
Unknown	37 (5.6%)	339 (6.5%)		4 (4.8%)	261 (3.8%)	
Age						
Median (IQR)	43 (38 - 49)	44 (39 - 51)	0.0102	40 (31 - 46)	42 (36 - 49)	0.0004
Total ARVs exposed to						
Median (IQR)	8 (6 - 12)	10 (7 - 15)	<.0001	6 (4 - 12)	12 (7 - 17)	<.0001
CD4 cell count (/mm³)						
Median (IQR)	481 (304 - 698)	484 (326 - 676)	0.9627	588 (361 - 790)	552 (391 - 743)	0.5725
HIV-RNA < 400 copies/ml						
No	151 (25.6%)	734 (15.1%)	<.0001	10 (16.1%)	403 (7.2%)	0.0068
Yes	438 (74.4%)	4122 (84.9%)		52 (83.9%)	5226 (92.8%)	

[1]P-value for comparison of population medians using the Kruskal-Wallis test or comparison of proportions using the chi-square test
A D4T-containing regimen was defined as D4T plus at least 2 other ARVs from any class, non-D4T-containing regimens were defined as at least 3 ARVs from any class

Figure 1

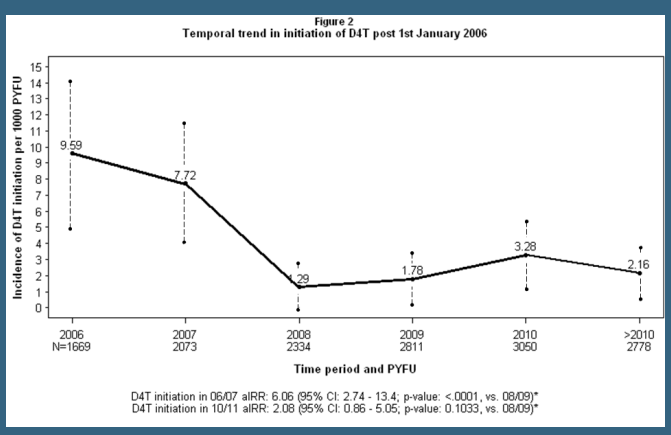
Decreasing prevalence of D4T use



Geographical regions: South: Greece, Italy, Portugal, Spain, Israel; West: Belgium, France, south Germany, Luxembourg, Switzerland, Austria; North: Denmark, UK, Finland, north Germany, Ireland, The Netherlands, Sweden, Norway; East Central: Hungary, Serbia, Czech Republic, Slovakia, Bulgaria, Poland, Romania, Croatia; East: Belarus, Russia, Estonia, Latvia, Lithuania, Ukraine

Figure 2

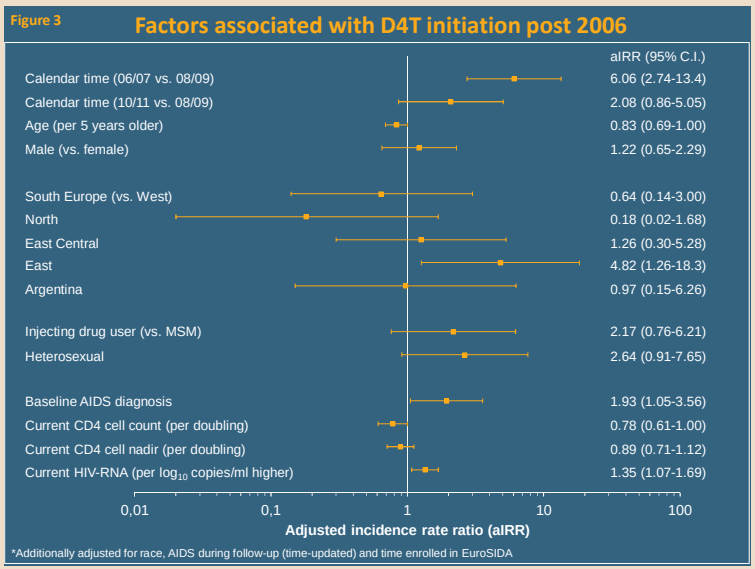
Decreasing incidence of D4T initiation post 2006



aIRR: Adjusted incidence rate ratio
*Adjusted for: age, gender, race region of Europe, HIV transmission risk group, baseline AIDS, AIDS during follow-up, current CD4 cell count, CD4 nadir, HIV-RNA and time enrolled in EuroSIDA

Figure 3

Factors associated with D4T initiation post 2006



*Additionally adjusted for race, AIDS during follow-up (time-updated) and time enrolled in EuroSIDA

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