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Experience Using AZT and d4T in TAHOD Patients: Treatment Duration and AZT Related Anaemia

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Introduction

In many Asian countries stavudine (d4T) has been more frequently prescribed in initial antiretroviral therapy (ART) regimens than zidovudine (AZT)[1], largely because of its availability in Fixed Dose Combinations, lower cost[2], and good short term tolerability.

There is mounting evidence that among the nucleoside reverse transcriptase inhibitors (NRTI) d4T is the most strongly associated with long term mitochondrial toxicity [3, 4] and accordingly the recently revised WHO guidelines recommend AZT or tenofovir as the preferred NRTI [5], while d4T is suggested as an alternative first line agent.

In an effort to balance the risk of early AZT-related side effects (including anaemia) with the long-term risk of d4T, a strategy of starting patients on d4T and switching to AZT after several months has been proposed. However it is unknown whether this strategy is effective in reducing AZT related anaemia.

This study aimed to investigate the experience of d4T and AZT ART using data from the TREAT Asia HIV Observational Database (TAHOD), a multicentre prospective observational HIV cohort in 15 sites in the Asia-Pacific Region[6].

Methods

Two separate analyses were performed using aggregate TAHOD data reported between September 2003 and September 2005. Inclusion criteria were patients who commenced ART containing three or more antiretroviral agents, either before or after entry to TAHOD, and had at least one subsequent follow up recorded in the database.

Factors associated with the time to discontinuation of initial regimens containing d4T or AZT were analysed using a proportional hazards regression analysis. The time to stopping AZT and D4T were estimated using the Kaplan-Meier method. The follow up period for ART containing regimens was divided into two periods for subsequent analysis as the incidence of stopping AZT and d4T did not maintain a consistent proportional relationship over time. A cut point at 9 months was determined by log – likelihood criteria to be the best fit to the data. Logistic regression analysis was used to identify factors associated with a diagnosis of anaemia within 6 months of commencement of AZT in initial or subsequent regimens.

All analyses were adjusted for sites. Multivariate models were fitted using forward stepwise selection. If the p-value in univariate models was less than or equal 0.10 then the variables were considered in the multivariate models. Variables with multiple categories were included if an overall test for trend or heterogeneity was significant. All the analyses were performed using STATA software, version 8.2 (STATA corp College Station, TX).

Results

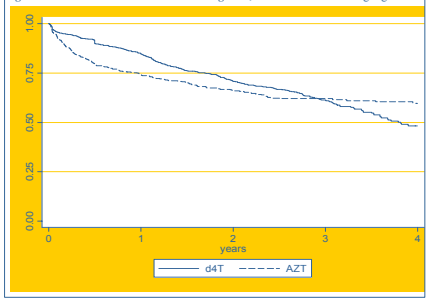
1. Analysis of time to discontinuation of initial regimens containing d4T or AZT
From September 2003 to September 2005, 2979 patients were recruited to TAHOD including 2345 who commenced ART, and 1655 who fulfilled criteria for the analysis of time to stopping initial regimen.

Baseline characteristics of patients commenced on initial AZT and d4T regimens
The mean age at baseline was 37 years, 70% were male, Chinese and Thai ethnicities were the most common, and heterosexual contact was the main risk HIV for acquisition. For the two thirds of patients in whom baseline CD4 count was recorded, more than 80% were below 200 cells/ µL. Previous (non TB) ADI were documented in 11% patients, prior TB in 10%, and ADI and TB were reported in 23% and 16% respectively at baseline or after commencement of ART.

Baseline Haemoglobin
Baseline Hb was available for 62% of patients who commenced ART containing AZT and for 53% in the d4T group ($p = 0.011$). Anaemia (Hb < 10 g/dL) was reported at baseline in 170/932 (18.2%) of patients tested, including severe anaemia (Hb < 7.5 g/dL) in 24 / 932 (2.6%) patients. Of the patients tested who commenced d4T, 24% were anaemic at baseline including 22 with severe anaemia, whilst of the patients who commenced AZT, 8.3 % were anaemic, including 2 with severe anaemia.

Time to cease initial treatment regimen
The overall rate of stopping initial regimens was 17 (95%CI 16-19) per 100 person-years and did not differ between the two regimens (Figure 1). However, the rate of stopping initial regimens within the first 9 months was 18 (95% CI 15 - 21) per 100 person years for those commenced on d4T and 37 (95% CI 31 - 44) per 100 person years for those commenced on AZT (p < 0.001).

Figure1. Time to cease initial treatment regimen, AZT vs D4T containing regimens



Factors related to stopping AZT or d4T containing first line regimens
Factors related to stopping AZT or d4T containing regimens in multivariate analysis included: age/10 years (HR1.10, 95%CI 1.01 – 1.20), female gender (HR1.24, 95%CI 1.03 – 1.50), and current TB (HR1.32, 95%CI 1.05 – 1.67). There was a trend to higher rates of stopping with lower baseline CD4 (p = 0.012). Stopping d4T was less common than stopping AZT within the first 9 months of ART (HR 0.51, 95%CI 0.39 – 0.67), whilst stopping d4T was more common than stopping AZT after 9 months of ART (HR 2.27, 95%CI 1.64 – 3.13).

Reasons for stopping AZT within the first 9 months:
The reasons reported for 128 patients who stopped AZT within the first 9 months included; 43% due to adverse event, 19 % patient decision, 5 % lost to follow up, 5% treatment failure, 3 % compliance difficulties, 2% clinical progression / hospitalization, 2% drug interaction, and 19 % "other" (data not shown).

2. Analysis of AZT related anaemia in patients on initial or subsequent regimens:
433 patients were recorded as having started AZT as an initial or subsequent ART regimen, and had Hb measurement within 6 months after commencement. Anaemia was reported in 57 (13%) patients, including severe anaemia in 11 (2.5%) (Table 1).

ART naïve patients had a slightly increased frequency of Hb testing during the 6 month period (1.6 tests in naïve patients compared to 1.3 in experienced patients p < 0.001). There was no statistical difference in the median time to the first test between the two groups (72 days vs 83 days p = 0.427).

Discussion

- The rate of stopping initial regimens within the first 9 months was higher in those who commenced AZT, compared with those who commenced d4T in initial ART regimens, and cessation appeared to be largely driven by side effects.
- Increasing age, female sex, and reported current TB, predicted an increased likelihood of stopping initial AZT or d4T containing ART regimen.
- A higher rate of cessation of d4T than AZT after 9 months on initial therapy may reflect the emergence of d4T associated toxicity, or pre-emptive switches within the nucleoside class in an attempt to reduce the likelihood of longer term d4T toxicity.
- Anaemia occurred in 13% of patients commenced on AZT. Anaemia was most strongly predicted by baseline anaemia but also by older age, female sex, and current (non TB) ADI. The only protective factor for anaemia in patients commenced on AZT was prior ART experience.
- Limitations include the observational nature of this study, inclusion of retrospectively collected data, and variations between sites regarding Hb testing and ART prescribing practices.

Table 1: Factors associated with anaemia within 6 months of starting AZT

Factor	N	# cases	%	Univariate logistic regression OR (95% CI)	p	Multivariate logistic regression OR (95% CI)	p
Age per 10 years	433	57	13	**1.40**	**0.004**	**1.71 (1.26 – 2.32)**	**0.001**
Sex							
- Male	333	40	12	1.00	…	**1.00**	**…**
- Female	100	17	17	1.50	0.258	**3.29 (1.20 – 9.08)**	**0.021**
Exposure					**0.015**		0.133
- Heterosexual	299	36	12	**1.00**	…	1.00	…
- IDU + others +unknown	58	15	26	**2.55**	**0.005**	1.87 (0.96 – 3.59)	0.059
- Homosexual	76	6	8	**0.63**	**0.369**	1.01 (0.31 – 3.30)	0.987
CD4 at baseline, cells/µL					**< 0.001***		**0.004***
- < 50	72	17	24	**1.00**	…	**1.00**	**…**
- 51 - 100	35	9	26	**1.12**	**0.755**	**0.90 (0.31 – 2.63)**	**0.842**
- 101 - 200	88	12	14	**0.51**	**0.012**	**0.49 (0.21 – 1.12)**	**0.091**
- > 200	111	6	5	**0.18**	**0.001**	**0.19 (0.03 – 1.26)**	**0.085**
- Missing	126	13	10				
Baseline anaemia							
- Normal	289	37	13	**1.00**	…	**1.00**	**…**
- Anaemic (Hb < 10 g/L)	18	10	56	**8.51**	**<0.001**	**7.20 (2.44 – 21.27)**	**<0.001**
- Missing	126	10	8				
Current ADI							
- No current ADI	348	34	10	**1.00**	…	**1.00**	**…**
- Current ADI	85	23	27	**3.43**	**<0.001**	**3.07 (1.87 – 5.04)**	**<0.001**
Current TB							
- No current TB	389	45	12	**1.00**	…	1.00	…
- Current TB	44	12	27	**2.87**	**0.010**	2.04 (0.86 - 4.83)	0.103
ART experienced							
- Naive	306	50	16	**1.00**	…	**1.00**	**…**
- Experienced	127	7	6	**0.30**	**<0.001**	**0.32 (0.12 – 0.84)**	**0.021**

* p-value from test for trend without missing values
Bold font: significant in multivariate models and adjusted for each other, others adjusted for those in bold.

Conclusion

- These data support baseline Hb testing and avoidance of AZT if anaemic.
- The protective effect of prior ART experience for the development of anaemia on AZT lends support to the short term safety of d4T to AZT switch where routine Hb monitoring of haemoglobin is available. However, if routine switch to AZT is to be widely considered, further studies in resource poor settings into the longer term efficacy and toxicities of ART switch strategies are needed.

References

1. J Zhou NP, R Ditangco, YMA. Chen, A Kamarulzaman, N Kumarasamy, CKC Lee, PCK Li, TP Merati, P Phanuphak, S Pujari, A Vibhagool, F Zhang, J Chuah, KR Frost, DA Cooper, MG Law on behalf of the TREAT Asia HIV Observational Database. Experience with the use of a first - line regimen of stavudine, lamivudine and nevirapine among TAHOD patients. HIV Medicine (2007), 8, 8–16.
2. Medicines Sans Frontiers. Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries. 8th Edition . 2005.
3. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 2000;14(10):1309-16.
4. Carr A. HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. AIDS 2003;17 Suppl 1:S141-8.
5. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access.Recommendations for a public health approach. 2006.
6. Zhou J, Kumarasamy N, Ditangco R, et al. The TREAT Asia HIV Observational Database: baseline and retrospective data. J Acquir Immune Defic Syndr 2005;38(2):174-9.

Acknowledgements

The TREAT Asia HIV Observational Database

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