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Short communication

The frequency and reasons for antiretroviral switching with specific antiretroviral associations: The SWITCH study

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ABSTRACT

Background: We investigated the reasons for switching antiretroviral regimens, an issue rarely addressed in cohort studies.
Methods: An observed toxicity switch rate (OTSR) was calculated by Poisson regression using the number of days individuals received each individual antiretroviral drug.
Results: Of 3333 individuals receiving HAART, a total of 14% of regimens were switched, the majority occurring after 6 months of therapy. Toxicity was the major reason for switching (61%) and there were no major statistically significant differences in OTSR between the protease inhibitor (OTSR 26.4, 95% CI 18.3–37) and non-nucleoside reverse transcriptase inhibitor (OTSR 22.2, 95% CI 13.6–34.4) based regimes. For individual antiretrovirals, stavudine and zidovudine had significantly higher "switch" scores than all other drugs.
Conclusions: There were no differences between the major HAART classes in OTSR. We suggest that newer antiretrovirals will require differentiation in terms of longer-term toxicity, as this is the major reason for switching.

1. Introduction

Although HAART has had a major impact on those living with HIV (Palella et al., 1998), the majority of patients will require changes at some point in their combination antiretroviral therapy. The reasons for such 'switching' are multifactorial, and include failure of current therapy, toxicity and potential drug interactions (Stebbing et al., 2005; Winston and Stebbing, 2005; Latham et al., 2005; Osterberg and Blaschke, 2005). While other studies have focused on the percentage of prescribed doses of medication taken, we aimed to investigate the rate that patients switch therapy, why they switch and when toxicity was the reason, we calculated an incidence rate for switching, for each antiretroviral.

2. Methods

The Chelsea and Westminster HIV cohort is the largest single centre cohort in Europe and we prospectively collect routine data on the individuals who attend. HIV positive patients are seen at regular intervals for trial follow-up, clinical and immunologic assessments. All HIV patients who have attended the Chelsea and Westminster since routine prospective data collection commenced in 1983 were identified and we have defined HAART as therapy consisting of at least three antiretroviral drugs in accordance with published guidelines (dual nucleoside analogues alone are not considered HAART though this is considered a 'backbone' of therapy) (Yeni et al., 2004; Hammer et al., 2008). This study focuses on a cohort who have continued to be followed up since the HAART era commenced (which we have defined as 1st January 1996 when HAART became routinely available at our Institution, and many others). All individuals who ceased follow-up before this date were excluded; appropriate ethical approval was obtained.

All patient details including prescriptions are held in the departmental database. To ensure full case ascertainment this record was cross-checked with the computer system in the pharmacy department. All reasons for changes in therapy were recorded by computer and when missing was observed, the prescribing clinician was contacted. The antiretrovirals switched and the reasons for the change of therapy were recorded for all the prescriptions that involved a switch in regimen.

The rate of toxicity for each individual ARV was calculated using the Poisson regression model where total number of days on each individual ARV was used as the denominator. In order to keep the coefficient of the denominator constant, this was log transformed and used as an offset in the Poisson model. The data were analyzed using the Genmod procedure in SAS version 9.1 with $\log_e$ link and Poisson error distributions. This fits generalized linear models

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allowing time dependent measures of probability. Data are presented as toxicity rate per 1000 patient years with 95% confidence intervals.

3. Results

A total of 3333 individuals receiving HAART were included in this study, and of these 14% ($n = 469$) of regimens were switched during the study period affecting 13% ($n = 433$) of patients. Excluding the tenofovir/lamivudine to Truvada switches and the switches away from a tenofovir/didanosine combination, this rate decreased to 10% ($n = 333$) of our studied cohort. The main reason for switching was toxicity at 61% ($n = 203$). Failure of the regimen was cited the cause in 14% ($n = 47$) of cases, simplification in 13% ($n = 43$), drug interactions in 4% ($n = 13$), and other causes in 8% ($n = 26$).

Of the 202 switches for toxicity, 44% were from zidovudine (85/88 due to actual and/or potential lipodystrophy), 9% were from tenofovir (18/19 renal complications), 8% from stavudine (14/16 actual and/or potential lipodystrophy), 8% from efavirenz (15/16 CNS side-effects), 5% were from lopinavir/ritonavir (7/10 diarrheoa), 4% from saquinavir (9/9 GI side-effects), 4% from atazanavir (7/8 jaundice) and 4% were switched from abacavir (5/8 suspected/actual hypersensitivity). The majority of individuals (81%) switched their therapy after a period of greater than 6 months, with 13% of patients switching within the first 3 months due to 'acute toxicity'.

Investigating the toxicity switches in more detail, for those receiving efavirenz a total of 40% ($n = 6$) switched from this antiretroviral for CNS toxicity in the first 3 months and 46% ($n = 7$) switched after more than 1 year on therapy. Those switching from tenofovir because of renal complications did show a small increase in creatinine levels after starting tenofovir which reduced once tenofovir has been stopped. However, the clinical significance of this increase is questionable, as is the use of creatinine as a surrogate marker for renal toxicity (Jones et al., 2004). The patients switching from abacavir because of a possible hypersensitivity reaction all had a negative HLA result before initiating the drug. No patch testing was performed on these patients.

An observed toxicity switch rate (OTSR) per 1000 patient years (95% CI) was calculated for each antiretroviral (Table 1 and Fig. 1). Stavudine was associated with the highest OTSR value at 304; stavudine and zidovudine had significantly higher OTSR scores than the other antiretrovirals. The other nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) showed no significant difference in OTSR score. There were no significance differences in OTSR between the two non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine. Within the protease inhibitor (PI) class there were also no significant differences between the drugs. Fosamprenavir has the highest OTSR but this is with wide confidence intervals reflecting the low number of patients taking fosamprenavir in our cohort. Confidence intervals overlapped between protease inhibitor and NNRTI-based regimens.

Table 1
Observed toxicity switch rate per 1000 patient years. Non-overlapping 95% CIs indicate statistical significance and we chose not to present p values for individual drugs to avoid too many significance tests (due to increased type II error rates).

NRTIs	OTSR (95% CI)	PIs	OTSR (95% CI)
Stavudine	304.9 (174.3–495.1)	*Fosamprenavir*	89.5 (10.8–323.5)
Zidovudine	224.6 (180.2–276.8)	*Saquinavir*	81.2 (37.1–154.0)
Didanosine	27.6 (9.0–64.4)	*Lopinavir*	46.9 (22.5–86.2)
Tenofovir	19.8 (11.9–30.9)	*Atazanavir*	27.0 (11.7–53.2)
Abacavir	15.1 (6.5–29.7)	NNRTIs	
Emtricitabine	9.9 (3.2–23.0)	*Efavirenz*	24.7 (14.1–40.1)
Lamivudine	1.2 (0.03–6.5)	*Nevirapine*	15.8 (4.3–40.4)

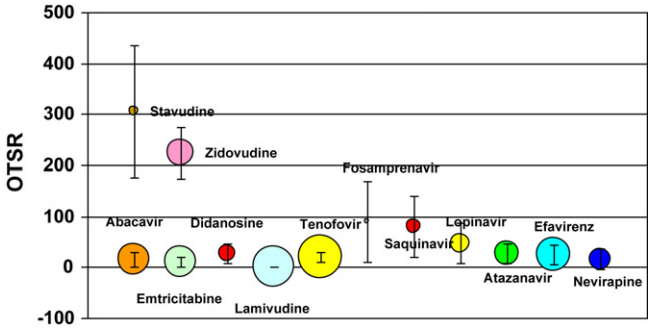

Fig. 1. A graph demonstrating the observed toxicity switch rate per 1000 patient years (OTSR) for the different classes of antiretrovirals with 95% confidence intervals. The size of the circle on the chart reflects the number of patients taking that antiretroviral in our cohort.

4. Discussion

This report deals with changes of treatment in patients treated with HAART as part of routine follow-up, an important question since adherence of therapy is a key parameter when choosing a treatment although this is rarely addressed in cohort studies. We show here using Poisson regression that approximately one in ten patients switched therapy over a period of 6 months with toxicity being the major cause, although rates were similar for PI- and NNRTI-based HAART. Of those who switched, the majority of individuals did so after 6 months of therapy highlighting longer-term toxicity considerations such as lipoatrophy with zidovudine, which may be extended to other toxicities. Whether these longer-term metabolic side-effects are intrinsically linked to the mode of action of the drug class rather than the specific drug remains to be firmly established and will be one of the main challenges in the future development of new drugs in these existing classes.

The OTSR showed that patients are switching from stavudine and zidovudine because of actual or potential lipoatrophy. One of the limitations of this study is that we were unable to assess whether these patients were actually suffering from lipoatrophy but the results provide an indication of current prescribing habits, and general perceptions of patients and clinicians which can be used to guide changes in local prescribing policy. A further limitation is that there may be multiple reasons for switching and we only considered the 'lead reason' in this study. Furthermore, this study is not focused to determine the role of adherence in the change of therapy and other toxicities such as hypersensitivity related to ABC were not shown.

Other than stavudine and zidovudine, the other NRTIs have similar OTSR scores. When examining the OTSR data for protease inhibitors, atazanavir had the lowest OTSR but there was no significant difference between this and the other PIs. The saquinavir OTSR score was statistically higher than both the efavirenz and nevirapine score.

In aggregate, this represents valuable observational data which confirms a proclivity in the last 5 or more years to switch to tenofovir and possibly abacavir from these NRTIs. It would be interesting to map the temporal pattern of switching, associated with the availability of alternative nucleoside and nucleotide analogues. As antiretrovirals become more effective, the key for their long-term success will be their toxicity profile (Gallant, 2000; Osterberg and Blaschke, 2005). New agents will be unlikely to show superior efficacy in naïve patients and therefore there will be a requirement for them to demonstrate safer toxicity profiles. The OTSR is a helpful method of measuring switching between antiretroviral regimens.

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