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Baseline Predictors of Efavirenz-Containing Antiretroviral Regimen Adverse Experiences

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Abstract

Purpose—We aimed to identify modifiable, routinely available patient characteristics associated with adverse experiences potentially attributable to efavirenz-based regimens in patients in Botswana.

Methods—HIV infected treatment naïve individuals starting a standard antiretroviral regimen including two nucleoside analog reverse transcriptase inhibitors and efavirenz in Botswana were enrolled in a prospective cohort. Adverse experiences were measured at one and six months using the efavirenz checklist, a 35 item instrument developed by the AIDS Clinical Trials Group.

Results—We enrolled 232 patients from March 11th, 2010 to March 17th, 2011. 196 were included in the month one analyses. Of the 196 included in the month one analyses, 157 (80%) completed the six month follow-up. Median efavirenz checklist score was 6 (interquartile range (IQR): 2 to 15) at month one and 1 (IQR: 0 to 5) at month six. The median change in efavirenz checklist score from month one to six was -4 (IQR: -11 to -1), representing an improvement. Depressive symptoms, low CD4 count and less alcohol use were associated with improvement in

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adverse experiences over time. Low weight was associated with increased extent of adverse experiences at month one and six. There was no confounding or effect modification.

Conclusions—Clinicians may want to consider more intensive and tailored adverse experience education and management in patients based on depressive symptoms, CD4 count, and weight. Further assessment of the mechanism of the effect of alcohol use on adverse experiences, including analysis of CYP2B6 genotype and plasma efavirenz concentrations, is warranted.

Keywords

efavirenz; HIV; adverse effects; highly active antiretroviral therapy

Introduction

Strict adherence to antiretroviral therapy (ART) must be maintained to successfully treat HIV and prevent development of drug resistance and virologic failure.¹⁻³ Patients who develop virologic failure with resistance must then switch to more expensive second-line antiretrovirals (ARVs) to achieve viral suppression. Tolerability is a major issue with respect to ART adherence. Adverse drug effects are a common reason for the discontinuation of ART regimens⁴ and are associated with an increased risk of poor adherence.⁵

Efavirenz is a non-nucleoside reverse transcriptase inhibitor commonly used as part of first-line treatment for HIV, making it one of the most frequently used ARVs worldwide. Efavirenz is associated with a number of adverse events such as insomnia, vivid dreams, impaired concentration, vertigo, and “dizziness” in approximately half of patients.⁶ Furthermore, these symptoms are severe enough to require treatment modification in up to 9% of patients.⁶ The effects generally occur within a few days of initiation and usually resolve within a few weeks, but not in all individuals.⁷

Pre-treatment prediction of drug toxicity may help target interventions to improve tolerability of ART and add to understanding of mechanisms of toxicity. This is particularly vital in settings with limited options for second- and third-line therapy. Therefore, we aimed to identify modifiable, routinely available patient characteristics associated with adverse experiences potentially attributable to efavirenz-based regimens in patients in Botswana.

Methods

We enrolled a prospective cohort of treatment naïve HIV infected individuals 21 years newly starting an ART regimen including efavirenz in combination with two nucleoside analog reverse transcriptase inhibitors in Botswana. Patients were recruited at the time of ART initiation by study nurses at one of six government-run HIV clinics located in and around the capital city, Gaborone. Clinic nurses identified all potentially eligible patients scheduled for visits and study staff offered participation to eligible patients willing to consider enrolling in a research study. Study nurses obtained informed consent by reading the consent form out loud to patients in the local language, Setswana. Enrollment ran from March 11th, 2010 to March 17th, 2011. Data were censored on November 10th, 2011. The study was approved by the Health Research and Development Committee of the Ministry of

Health of Botswana and the University of Pennsylvania Committee on Human Subjects Research.

Our dependent variable in analyses was the score on the efavirenz checklist, an instrument developed by the AIDS Clinical Trials Group⁸ to assess extent of adverse experiences. The score was assessed at one and six months and included 35 items scored 0–4 based on severity of each reported side effect, with a total possible score of 140. Higher scores reflect increased reported number and/or intensity of symptoms. Elevated scores are associated with efavirenz plasma concentrations.⁹ Our independent variables were potential risk factors for the outcome and included CD4 cell count, age, sex, BMI, and weight, which were abstracted from the medical record, month one pharmacy refill adherence, viral load, which was drawn by study nurses, along with a version of the Mood Module (MM) of the Primary Care Evaluation of Mental Disorders (PRIME-MD), scored out 9 points, with 5 or greater suggesting the diagnosis of major depressive disorder,¹⁰ and a modified Alcohol Use Disorders Identification Test (AUDIT) scored out of 16 points, with higher scores reflecting more reported drinking.¹¹ The questionnaires were administered by study nurses.

We used linear regression to assess the association between baseline characteristics and efavirenz checklist scores. Separate models were constructed for month one and month six scores, and change in score between months one and six. CD4 count was treated as a dichotomous variable with a cutoff of 100 cells/mm³, all other variables were treated as continuous measures.

All baseline variables significantly associated with efavirenz checklist score ($p < 0.05$) in univariate models were included in the initial multivariate model. The multivariate model was first constructed to include all hypothesized risk factors that were significant in univariate analysis. Additional variables including age, sex, adherence, viral load, and BMI were chosen based on a conceptual framework of potential association with adverse effects. These were added in a stepwise manner to the initial multivariate model. Predictor variables significantly associated with efavirenz checklist score ($p < 0.05$) in multivariable analyses were included in the final model. Although both weight and BMI were significantly associated with month 1 efavirenz score in univariate analysis, to avoid collinearity, only weight was included in the final model. The model using weight had a higher R^2 and was therefore selected over the one using BMI. Potential confounding variables were included in a stepwise manner and retained if they changed any risk factor point estimate by 15%. Effect modification was assessed by visual inspection of point estimates after inserting interaction terms into the model. Variables included in the month one model were also included in all other models. All analyses were performed using STATA 11.0 (STATA Corp, College Station, TX).

Results

We collected data on 232 patients with baseline visits of whom 196 were included in the month one analyses. Figure 1 displays the disposition of participants including deaths, transfers out of the study site, consent withdrawals, loss to follow-up, and incomplete baseline data. The characteristics are described in Table 1 with a small predominance of

males and relatively advanced disease at initiation. In addition to efavirenz, almost all (192, 98%) of the regimens included tenofovir and emtricitabine in fixed dose combination; 4 were prescribed zidovudine and lamivudine. Of the 196 included in the month one analyses, 157 (80%) completed the six month follow-up. The 39 patients who did not complete follow-up had significantly higher rates of reported alcohol use compared to the 157 who did (median modified AUDIT scores: 7 and 0, respectively, $p < 0.01$). There was no difference in weight, CD4 count or depressive symptoms between those included and the dropouts. Pharmacy refill adherence data was available for 179 patients at month one. Overall, patients had very high levels of adherence to antiretroviral therapy, with a median adherence rate of 100% (interquartile range (IQR): 96.6% to 100%).

A total of 142 (72%) and 94 (60%) patients reported any adverse experiences at months one and six, respectively (Table 2). Median efavirenz checklist score was 6 (IQR: 2 to 15) at month one and 1 (IQR: 0 to 5) at month six. The median change in efavirenz checklist score from month one to six was -4 (IQR: -11 to -1), representing an improvement in extent of adverse experiences. Table 3 shows the results of linear regression models for extent of adverse experiences at months one, six, and change between months one and six. Increased weight was associated with a lesser degree of adverse experiences. A 10kg higher baseline weight was associated with a 1.8 point lower score at month one (95% confidence interval (CI): -3.0 to -0.6) and a 0.8 point lower efavirenz score at month six (95% CI: -1.4 to -0.2). Baseline depressive symptoms were associated with a greater degree of adverse experiences at month one. One point higher in MM score was associated with a 1.59 point higher score at month one (95% CI: 0.68 to 2.50) and a 0.44 point higher score at month six (95% CI: -0.02 to 0.91). Alcohol use was associated with lower scores at month one. For every point increase in modified AUDIT score, signifying increased alcohol use, there was a 0.35 lower score (95% CI: -0.61 to -0.09) at month one. At month six, this inverse association was no longer present.

In patients with a baseline CD4 count < 100 cells/mm³, adverse experiences improved significantly between months one and six. In contrast, greater baseline alcohol use was associated with worsening of efavirenz checklist scores. Depressive symptoms were associated with an improvement in scores. Neither baseline weight nor BMI were associated with a change in adverse experiences from month one to month six. We found no evidence of confounding or effect modification. Additionally, we repeated the regression model for month one efavirenz score including only the 156 patients who completed all six months of follow-up and found no significant difference (data not shown).

Discussion

Although efavirenz-based antiretroviral therapy is used worldwide, there are few studies on adverse experiences in patients outside Europe and North America. In Botswana, the proportion of patients reporting adverse experiences was relatively high at both months one and six. As anticipated,⁷ adverse experiences improved over time in a large proportion of individuals.

We also found that alcohol use was initially protective at month one, but associated with worsening adverse experiences over time. We did not find any evidence that adherence confounds this relationship. It is possible that longitudinal alcohol use causes impaired hepatic metabolism and higher efavirenz plasma concentrations. Prior studies have shown that patients with elevated efavirenz concentrations are more likely to experience side effects⁹ although not uniformly.¹² Patients in Botswana may be particularly susceptible to this phenomenon: slow metabolizer CYP2B6 genotypes have been associated with both increased plasma concentrations and increased side effects⁹ and in Botswana the prevalence of the slow metabolizer is over 15%.¹³

Our study supports the concern that patients with mood disorders are more likely to report a greater degree of adverse experiences after starting efavirenz-based regimens.¹⁴ However, depressive symptoms were associated with an improvement in scores from month one to month six, suggesting that this phenomenon may be transient and may not preclude the tolerability of long-term efavirenz-based therapy. Low CD4 count was also associated with an improvement of adverse experiences from month one to month six. It is possible that this is due to advanced disease state at ART initiation, although CD4 count was not significantly associated with adverse experiences in our month one model.

There are several limitations that should be mentioned. In this study there was no measurement of baseline, pre-treatment, efavirenz checklist score. This prevents us from concluding that the adverse experiences were due to efavirenz rather than pre-existing symptoms unrelated to ART. However, this does not apply to analysis of the change in efavirenz score from month one to month six which accounts for prior presence of symptoms. Moreover, our results remain relevant to adverse experiences suffered by patients initiated on efavirenz-based regimens, especially in settings where remaining on efavirenz is the most likely approach given the few available alternatives. Another potential limitation is the effect of dropouts. Patients who did not complete follow-up at six months had higher AUDIT scores. However, this would create a selection bias towards including patients without the exposure of interest, with a likely effect of weakening any observed relationship between alcohol and month six outcomes. Additionally, participation in this study was not universal which may limit the generalizability of the results if those who did not enroll had differing degrees of adverse experiences than those who enrolled. Nevertheless, the chances this introduces directional bias into our results are minimal if the mechanisms driving adverse experiences are primarily physiologic, since a decision to participate is unlikely to be related to properties such as efavirenz concentrations. Finally, Botswana is relatively homogenous and the results may not apply to other populations. However, given the sheer number of patients on ART in Botswana alone, even if these results were not generalizable to other settings, they would still be relevant to many patients.

Based on our findings of associations between adverse experiences in patients on efavirenz-based regimens with alcohol use, depressive symptoms, CD4 count, and weight, clinicians may want to consider more intensive and tailored adverse experience education and management for these patients. Further assessment of the mechanism of the effect of alcohol use on adverse experiences, including analysis of CYP2B6 genotype and plasma efavirenz concentrations, is warranted to determine if sub- or super-therapeutic drug concentrations

are present in alcohol users, putting them at increased risk of adverse experiences, poor adherence, and treatment failure.

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Key points

- Using data from a cohort of patients attending outpatient HIV clinics in Botswana, we aimed to identify characteristics associated with adverse experiences on efavirenz-containing regimens.
- Depressive symptoms, low CD4 count and less alcohol use were associated with improvement in extent of adverse experiences over time.
- Low weight was associated with increased extent of adverse experiences at month one and six.
- Clinicians may be able to identify patients at risk and provide anticipatory guidance

Figure 1.

Table 1
Baseline Characteristics of Cohort

N	196
Male sex <i>N (%)</i>	123 (63%)
Age <i>Median (IQR)</i>	40 years (34 to 48)
CD4 cell count <i>Median (IQR)</i>	168 cells/mm ³ (101 to 218)
CD4 < 100 cells/mm ³ <i>N (%)</i>	49 (25%)
Weight <i>Median (IQR)</i>	59.6 kg (53.8 to 68.9)
BMI <i>Median (IQR)</i>	21.4 (19.2 to 23.6)
MM score <i>Median (IQR)</i>	1 (0 to 3)
Modified AUDIT score <i>Median (IQR)</i>	3 (0 to 8)
Viral load <i>Median (IQR)</i>	5.15 log ₁₀ copies/ml (4.48 to 5.53)
Month 1 adherence* <i>Median (IQR)</i>	100% (96.6% to 100%)

* Month 1 adherence available for 179 patients

Table 2
Efavirenz Score at Month 1 and Month 6

	Month 1	Month 6
N	196	
Efavirenz Score <i>Median (IQR)</i>	6 (2 to 15)	1 (0 to 5)
Patients reporting any symptoms (EFV score>0) <i>N (%)</i>	142 (72%)	94 (60%)

Table 3
Baseline Characteristics Associated with Adverse Experiences

	Month 1 Score* N=196 <i>Point Estimate (95% CI)</i>	Month 6 Score§ N=157 <i>Point Estimate (95% CI)</i>	Change in Score‡ N=157 <i>Point Estimate (95% CI)</i>
Weight (per 10kg)	-1.8 (-3.0 to -0.6)	-0.8 (-1.4 to -0.2)	0.9 (-0.5 to 02.2)
MM score	1.59 (0.68 to 2.50)	0.44 (-0.02 to 0.91)	-1.08 (-2.07 to -0.09)
AUDIT score	-0.35 (-0.61 to -0.09)	0.03 (-0.11 to 0.17)	0.46 (0.16 to 0.76)
CD4<100	--	--	-5.10 (-8.86 to -1.34)

* adjusted R²: 0.111

§ adjusted R²: 0.047

‡ adjusted R²: 0.109

† The point estimate for weight reflects the associated change associated with a 10kg increase in baseline weight. Point estimates for other variables reflect the change associated with an increase of 1 unit.