

Racial Differences in Efavirenz Discontinuation in Clinical Practice

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ABSTRACT

Background: Recent research suggests that African-American (AA) patients may have differences in the metabolism of Efavirenz (EFV) compared to whites, resulting in prolonged drug clearance, higher drug levels, and possibly a higher incidence of adverse effects. We sought to determine if there was a difference between AA and whites in durability of EFV use in clinical practice. **Methods:** AA and non-Hispanic white (NHW) patients followed longitudinally in the Johns Hopkins HIV Clinic who received EFV as part of their first HAART regimen started after Jan 1, 2000 were compared for duration of EFV use. Race was self-identified. A Kaplan-Meier approach was used to compare time to discontinuation of EFV. Cox proportional hazards regression assessed discontinuation by race adjusting for other demographic, clinical and therapeutic factors. Time to suppression of HIV-1 RNA (<400 fmI) was assessed. A control group of patients receiving a boosted protease inhibitor (PI) was also compared. Loss to follow-up was low (<2%). **Results:** 218 AA and 65 NHW patients who received EFV. 92 (42%) AA and 15 (23%) NHW discontinued therapy. Probability of discontinuation of EFV by 1 year was 32% in AA, and 16% in NHW (p=0.002). Probability of HIV-1 RNA suppression was 59% at 6 months and 66% at 1-year in AA, and 72% at 6 months and 82% at 1-year in NHW (p=0.01). By Cox regression, AA was associated with a relative hazard= 2.06 (95% CI: 1.16, 3.68) compared to NHW for discontinuing EFV, adjusting for age, sex, risk group (IDU vs. non-IDU), NRTI backbone, CD4 and HIV-1 RNA at start of therapy. By genotype, a primary NNRTI mutation was found in 26 (28% of d/c and 12% total) of AA and 4 (27% of d/c and 6% total) of NHW who discontinued EFV. In contrast, for 69 AA and 16 NHW receiving a boosted-PI, the 1-year probability of discontinuation of boosted-PI was 41% in AA and 36% in NHW (p=0.84), and the probability of HIV-1 RNA suppression was 69% in AA and 61% in NHW at 6 months.

Conclusion: AA were more likely than NHW to discontinue an EFV-based HAART regimen in our clinical practice. Suppression of HIV-1 RNA was less strongly affected. There was no difference between AA and NHW when a boosted PI was used. Our results support racial differences in EFV durability, that appear to be associated with differences in viral suppression and possibly with resistance to NNRTIs.

BACKGROUND

Recent research suggests that Black and African-American patients may have differences in the metabolism of efavirenz (EFV) compared to whites (1,2,3). There is evidence of a longer half-life of efavirenz which results in prolonged drug clearance and higher drug levels that may be measurable for several weeks after a dose of the drug. There is the potential for a higher incidence of non-tolerability of EFV in Black and African-Americans. The Johns Hopkins HIV Clinical Cohort follows a racially diverse population of HIV-infected patients who are in HIV clinical care. We sought to determine if there was a racial difference in discontinuing EFV use in our clinical practice.

METHODS

The Johns Hopkins HIV Clinical Cohort is a longitudinal, cohort which collects demographic, diagnostic, laboratory and therapeutic data documenting the clinical care of HIV-infected patients. Enrollment corresponds to the first visit to the Johns Hopkins HIV Clinic. Data are collected by trained abstractors from paper and electronic medical records and other institutional databases. Baseline data collection summarizes past medical information, and follow-up data collection tracks clinical care longitudinally.

Definitions:

EFV Use: We determined all patients who received EFV as the 'cornerstone' of their initial HAART regimen after January 1, 2000. We determined the duration of time that each of these patients remained on their baseline ARV according to the providers recorded information from medication flow sheets and progress notes.

Race: We used patient self-identification of race for our categories of African-American (AA) and non-Hispanic white (NHW).

METHODS (continued)

Laboratory: HIV-1 RNA, CD4 and genotypes were those done as part of clinical management.

Analysis:

We focused our analysis on patients who discontinued EFV during the first year after starting therapy. A Kaplan-Meier analysis was used to plot the discontinuation of EFV for 1-year following the start of this therapy. To be counted, EFV had to be discontinued by the patient or provider while in care. Death or leaving the practice while still on EFV was not considered discontinuation. Plots were done stratified by race (AA vs. NHW). The time of origin was the start of the initial HAART regimen that contained EFV. Differences in discontinuation by race were determined by log-rank statistic. We also used Kaplan-Meier analysis to determine first HIV-1 RNA suppression to < 400 copies/ml over 1-year, again stratified by race.

A multivariate analysis was done using Cox proportional hazards regression. We assessed discontinuation of EFV by race (AA vs. NHW) adjusting for the patient's age, sex, HIV transmission risk category, backbone NRTIs, and CD4 and HIV-RNA levels at the start of therapy.

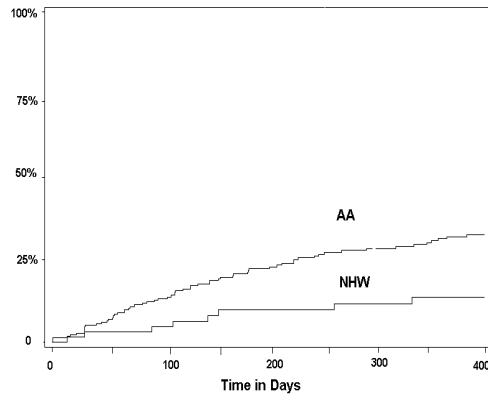
Controls: We also assessed use of a ritonavir-boosted PI as the cornerstone of therapy using the same methods as described above.

RESULTS

218 AA and 65 NHW patients received EFV. Median longitudinal duration of follow-up was not significantly different (718 days for AA and 702 days for NHW). Overall, 92 (42%) AA and 15 (23%) NHW discontinued therapy during all follow-up.

During the first year of follow-up, 62 (28%) AA and 9 (14%) NHW discontinued therapy. Kaplan-Meier plots of EFV discontinuation over 1-year beyond the beginning of therapy are shown in **Figure 1**.

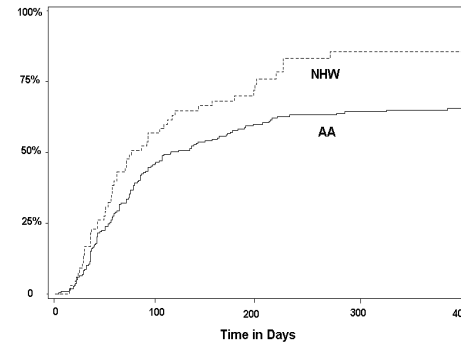
Figure 1: Discontinuation of EFV During First Year



The probability of discontinuation of EFV by 1 year was 32% in AA, and 16% in NHW (p=0.002 by log-rank statistic).

Kaplan-Meier plots of HIV-1 RNA suppression to < 400 copies/ml over 1-year beyond the beginning of therapy are shown in **Figure 2**.

Figure 2: HIV-1 RNA < 400 copies/ml During First Year



The probability of HIV-1 RNA suppression was 59% at 6 months and 66% at 1-year in AA, and 72% at 6 months and 82% at 1-year in NHW (p=0.01 by log-rank statistic).

The multivariate Cox proportional hazards regression analysis is shown in **Table 1**.

Table 1: Multivariate Association of Race and Other Variables with Discontinuation of EFV

Variable	Relative Hazard (95% Confidence Intervals)
Race: AA vs NHW	2.06 (1.16, 3.68)
HIV Transmission: IDU vs Others	1.87 (1.21, 2.87)
Sex: Male vs Female	0.87 (0.57, 1.31)
Age: ≥35 (median) vs < 35 years	0.83 (0.55, 1.28)
CD4: < 200 cells/mm ³	1.09 (0.59, 1.99)
200-350 cells/mm ³	0.83 (0.41, 1.67)
> 350 cells/mm ³	1.0 (Ref)
HIV-1 RNA: < 20,000 c/ml	1.18 (0.71, 1.98)
20-100,000 c/ml	0.88 (0.53, 1.47)
> 100,000 c/ml	1.0 (Ref)
ARV naïve vs not ARV naïve	0.99 (0.58, 1.69)
Associated NRTI:	
Stavudine	1.07 (0.64, 1.80)
Didanosine	0.97 (0.46, 2.07)
Tenofovir	0.73 (0.26, 2.08)
Abacavir	1.28 (0.72, 2.29)
Zidovudine	1.0 (Ref)

RESULTS (continued)

AA was associated with a relative hazard= 2.06 (95% CI: 1.16, 3.68) compared to NHW for discontinuing EFV, adjusting for age, sex, risk group (IDU vs. non-IDU), NRTI backbone, CD4 and HIV-1 RNA at start of therapy.

By record review, we determined reasons for discontinuing EFV during the first year of therapy (**Table 2**).

Table 2: Reasons for Discontinuing EFV in First Year

Reason	AA (n=62 discontinued) (n=218 total)	NHW (n=9 discontinued) (n=65 total)
Adverse Event:		
CNS	12 (19% of dc) (6% of total)	2 (22% of dc) (3% of total)
Other	9 (15% of dc) (4% of total)	1 (11% of dc) (1.5% of total)
1 ^o EFV Resistance*	11 (18% of dc) (5% of total)	2 (22% of dc) (3% of total)
Patient Choice (no reported ADR)	30 (48% of dc) (14% of total)	4 (44% of dc) (6% of total)

*Over total follow-up beyond 1 year, a 1^o NNRTI mutation was found in 26 (28% of 92 who d/c and 12% total) of AA and 4 (27% of 15 who d/c and 6% total) of NHW who discontinued EFV.

CONTROLS (Ritonavir-boosted PIs)

69 AA and 16 NHW who received a ritonavir-boosted PI during this same time period. The 1-year probability of discontinuation of boosted-PI was 41% in AA and 36% in NHW (p=0.84 by log-rank statistic), and the probability of HIV-1 RNA suppression was 69% in AA and 61% in NHW at 6 months (p=0.91 by log-rank statistic).

CONCLUSIONS

AA were more likely than NHW to discontinue an EFV-based HAART regimen in our clinical practice. Discontinuations in both groups were due principally to patient non-adherence and not adverse events, although it is possible that adverse events contributed to non-adherence. In the controls who received ritonavir-boosted PIs, there was no significant difference between AA and NHW, but the numbers of patients who started a boosted PI was relatively low.

Other barriers to adherence not captured in this analysis may be occurring more commonly in AA than NHW in our practice. For example, lack of stable housing and active substance use. Whether our results are unique to our practice or generalize to other clinical practices would need to be assessed.

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