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Treatment can be continued for mild cutaneous reactions associated with efavirenz

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TO THE EDITOR:

Non-nucleotide reverse transcriptase inhibitors (NNRTIs), nevirapine and efavirenz, cause adverse reactions including cutaneous adverse drug reactions (CADRs). CADR includes transient morbilliform reactions, drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. CADR is more common in HIV infection, occurring in 10% to 17% of all those initiating NNRTIs.^{1,2} In sub-Saharan Africa, efavirenz is used in complex settings of multiple comorbidities and limited drug options as a key component in many antiretroviral regimens, fixed dose combination antiretrovirals (FDC-ART), and as the preferred NNRTI in rifampicin-containing antituberculosis regimens.^{2,3} Elimination from a regimen after CADR potentially reduces compliance, and increases drug exposures, drug interactions, and side effects. Limited data exist on the clinical spectrum of efavirenz-CADR, indications for hospitalization, and criteria for efavirenz treat-through, interruption, or discontinuation strategies. This is further complicated by polymorphisms in cytochrome P450 2B6 that slow efavirenz metabolism resulting in higher plasma concentrations in African populations.³ This negatively impacts extrapolation of studies from other populations to Africa. Currently, clinicians lack clear guidance on the management of efavirenz-CADR. We previously described photodistributed annular and palmar erythemas and absence of treatment-altering systemic involvement as features of efavirenz-CADR.^{4,5} These small studies (n = 12) could not delineate treatment-altering and mild transient features. Here we describe a larger cohort highlighting evolution of our management of efavirenz-CADR and describe predictors of successful efavirenz treat-through or discontinuation.

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The study population comprised in-patients referred to the dermatology service at Groote Schuur Hospital, a referral center in South Africa, between July 2004 and December 2015 for efavirenz-CADR having initiated efavirenz 8 weeks earlier. Uncertainty about progression to severe CADR led to hospitalization for monitoring. Ethics approval was obtained from the institutional ethics review committee. The following data were retrospectively extracted from clinical records: age; sex; admission CD4 count; drugs used in the preceding 8 weeks and date of initiation; date of CADR; clinical and laboratory parameters preceding and during CADR; management strategy; and final outcomes. Patients with missing data were contacted telephonically. We used the Naranjo score to assess the probability of efavirenz causality and only included “definite” or “probable” cases.⁶ The severity of each clinical/laboratory feature was graded using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) of the National Cancer Institute.⁷ Data were analyzed using STATA statistical package (Version 13; StataCorp, College Station, Texas). Descriptive analysis using medians with interquartile ranges (IQR) was used to summarize numerical variables. Proportions were depicted as percentages for categorical variables. A Pearson’s χ^2 or Fisher’s exact test was used to test for strength of association between categorical variables. A significance level of $P < .05$ was used for all analysis. Univariate and multivariate logistic regression was conducted to identify predictors for efavirenz discontinuation.

Thirty-eight patients were eligible for inclusion, but 3 were excluded from further analysis for missing data. Eighty-percent were female; the median (IQR) age, nadir CD4 cell count, and days from efavirenz exposure to CADR onset were 34 (27–41) years, 270 (158–455) cells/mm³, and 12 (7–20) days, respectively. Twenty-nine (83%) and 6 (17%) were black Africans and mixed descent, respectively. All had efavirenz terminated before hospitalization. Clinical features of the included 35 are summarized in Table I. Treat-through was successful in 11 of 35, and efavirenz was interrupted in 24 of 35. Efavirenz was not reinitiated in 17 of 24 interruptions, whereas 7 of 24 were successfully rechallenged. Failed rechallenges were due to progressively rising transaminases and eosinophilia, respectively. In descending order, palmar erythema, morbilliform eruption, indurated erythema, facial oedema, photodistributed rash, annular erythema, and nonerosive mucositis were the cutaneous features. Annular erythema was consistently photodistributed. All cutaneous manifestations were CTCAE graded mild. Hepatitis and fever (both in 10/35) and eosinophilia (8/35) were the only systemic features. Transaminase elevation was mild, moderate, severe, and life-threatening in 6 of 10, 1 of 10, 2 of 10, and 1 of 10 of these, respectively. One severe and the life-threatening case of elevated transaminases had similarly graded cholestatic enzyme elevation. Facial oedema coexisted with hepatitis in 6 of 10 cases. Overall, 31 of 35 (89%) efavirenz-CADRs were graded mild. Only hepatitis upped the CTCAE grade beyond mild. Only a post-2013 admission predicted successful treat-through or rechallenge (Table II). Pre-2013 discontinuations (n=9) were due to mild hepatitis (2/9), severe hepatitis (1/9), eosinophilia (3/9), and unknown (3/9). Post-2013 discontinuations (n=8) were due to mild hepatitis (3/8), eosinophilia (2/8), moderate hepatitis (1/8), life-threatening hepatitis (1/8), and 1/8 declined rechallenge. In the univariate analysis of the study population (n=35), fever was a significant predictor of discontinuation, odds ratio 0.084 (0.008–0.786), $P = .030$ (95% confidence interval). Restricting of the multivariate

analysis to post-2013 (n=25), there were no predictors of successfully treating-through or rechallenging (Table II). All the terminated cases were uneventfully on second-line ART 8 weeks after hospital discharge.

We show that despite overlaps with severe CADR such as DRESS, at least two-thirds of efavirenz-CADR patients, as demonstrated by our post-2013 strategy, can successfully continue efavirenz. We postulate that clinical experience, awareness of mildness and transiency of most efavirenz-CADRs, and introduction of convenient single daily dose efavirenz-containing FDC-ART to South Africa in 2013 result in decreased motivation for efavirenz termination and informed change in referral patterns and management strategy. Hepatitis and eosinophilia were the treatment-limiting manifestations. The appropriateness of some post-2013 terminations is unclear, a matter further complicated by discretionary nature of decision making by treating physicians. Facial oedema and fever seem to predict systemic involvement and a more severe phenotype. Efavirenz-CADR needs to be differentiated from efavirenz-drug-induced liver injury described in the same population.⁸ The latter lacks skin involvement, presents much later, and is more severe. We conclude that efavirenz can be continued in efavirenz-CADR, while monitoring for systemic features. In cases with severe to life-threatening hepatitis, efavirenz should be discontinued. We confirm our previous description of the rash in efavirenz-CADR and suggest photodistributed annular erythema as a distinct feature of efavirenz-CADR.^{4,5}

Sampling bias toward hospitalization and small sample size are the study's major limitations. Regardless, as the largest study of in-patients with efavirenz-CADR, this study sets a platform for developing management guidelines of efavirenz-CADR. Further studies are needed to confirm the clinical features, confirm eosinophilia as an indication for treatment interruption and transiency of higher hepatitis grades.

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Clinical Implications

- The clinical spectrum of efavirenz-associated rash includes facial oedema, morbilliform eruptions, palmar erythema, and annular erythema that is sometimes photodistributed. Associated systemic features include fever, eosinophilia, and hepatitis. A majority (more than two-thirds) can be treated through monitoring of liver enzymes.

TABLE I.

Clinical and laboratory characteristics of patients with efavirenz-CADR during hospitalization according to treatment groups

Variable	Total efavirenz-CADR (n = 35)	Successful treat-through or rechallenge (n = 18)	Terminated (n = 17)
Palmar erythema	24 (69%)	14 (78%)	10 (58%)
Rash			
Morbilliform	19 (54%)	13 (72%)	6 (35%)
Indurated erythema	17 (49%)	7 (39%)	10 (59%)
Facial oedema	15 (43%)	6 (33%)	9 (53%)
Photodistribution	13 (37%)	4 (22%)	9 (53%)
Fever	8 (23%)	1 (6%)	7 (41%)
Mucositis	1 (3%)	0	1 (6%)
Eosinophilia ($>0.4 \times 10^9/L$)	11 (31%)	2 (11%)	9 (53%)
Transaminase elevation *			
$>ULN-3.0 \times ULN$ (mild)	6 (17%)	1 (6%)	5 (29%)
$>3.0-5.0 \times ULN$ (moderate)	1 (3%)	0 (0%)	1 (6%)
$>5.0-20.0 \times ULN$ (severe)	2 (6%)	1 (6%)	1 (6%)
$>20.0 \times ULN$ (life-threatening)	1 (3%)	0 (0%)	1 (6%)
CTCAE severity			
Grade 1 (mild)	31 (89%)	17 (94%)	14 (40%)
Grade 2 (moderate)	1 (3%)	0 (0%)	1 (3%)
Grade 3 (severe)	2 (6%)	1 (6%)	1 (3%)
Grade 4 (life-threatening)	1 (3%)	0 (0%)	1 (3%)

CADR, Cutaneous adverse drug reaction; CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal.

* Based on the CTCAE grading.

TABLE II.
Univariate and multivariate analyses of successful efavirenz treat-through or rechallenge

Covariate	Univariate OR (95% CI)	P value	Multivariate OR (95% CI) All patients (n = 35)	P value	Multivariate OR (95% CI) Post-2013 (n = 25)	P value
Admission 2013 onwards	19.1 (2.06–177.92)	.010	90.4 (2.62–3116.8)	.013	N/A	
Age	0.97 (0.91–1.04)	.409				
Gender	0.65 (0.12–3.46)	.613				
Fever	0.084 (0.008–0.786)	.030			0.09 (0.002–2.94)	.178
Days between drug initiation and CADR	0.999 (0.958–1.041)	.962				
CD4 cell count	1.000 (0.997–1.002)	.925				
Eosinophilia	0.09 (0.004–1.715)	.109			0.12 (0.00–7.52)	.181
Palmar erythema	2.45 (0.56–10.68)	.233			0.12 (0.001–10.4)	.353
Morbilloform rash	4.77 (1.14–20.00)	.033			5.48 (0.25–122.6)	.283
Photosensitivity	0.25 (0.06–1.10)	.066			0.82 (0.04–18.3)	.902
Induration	0.45 (0.12–1.72)	.241				
Oedema	0.44 (0.11–1.74)	.245				
Annular	0.69 (0.15–3.15)	.628				
Transaminases > ULN	0.29 (0.06–1.38)	.118			0.13 (0.01–2.85)	.194

CADR, Cutaneous adverse drug reactions; CI, confidence interval; OR, odds ratio; ULN, upper limit of normal.