

Increased risk of dizziness in human immunodeficiency virus-infected patients taking zidovudine and efavirenz combination: a Brazilian cohort study

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Keywords

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Abstract

Objectives Neuropsychiatric adverse effects (NPAE) related to efavirenz, mainly dizziness, is detrimental to human immunodeficiency virus (HIV) treatment. Our study aims at evaluating if zidovudine use potentiates the risk of dizziness related to efavirenz when used together and whether there are significant differences in over time distribution of this NPAE and others relatively frequent regarding efavirenz regimen without zidovudine.

Methods Human immunodeficiency virus-infected patients under efavirenz-containing different therapy were enrolled. A retrospective analysis of official medical records was accomplished to collect clinical data regarding NPAE occurrence and severity. Univariate statistic and statistical model based on survival analyses were performed.

Key findings One hundred sixty-two patients were included, of these seventy-seven (47.5%) had NPAE reported, such as dizziness (more frequent), depression and insomnia. Univariate statistical analysis demonstrated that the combined use of efavirenz with zidovudine increased the NPAE risk (OR: 2.5; *P*-value: 0.008), mainly dizziness risk (OR: 3.5; *P*-value: 0.009) and survival analysis showed that such combination is associated with dizziness occurrence faster (HR: 2.9; *P*-value: 0.02).

Conclusions The results may contribute to clarify the dizziness occurrence dynamics in therapy with efavirenz and zidovudine by identifying susceptibilities and assisting in the choice of combined antiretroviral therapy.

Introduction

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI), an antiretroviral widely used in many countries in antiretroviral therapy (ART) against human immunodeficiency virus (HIV). Although frequently prescribed together with zidovudine and lamivudine because of the availability of formulations and its effectiveness, it is no longer included at the first-line ART regimen.^[1–3] However, the efavirenz is naturally related to higher rate of neuropsychiatric adverse effects (NPAE) and minimizing these effects is a necessity because they undermine patients' health and adherence to therapy.^[4–7]

The low adherence to HIV therapy, because of adverse events, is the main cause of treatment failure (inability to suppress HIV viral load to undetectable levels), usually resulting in ART interruption.^[8–10] Since antiretroviral treatment is a lifelong one, it is difficult to measure the damage of long-term adverse effects.^[4–6,11] NPAE due to efavirenz is related to elevated plasma concentrations of this drug, being the effects most common: dizziness, insomnia, somnolence, irritability, tremors and hyperhidrosis, with some patients coming to develop more serious effects such as depression, psychosis, mania, suicidal thoughts, paranoia and cognitive impairment.^[10,12–15]

Does zidovudine use increase the risk of any NPAE related to efavirenz when used together? This question is one of the objectives of this study besides to evaluate the frequency of reported neuropsychiatric effects during efavirenz-containing treatment.

Methods

Study design

HIV-infected subjects under efavirenz-containing ART regimens, followed at Institute of Integral Medicine Professor Fernando Figueira (IMIP) in Recife, Pernambuco state (Northeast Brazil), were enrolled. The IMIP research ethics committee approved the study (protocol number 3629-13), in accordance with the Declaration of Helsinki, and all patients consented to their participation through interviews and signed a written informed consent form. A retrospective analysis of official medical records of these patients was performed to collect clinical data regarding efavirenz-related NPAE occurrence and severity. Medical records are clinical and laboratory data annotated in standard document of medical assessments of treatment every two months for each patient, where the doctor evaluated the clinical status, effectiveness of anti-HIV treatment, including the occurrence of adverse effects. All patients underwent the same clinical evaluation procedure. Inclusion criteria were as follows: older than 18 years; received ART regimen at standard dose according to guideline (for efavirenz an oral dose 600 mg once a day)^[2]; optimal therapy adherence (estimated indirectly by medication possession ratio (MPR),^[16] where optimal adherence was defined as $MPR \geq 95\%$); and no reported history of neurological diseases or neuropsychiatric treatment. Exclusion criteria were as follows: virological treatment failure and comedication with drugs known to be inducers or inhibitors of antiretroviral metabolism.^[5,7]

The patients were characterized according to efavirenz-containing ART regimens used during treatment. Then, they were classified according to efavirenz-related adverse effects occurrence: individuals who discontinued efavirenz-containing regimens due to NPAE versus those who did not. Another classification was performed according to adverse effect period: patients that reported NPAE until the fourth week of therapy versus who that reported these effects after such period since the NPAE reported in therapy with efavirenz occur for two up to four weeks, then disappear.^[8,10,12,17]

Demographical and clinical evaluations

In medical record analysis, information from queries in the period of ART containing efavirenz was collected, including

the date of each event. Demographic (sex and age at the beginning of treatment with efavirenz) and clinical information (viral load and CD4+ T lymphocyte counts during the treatment period with efavirenz) were also assessed.

Statistical analysis

Statistical analyses were performed by R software, version 3.5.1 for Windows. Fisher exact test was used to test neuropsychiatric effects occurrence risk regarding sex and zidovudine and efavirenz combination use. Odds ratios (OR) and their respective 95% confidence intervals (95% CI) were calculated.

Additionally, a survival analysis was used to evaluate if zidovudine and non-zidovudine in efavirenz-containing ART regimens differ significantly regarding the NPAE occurrence as time-dependent exposure. In summary, it means assessing whether a variable influence in adverse effects occurrence in less time or if there are no significant differences. The time (therapy duration) was registered in weeks and analysis was done retrospectively through patient's medical record, measuring exposure time until the report of NPAE. Endpoint primary: occurrence of any NPAE. Second endpoint: dizziness, depression or insomnia occurrence.

The log-rank test was used for univariate survival analyses and Cox proportional hazards regression demonstrated the contribution of each variable in modulation the efavirenz-related NPAE risk. Hazards ratios (HR) and their 95% CI were calculated. The level of statistical significance for all analysis was set at $\alpha = 0.05$.

Results

Study population

One hundred and sixty-two patients (87 female and 75 male) treated with efavirenz-containing backbone met all the criteria and were included in the analysis. Demographical and clinical characteristics of the patients are summarized in Table 1. The follow-up time of therapy varied between 1.4 and 723 weeks (approximately 14 years), with a mean follow-up time of 143 weeks (approximately 3 years). In general, the patients presented an efficient clinical response during the treatment. The mean CD4+ lymphocyte cell count before treatment was about 395 cells/ μ l and after efavirenz-containing therapy was about 499 cells/ μ l, in addition over 90% of patients reduced viral load to an undetectable (<40 copies/ml) plasma HIV load. However, 22% of the patients that presented NPAE had also detectable viral load peaks interspersed with undetectable viral load periods during ART. Sixty-three per cent of patients ($n = 102$) were therapy naïve at the beginning of efavirenz treatment.

Neuropsychiatric adverse effects clinically diagnosed during quarterly medical appointments were dizziness, headache, hallucinations, insomnia, somnolence, abnormal

dreams (nightmares), sleep disturbances, photophobia, phonophobia, memory ailments, sadness, depression and suicidal thoughts, anxiety, irritability, hyperactivity, convulsions, hyperhidrosis, paresthesia and fatigue. Others non-specific NPAE that caused efavirenz intolerance were described in official medical records as ‘intolerance to efavirenz’.

Table 1 Demographic and clinical data of study population, (*n* = 162)

Characteristics	Value, mean ± SD (range) or <i>n</i> (%)
Age at efavirenz-containing ART start (years)	32.3 ± 8.4 (18–62)
Sex – <i>n</i> (% female)	87 (53.7%)
AZT/3TC/EFV regimen ^a	127 (69.4%)
TDF/3TC/EFV regimen ^a	50 (27.3%)
Other/EFV regimens ^a	6 (3.3%)
Presence of NPAE	77 (47.5%)
Discontinued efavirenz-containing regimens due to NPAE	23 (29.9%)
NPAE frequency in AZT/3TC/EFV regimen ^a	65 (51.2%)
NPAE frequency in non-AZT/3TC/EFV regimens ^a	16 (29.6%)
Therapy naive at efavirenz-containing ART start	102 (63%)
Duration of efavirenz-containing ART (weeks)	143.5 ± 147.3 (1.4–723.4)
Duration of AZT/3TC/EFV therapy (weeks)	145.6 ± 139.2 (1.4–705.1)
Duration of TDF/3TC/EFV therapy (weeks)	73 ± 84 (1.6–398.4)
Duration of Other/EFV therapy (weeks)	197.6 ± 267 (9.4–723.4)
Duration of efavirenz-containing ART until discontinuation due to NPAE (weeks)	51.8 ± 60 (1.4–219)
CD4+ T cell counts (cells/μl) before starting efavirenz-containing ART	395 ± 237.5 (36–1008)
CD4+ T cell counts (cells/μl) during efavirenz-containing ART	499 ± 236.7 (35–1259)
Undetectable plasma viral load	149 (92%)
Patients who reduced viral load after efavirenz-containing ART	152 (94%)
Patients who had NPAE and detectable viral load peaks interspersed with undetectable viral load periods	17 (22%)

3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz; Non-AZT, other nucleoside reverse transcriptase inhibitors except zidovudine; NPAE, neuropsychiatric adverse effects; TDF, tenofovir. ^aNineteen patients used two different efavirenz-based regimens, while one patient used three different efavirenz-based regimens during the therapy.

Neuropsychiatric adverse effects occurrence

One hundred twenty-seven patients used zidovudine/lamivudine/efavirenz regimen, fifty patients received tenofovir/lamivudine/efavirenz combination and six patients were submitted to other efavirenz-containing regimens. It is noteworthy that nineteen patients used two different efavirenz-containing regimens and one patient was submitted to three efavirenz-containing regimens. In our study, 47.5% (*n* = 77) of patients reported NPAE during efavirenz therapy. Specifically, 51.2% (*n* = 65) of exposure periods to zidovudine/lamivudine/efavirenz regimen resulted in efavirenz-related NPAE, while that exposure periods to efavirenz-containing regimens without zidovudine (non-zidovudine/lamivudine/efavirenz) had NPAE occurrences in 29.6% (*n* = 16; Table 1). Among patients who used zidovudine/lamivudine/efavirenz and non-zidovudine/lamivudine/efavirenz regimens in different moments of treatment, 40% (*n* = 8) reported NPAE only when zidovudine was present, 10% (*n* = 2) only when zidovudine was not present, and 15% (*n* = 3) in both cases.

The most common reported NPAE was dizziness, present in 24.1% (*n* = 39) of the patients, followed by depression 10.5% (*n* = 17), insomnia 8.6% (*n* = 14) and asthenia 7.4% (*n* = 12). Other less-frequent (*n* ≤ 10) effects were also reported, such as sadness, anxiety, sleeps disturbance, paresthesia, abnormal dreams, somnolence, irritability, hallucinations and photophobia. Unspecific NPAE reported as ‘intolerance to efavirenz’, occurred in 6.2% of patients (*n* = 10). Phonophobia, memory loss, suicidal thoughts, hyperactivity, convulsion and cognitive impairment were also observed but with low frequency (*n* ≤ 3), and hyperhidrosis was not reported in our cohort. Headache was reported in 13.6% (*n* = 22) of patients, but this symptom is commonly attributed to zidovudine alone, therefore, was not considered.^[7,10] The NPAE frequencies are summarized in Figure 1.

Among the seventy-seven patients who presented efavirenz-related NPAE, 29.9% (*n* = 23) had the efavirenz-containing regimen discontinued after the occurrence of these events (Table 1). They represent 14.2% of all HIV-positive patients treated with efavirenz. Zidovudine/lamivudine/efavirenz combination was the most discontinued ART regimen with 14.2% of the cases (*n* = 18) whereas the discontinuation of non-zidovudine/lamivudine/efavirenz occurred in 9% (*n* = 5).

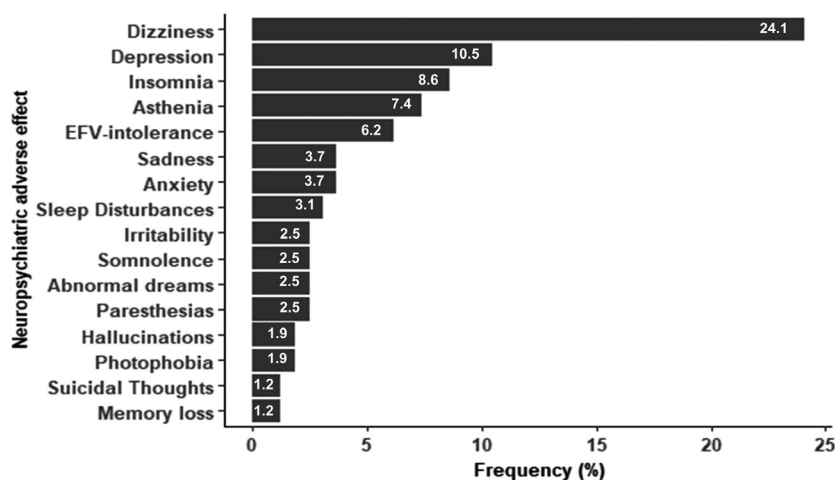


Figure 1 Neuropsychiatric adverse effects frequency in human immunodeficiency virus-positive patients under efavirenz-containing antiretroviral therapy. The data were extracted through a retrospective analysis in the official medical records of patients.

Regarding the NPAE occurrence distribution before or after the fourth week of efavirenz therapy, dizziness was the unique effect that had similar occurrence distribution in these two periods, averaging 67.0 weeks among those who reported it after the fourth week of treatment. Despite that, insomnia, 78.5% ($n = 11$, mean = 61.3 weeks) and depression, 100% (mean = 78.6 weeks), were more frequent after the fourth week of treatment. Dizziness and insomnia persisted in about 45% ($n = 9$; $n = 5$, respectively) of the patients who reported such effects after the fourth week, with respective persistence mean duration of 36.5 and 43.6 weeks. Depression persisted in 6% ($n = 1$) of patients; however, 41% ($n = 7$) had medical intervention to prevent persistence. These data are summarized in Table 2.

Univariate statistical analysis results

Neuropsychiatric adverse effects in patients who received regular doses of efavirenz was twice more

common in women than men (OR = 2.1; 95% CI = 1.1 to 4.3; P -value = 0.01). Moreover, when comparing such effects in exposure periods to zidovudine/lamivudine/efavirenz regimen versus non-zidovudine/lamivudine/efavirenz combinations, we observed that the zidovudine presence increases by two-and-half-fold the risk to develop any NPAE (OR = 2.5; 95% CI = 1.2 to 5.3; P -value = 0.008). When dizziness is assessed, the risk is about three-and-half-fold higher (OR = 3.5; 95% CI = 1.3 to 12.4; P -value = 0.009). For depression (OR = 3.4; 95% CI = 0.7 to 32.3; P -value = 0.1), and insomnia (OR = 0.7; 95% CI = 0.2 to 3; P -value = 0.76) we found no statistical significant differences according to Fisher Exact test. Somnolence, sleep disturbances, abnormal dreams and insomnia were also analysed, but all together as sleep-related NPAE. However, we did not observe a significant difference when comparing sleep-related NPAE in efavirenz-containing regimen with and without zidovudine (OR = 1.7; 95%

Table 2 Occurrence distribution of dizziness, depression and insomnia before or after the fourth weeks of efavirenz-containing antiretroviral therapy

Event	Under EFV-related NPAE occurrence							
	$T = 0-4$ weeks			$T \geq 4$ weeks				
	Occurrence distribution n (%)	Mean (weeks)	EFV swap ^a n (%)	Occurrence distribution n (%)	Mean (weeks)	EFV swap ^a n (%)	Effect persistence ^b n (%)	Mean (weeks) ^b
Dizziness	19 (48.7)	2.4	1 (5.2)	20 (51.3)	67.0	5 (25.0)	9 (45.0)	36.5
Depression ^c	0 (0.0)	–	–	17 (100.0)	78.6	6 (35.3)	1 (5.8)	–
Insomnia	3 (21.4)	1.6	1 (33.3)	11 (78.5)	61.3	2 (18.2)	5 (45.4)	43.6

EFV, efavirenz; NPAE, neuropsychiatric adverse effects; T , duration on of EFV therapy. ^aChange for a non-efavirenz-containing therapy. ^bEffect persistence' refers to the patients who had the NPAE for a long time. ^cForty-one per cent ($n = 7$) of depression-patients had medical intervention to prevent persistence.

Table 3 Univariate analysis results for NPAE occurrence between efavirenz-containing regimens with and without zidovudine

Event	EFV-containing ART regimens		Fisher exact test	
	Non-AZT/ 3TC/EFV <i>n</i> = 54 (%)	AZT/3TC/ EFV <i>n</i> = 127 (%)	OR (95% CI)	<i>P</i> -value (α = 0.05)
Any NPAE	16 (29.5)	65 (51.2)	2.5 (1.2–5.3)	0.008
Dizziness	5 (9.2)	34 (26.8)	3.5 (1.3–12.4)	0.009
Depression	2 (4.0)	15 (11.8)	3.4 (0.7–32.3)	0.1
Insomnia	5 (9.2)	9 (7.0)	0.7 (0.2–3)	0.76
Sleep-related NPAE	6 (11.0)	22 (17.3)	1.7 (0.6–5.4)	0.37

3TC, lamivudine; 95% CI, 95% confidence interval; ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz; Non-AZT, any nucleoside reverse transcriptase inhibitor, except zidovudine; NPAE, neuropsychiatric adverse effects; OR, odds ratio.

The level of statistical significance for all analysis was set at α = 0.05 (in bold).

CI = 0.6 to 5.4; *P*-value = 0.37). These results are summarized in Table 3.

Survival analysis results

Survival analyses were used for assessing any NPAE, as primary endpoint, and dizziness, depression and insomnia occurrence as secondary endpoint. Such outcomes were chosen because they were the most frequent effects in our cohort. Survival curves for any NPAE, dizziness, depression and insomnia are showed in Figure 2. Concerning dizziness, the log-rank test showed significant differences in treatment time until its occurrence, when comparing zidovudine/lamivudine/efavirenz to non-zidovudine/lamivudine/efavirenz use (log-rank χ^2 = 5.4; *P*-value = 0.02). The Cox regression showed that dizziness appeared 2.9 times faster when the patients used zidovudine and efavirenz combination (HR = 2.9; *P*-value = 0.02). Furthermore, the zidovudine presence or absence in efavirenz-containing regimens did not influence either on depression (log-rank χ^2 = 0.9; *P*-value = 0.3; HR = 2.0; *P*-value = 0.35), or insomnia occurrence (Log-rank χ^2 = 0.8; *P*-value = 0.4; HR = 0.6; *P*-value = 0.37) and any NPAE as primary endpoint (Log-rank χ^2 = 3.8; *P*-value = 0.05; HR = 1.7; *P*-value = 0.05; Table 4).

Discussion

The frequency of efavirenz-treated patients enrolled in our study that reported NPAE (47.5%) was like previous studies performed in different populations. Decloedt and Maartens reported that NPAE affected about 68% of efavirenz-receiving patients.^[6] In fact, it has been described in other

studies that the frequencies of patients with such effects range from 40% to 70%.^[8,18,19] Efavirenz is a neuroactive drug being able to easily cross the blood–brain barrier.^[8,18]

The high proportion of patients affected by these events, especially dizziness, shows the importance of studying the distribution of efavirenz-related NPAE and their impact on patients receiving ART. Given the effectiveness of this drug,^[5,8,19] it is noteworthy that these symptoms occurred despite an efficient clinical response to treatment, undetectable viral load in 92% of patients, 94% reducing the HIV load and 499 cells/ μ l CD4+ lymphocyte T cell mean counts, after an average count of 395 cells/ μ l before efavirenz-based therapeutics.

In our cohort, 28% of patients need to change the efavirenz-containing regimens, despite the high frequency of patients who reported NPAE (47.5%), showing that the continuity of neuropsychiatric effects could favour the irregular use of therapy and, consequently, treatment failure or a transient response.^[5,18] In fact, we observed that 22% of the patients who reported NPAE showed detectable viral load peaks interspersed with undetectable viral load periods, which may be consequence of the irregular use of ART because of an underlying adverse effect.^[8]

The most frequent NPAE reported worldwide in therapy with efavirenz are as follows: dizziness, insomnia, abnormal dreams, irritability, somnolence, paresthesia, anxiety and depression.^[5,10,20] These effects were also very frequent in our cohort, being dizziness twice more frequent compared to the second one efavirenz-related NPAE. It generally does not show a high frequency as observed in our cohort compared to other efavirenz-related NPAE.^[10,12–15]

Some studies have reported that these symptoms could appear between the second and fourth week after the beginning of treatment and then disappear.^[7,10,12,17] However, we observed that insomnia and depression frequently occurred after the fourth week of treatment. Dizziness and insomnia persisted for several weeks in about 45% of patients who had events after the fourth week, while in the other 55% such effects did not persist. In contrast, depression persisted among 6% of the individuals. This may be due to medical intervention to prevent the effects in the long term. Previous studies also evidenced that NPAE may last longer in some patients^[5,8,12,13] and some patients could develop more serious effects such as psychosis, mania, suicidal thoughts and depression at long term.^[10,14,15,21]

The incidence of NPAE in patients, followed up in our study, under the efavirenz treatment was about twice more common in women. In fact, Burger *et al.*^[22] showed that the mean plasma efavirenz concentration was 30% higher in women than in men, possibly due to differences in efavirenz clearance between genders, even if these differences are not sufficient to suggest dose adjustments.^[23,24]

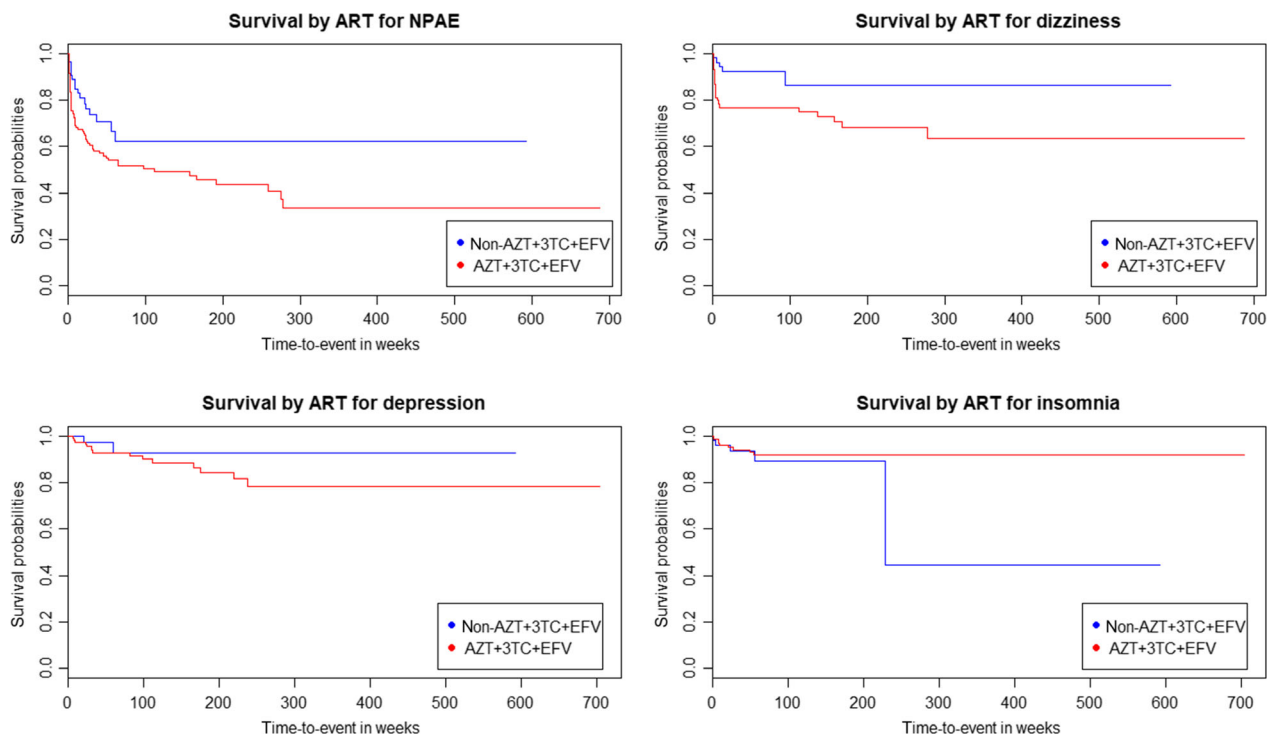


Figure 2 Survival curves generated from survival probabilities versus time-to-event in weeks regarding efavirenz-containing regimens with and without zidovudine for NPAE, dizziness, depression and insomnia. Survival probabilities decrease over time in the zidovudine and efavirenz combination presence. 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; EFV, efavirenz; Non-AZT, any nucleoside reverse transcriptase inhibitor, except zidovudine; NPAE, neuropsychiatric adverse effects.

Our results showed that the zidovudine presence in efavirenz-containing regimen significantly increases the risk of NPAE, mainly for dizziness in univariate analysis and in time-dependent exposure. Although univariate analysis showed increase to NPAE risk, it was clear that this result reflects the risk of dizziness because of its high frequency in our cohort; furthermore, the other symptoms analysed showed no significant differences in efavirenz-containing regimens with and without zidovudine. In addition, dizziness appeared faster when the patients used ART regimen with zidovudine and efavirenz. Although zidovudine has been associated with occurrence of anaemia, which dizziness is one of the symptoms, this antiretroviral by itself has never been implicated directly in dizziness regardless anaemia presence, though be involved in others NPAE occurrence.^[7,25,26] Moreover, of the patients treated with zidovudine-containing ART that reported dizziness, only two individuals developed anaemia and had to change ART regimen. Even without these two patients, the statistical analyses maintained the association results, showing the increased dizziness risk in patients treated with zidovudine and efavirenz-containing regimens.

Thus, the differences observed between zidovudine/lamivudine/efavirenz and non-zidovudine/lamivudine/efavirenz combination regimens in regarding a higher risk for dizziness occurrence could exist because of a zidovudine and efavirenz synergic effect, potentiating efavirenz dizziness only when both are combined, and not an additive effect of zidovudine with efavirenz. In fact, the overall effect of these two drugs combined is greater than it could be the individual effects summing both antiretrovirals, thus, increasing efavirenz-related dizziness. If it would be merely an additive effect, zidovudine/efavirenz and non-zidovudine/efavirenz regimens should not present differences in dizziness occurrence, since both drugs without the efavirenz presence do not present differences in dizziness occurrence, as demonstrated in this work. Although no longer used in combination at the first-line ART regimen, zidovudine/efavirenz treatment is still recommended as an alternative option when the first-line regimens are contraindicated or not available.^[3] However, our study shows the impact of this therapy combination choice on HIV-positive patients under ART.

Efavirenz and zidovudine have already been cited as competing for the major glucuronidation enzyme for both

Table 4 Survival analysis results for any NPAE, dizziness, depression and insomnia occurrence

Risk factor	Event	Log-rank test (<i>P</i> -value, $\alpha = 0.05$)	HR [95% CI] (<i>P</i> -value, $\alpha = 0.05$)
NPAE occurrence, <i>n</i> (%)			
Non-AZT + 3TC + EFV (<i>n</i> = 54)	16 (29.6)	3.8 (0.05)	Reference
AZT + 3TC + EFV (<i>n</i> = 127)	65 (51.2)		1.7 [1.0–2.98] (0.05)
Dizziness occurrence, <i>n</i> (%)			
Non-AZT + 3TC + EFV (<i>n</i> = 54)	5 (10.0)	5.4 (0.02)	Reference
AZT + 3TC + EFV (<i>n</i> = 127)	34 (26.7)		2.9 [1.13–7.48] (0.02)
Depression occurrence, <i>n</i> (%)			
Non-AZT + 3TC + EFV (<i>n</i> = 54)	2 (2.0)	0.9 (0.3)	Reference
AZT + 3TC + EFV (<i>n</i> = 127)	15 (11.8)		2.0 [0.46–9.02] (0.35)
Insomnia occurrence, <i>n</i> (%)			
Non-AZT + 3TC + EFV (<i>n</i> = 54)	5 (10.0)	0.8 (0.4)	Reference
AZT + 3TC + EFV (<i>n</i> = 127)	9 (7.0)		0.6 [0.20–1.83] (0.37)

3TC, lamivudine; 95% CI, 95% confidence interval; AZT, zidovudine; EFV, efavirenz; HR, hazard ratio (by Cox proportional model); Non-AZT, any nucleoside reverse transcriptase inhibitor, except zidovudine; NPAE, neuropsychiatric adverse effects.

The level of statistical significance for all analysis was set at $\alpha = 0.05$ (in bold).

UGT2B7 when coadministered and, therefore, exhibiting inhibited glucuronidation by one another in a concentration-dependent manner.^[27] This glucuronidation mechanism is responsible for the clearance of these antiretroviral drugs, and this interaction can affect the bioavailability of efavirenz in the body.^[27,28]

Because of the retrospective nature, there are some limitations of this study that has to be addressed. First, the small sample number in this study may not reflect the real NPAE frequency related to efavirenz-containing ART. Another point is the occurrence of dizziness, it is known that there are many other causes of dizziness in ART-treated patients, including genetic factors, which may or may not be related to efavirenz-containing regimen or combined with zidovudine, and that could not be assessed since it was not available in medical records. However, some patient’s inclusion and exclusion criteria (history of neurological diseases or neuropsychiatric treatment, for example) were established to minimize bias. Finally, it is important to note that the number of patients who used zidovudine in efavirenz-containing regimens is greater than the number of patients who used non-zidovudine/efavirenz in our

cohort, which may influence the results. Faced with these, controlled studies are recommended with higher and similar numbers of individuals between groups.

Conclusions

Our study showed a high percentage of patients who presented dizziness and other NPAE related to efavirenz therapy, and these effects were not restricted to the beginning of treatment. It has been shown that the incidence of such effects was twice more common in women. In addition, the zidovudine/lamivudine/efavirenz combination was more likely to cause dizziness than the non-zidovudine combined to lamivudine and efavirenz in HIV treatment, specifically dizziness. Therefore, the study of ART adverse effects should not be limited to a single drug, but also the possible pharmacological interactions, a way to conduct better the treatment regimen choices. These susceptibility factors could be relevant to understand the dynamics of toxicity in efavirenz therapy and to direct pharmacokinetic and pharmacogenetic studies to minimize the risk of adverse effects in people living with HIV/AIDS.

Declarations

Conflicts of interest

Authors did not declare interest conflicts.

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Author’s contribution statement

Valeriano is the first author, performed the collection, interpretation, analysis of the data, and wrote the paper. Carvalho-Silva made substantial contributions to the paper design and participated in data collection and drafting of the manuscript. Coelho and Moura

contributed to data collection and interpretations, statistical analysis, and study design. Arraes and Brandão made an essential contribution to the clinical study design adopted and data interpretation. Crovella and Guimarães coordinated all the study and the result analysis. All authors critically reviewed the intellectual content of the manuscript and your writing and agree to be accountable for all aspects of this work.

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Data accessibility statement

Those interested in the data supporting the results of this paper should send an email to the author at jeyzon_@live.-com.

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