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Adverse Effects of First-Line Antiretroviral Therapy in Bangui

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Abstract

Objective: To describe the adverse effects of fixed combinations of antiretroviral drugs based on tenofovir+emtricit abine+efavirenz (TDF/FTC/EFV) and zidovudine+lamivudine+nevirapine (AZT/3TC/NVP) and to identify the factors associated with their occurrence.

Patients and methods: An analytical cross-sectional study included after informed consent people living with HIV (PLHIVs). We used an exhaustive sampling by recruiting all the patients who came to get antiretroviral drugs during the study period, aged at least 18 years, treated with TDF/FTC/EFV or AZT/3TC/NVP. Socio-demographic, clinical and therapeutic data were collected, entered and analyzed with the software Epi-Info 7. The chi-square test was used to compare the proportions with a significant level of 5%.

Results: A total of 282 patients were included, of which 75.53% were females, 53.55% lived in couples; the average age was 38.99 ± 9.5 years old. The TDF/FTC/EFV combination was used in 64.54% of cases. The median duration of treatment was 24.66 months (range 0.66 and 138 months] and adherence was good in 79% of cases. The overall prevalence of adverse events was 82.98% (234/282). We observed neuropsychiatric, digestive and lipodystrophy disorders in 65.25%, 43.62% and 10.99%, respectively. The occurrence of adverse effects was independent of socio-demographic, clinical and therapeutic characteristics (p>0.05).

Conclusion: The prevalence of adverse events is high during the first-line antiretroviral therapy (ART) in Bangui and their occurrence is independent of socio-demographic, clinical and therapeutic characteristics. It is necessary to systematically research them for early management and ensure therapeutic success.

Keywords: Antiretroviral therapy; Bangui; Tolerance; Central African Republic; HIV

Introduction

The introduction of highly active antiretroviral therapy has improved the prognosis of HIV infection. They allow the restoration of the immune system and the control of viral replication in order to make the viral load undetectable. They have led to a significant reduction in mortality and new HIV infections [1]. In sub-Saharan Africa, the implementation of antiretroviral (ARV) access initiatives has resulted in the treatment of an increasing number of people living with HIV (PLHIVs) [2].

The HIV epidemic in the Central African Republic (CAR) is of a generalized type with a prevalence of 4.9% among people aged 15-49 years [3]. Fixed-dose combinations of tenofovir+emtricitabine+e favirenz (TDF/FTC/EFV) and zidovudine+lamivudine+nevirapine (AZT/3TC/NVP) are the main first-line antiretroviral combinations [4]. These first-line associations have adverse effects that can hinder adherence to treatment and compromise therapeutic efficacy or have a negative impact on the daily activities of PLHIVs. Some African authors have reported high prevalence of adverse effects of these ARVs [5,6]. Some toxicities are serious and life-threatening [7]. In CAR, the safety of the main first-line antiretroviral combinations has not been documented. In order to improve the quality of care for PLHIVs, this study was conducted to describe the adverse effects of fixed-dose combinations of TDF/FTC/EFV and AZT/3TC/NVP and identify the factors associated with their occurred.

Patients and Methods

This was a cross-sectional analytical study, from August 1, 2016 to January 30, 2017, in the infectious diseases department of the Hôpital de l'Amitié in Bangui. The study population consisted of PLHIVs on antiretroviral therapy who attended follow-up visits, during which efficacy, tolerance, and adherence to treatment were assessed. We conducted exhaustive sampling by recruiting patients who came for antiretroviral drugs during the study period. We included PLHIVs aged 18 years and older, on first-line treatment with fixed-dose combinations of TDF/FTC/EFV or AZT/3TC/NVP. An individual survey card was used to collect data on socio-demographic variables (age, sex, occupation and marital status), clinical (history, clinical stage of HIV infection by World Health Organization (WHO), body mass index, and adverse effects), therapeutic (Antiretroviral treatment history, duration and adherence to ART). A patient was non-adherent to treatment if

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he reported more than one ARV intake jump in the last four days. For the evaluation of the clinical safety of ART, we designated by adverse effect all the symptoms reported by the patient or observed by the doctor that occurred after initiation of ART without obvious etiology or if it was reported in literature as being possible with this drug. An adverse event was considered serious if it resulted in hospitalization or discontinuation of ART, a blood transfusion, or a change in the regimen.

Patient participation in the study was voluntary after informed consent. The analysis of the data was done using the software Epi-Info 7. The Chi-square test was used to compare the proportions with a significant level of 5%.

Results

Sociodemographic, clinical and therapeutic characteristics

A total of 282 PLHIVs were recruited, of which 213 women (75.53%) were a sex ratio (whomen/men) of 3.08. The average age was 39 ± 9.5 years old. Patients aged 25 to 44 accounted for 67.73%. Men were older than women with a mean age of 45 ± 9.14 years compared with 37 ± 8 years ($p<0.05$). Patients who had no employment accounted for 67.02%, and finally 53.55% were married. The antecedent of the tuberculosis was reported in 31.21% of cases. The median CD4 count was 298/mm^3 with extremes ranging from 3 to 609/mm^3. At initiation of treatment, 62.06% of patients were in advanced stages of HIV infection by stage of WHO (3 and 4). The fixed-dose combination of TDF/FTC/EFV was used in 182 cases (64.54%). The mean duration of first-line ART was 29 (± 22) months; it was 45.82 ± 21.89 months for AZT/3TC/NVP vs 19.74 ± 17.18 months for TDF/FTC/EFV ($p<0.05$). Patients on TDF/FTC/EFV had antecedent of antiretroviral treatment (AZT/3TC+EFV or TDF/FTC+NVP) in 81.87% compared to 92% for those treated with AZT/3TC/NVP. Adherence to ART was rated as good in 79.08% of cases. In addition to the ART, 62.06% of patients were on cotrimoxazole prophylaxis and 2.13% were on tuberculosis treatment.

Adverse effects of first-line ART

The overall prevalence of clinical adverse effects was 82.98%, or about four out of five patients. This prevalence was 83.52% among patients on TDF/FTC/EFV versus 82.00% among those under AZT/3TC/NVP ($p>0.05$). The main adverse effects observed were neuropsychiatric (65.65%), digestive (43.62%), musculoskeletal (35.82), dermatological (34.40%), general (anorexia and asthenia) in 23.76%, respiratory disorders (17.73%) and lipodystrophies (10.99%). The frequency of these disorders was variable according to the therapeutic combinations but without significant difference ($p>0.05$) (Figure 1).

Neuropsychiatric symptoms were represented by decreased libido (36.52%), headache (36.52%), vertigo (33.69%), insomnia (27.66%) and nightmares (27.66%), frequent forgetfulness (25.18%), somnolence (19.50), paresthesia (18.79%), anxiety (18.44%), suicidal thoughts (5.32%), hallucinations (2.48%), delirium (1.06%), depression (0.71%), tremor (0.35%) and nervousness (0.35%).

The main digestive disorders were represented by abdominal pain including epigastric pain (43.66%), nausea (15.25%), diarrhea (10.64%), jaundice (7.45%), vomiting (6.03%) and dyspepsia (6.03%). Gastrointestinal manifestations reported in a low frequency were hyposialorrhea (1.06%) and oral erosions (0.71%).

The main musculoskeletal disorders consisted of arthralgia (32.62%), myalgia (17.73%), recent pathological fracture (1.42%), back pain and muscle cramps in the calves (2.13%).

Dermatologically, adverse effects were pruritus, maculopapular exanthema (9.57%), melanonychia (1.06%), pallor (1.06%), urticaria (1.06%), melanoderma (1.06%). General disorders included physical asthenia (23.76) and anorexia (14.18%). Among respiratory disorders, we had cough (16.67%) and dyspnea (3.9%). A total of 31 patients (10.99%) received symptomatic treatments, including four blood transfusions (1.42%), four first-line treatment changes (1.42%) with AZT/3TC/NVP replacement by TDF/FTC/EFV.

Risk factors for the occurrence of adverse effects under first-line antiretroviral therapy

We did not find a statistically significant association between sociodemographic, clinical and therapeutic characteristics and the risk of occurrence of adverse effects in our study (Table 1).

Discussion

Sociodemographic, clinical and therapeutic data

Our study population is characterized by a clear predominance of women, this result superimposed on the national demographic data which indicate a sex ratio (whomen/ men) of 2.10 [3]. Mbelesso et al. had found a strong representation of the female sex in a hospital in Bangui [4]. Our sample consisted of young adults, with an average age of 39 years. In the sub-Saharan Africa region, young adults in the 35-44 age group, female, are the most affected by HIV infection [8-10]. A French study in a cohort of PLHIVs on ART among sub-Saharan Africans also reported similar data [11].

The antecedent of tuberculosis was the most recorded in our study population (31.21%). The development of tuberculosis is favored by the decrease of HIV-induced cellular immunity [12,13]. This result has been reported by African authors [14,15]. A large proportion of our patients (62.06%) started ART at advanced stages of HIV infection (stages 3 and 4 of the WHO classification). This late recourse to care is a reflection of the late diagnosis of HIV infection [16]. The median CD4 T cell count at initiation of ART was low (298 cells / mm 3), but this rate observed in our study is higher than that recorded in a 2015 in Bangui (185 CD4 / mm^3) [4]. In fact, a CD4 T lymphocyte count less than 200 cells/mm^3 is often associated with serious opportunistic infections [8]. This increase in the CD4 T lymphocyte rate in our series would be explained by improving the eligibility criteria for TAR, with a threshold of eligibility set at 350 CD4/mm^3 in 2009, then 500 CD4/mm^3 in 2014 in the central African national guidelines based on WHO recommendations [17].

Adverse effects

The combination TDF/FTC/EFV was the most used (64.54%) in the first line according to national guidelines. Adherence to ART was quite high (79.08%) but seems lower than that reported in 2006 (86.5%) in Bangui [18]. This result suggests good compliance, as it is above the 77% threshold recommended by some African authors [19,20]. This good level of compliance can be explained by the quality of follow-up of PLHIVs treated with ARVs.

The overall prevalence of adverse events was high (82.98%) but without serious consequences for continued treatment. This prevalence is high regardless of the therapeutic combination of ARVs. Indeed, combinations containing EFV or AZT have many adverse effects. Seydi et al. found a high prevalence of adverse events (75%) in a cohort of PLHIVs treated with AZT/3TC/NVP in Dakar [6]. Similar results were recorded in a cohort of first- and second-line ARV patients in Benin [5].

Characteristics of Patients	Adverse effects Yes	Adverse effects No	OR [95% CI[a]]	p-value
Sex				
Female	178	35	1	
Male	56	13	1.18 [0.58 - 2.38]	0.643
Age (years)				
≤ 34	85	18	1	
>34	150	32	1 [0.53-1.19]	0.980
Alcohol consumption				
Yes	103	21	1	
No	131	27	1.01 [0.54-1.89]	0.972
WHO clinical stage				
1 and 2	90	17	0.99 [0.51 - 1.92]	
3 and 4	144	31	1	0.692
Hemoglobin before ART (g / dl)				
< 10	59	13	1	
≥ 10	138	26	0.85 [0.41-1.77]	0.674
TCD4 lymphocytes before ART (cells/mm³)				
<200	105	19	1	
≥ 200	114	27	1.30 [0.68-2.49]	0.411
TB/HIV coinfection				
Yes	73	20	1	
No	161	28	0.63 [0.33 -1.20]	0.159
HBV/HIV coinfection				
Yes	17	5	1	
No	217	43	0.67 [0.23 -1.92]	0.458
Antecedent of ART				
Yes	32	9	1	
No	202	39	0.68 [0.30 -1.55]	0.363
ARV treatment				
AZT/3TC/NVP	84	16	1.12 [0.58-2.16]	
TDF/ FTC/EFV	150	32	1	0.735
Cotrimoxazole prophylaxis				
Yes	148	27	1	
No	86	21	1.33 [0.71-2.51]	0.362

[a]: Confidence Interval

Table 1: Relationship between socio-demographic, clinical and therapeutic characteristics and risk of occurring adverse effects under first-line antiretroviral therapy.

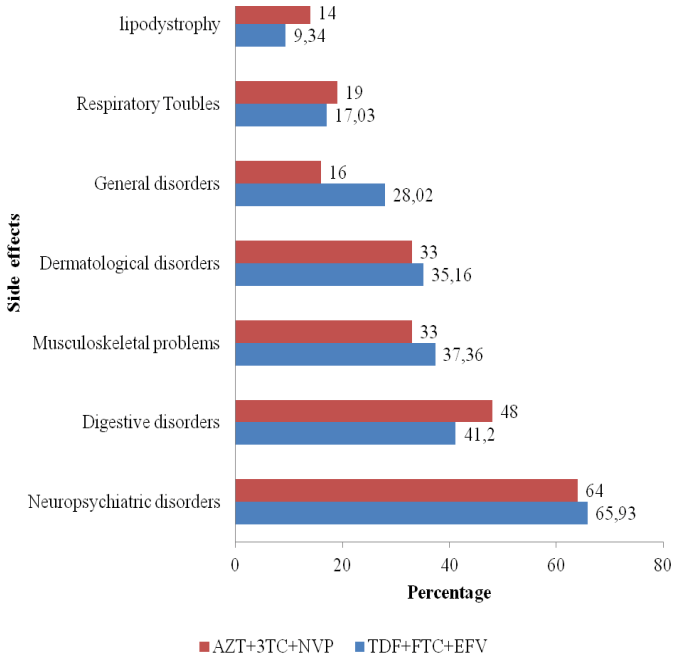

Figure 1: Main adverse effects of first-line antiretroviral therapy in Bangui.

The high prevalence of neuropsychiatric, digestive, musculoskeletal and dermatological disorders during antiretroviral therapy has been reported by several African authors [6,15]. Among neuropsychiatric disorders, headache and decreased libido were the most common complaints; EFV is the most incriminated molecule in the development of neuropsychiatric disorders [21]. There is a correlation between the plasma concentration of EFV and the onset of neurosensory disorders [5]. These disorders, which are mostly early, disappear after a few weeks of treatment with EFV, but sometimes, can persist for several months.

The most reported digestive symptoms were vomiting and abdominal pain. A significant association has been found between the occurrence of digestive disorders and the taking of AZT by an African author [22]. These digestive disorders were benign for the most part, but require special attention, as they can disrupt the appetite of the patients and compromise their nutritional status but also the observance of ART.

Musculoskeletal disorders are thought to be due to the mitochondrial toxicity of antiretrovirals. A study in Burkina Faso had found similar frequencies of arthralgia (45%) and myalgia (21.74%) [23].

Lipodystrophies are described in the West as the most troublesome side effect [23]. They are part of late side effects [6,23]. In our series, the prevalence of lipodystrophy was higher in the cohort of patients receiving AZT/3TC/NVP, but not significantly ($p>0.05$). This result is in agreement with the literature that incriminates AZT in the occurrence of lipodystrophies [24]. Pruritus was the most reported dermatologic symptom (27.66%). Dermatological disorders related to ART are due mostly to NNRTIs, mainly NVP; AZT is incriminated in hyperpigmentation of integuments (melanonychia) [25].

Anemia has been the main cause of change in treatment regimens. Anemia and neutropenia are due to therapeutic combinations containing AZT [26,27].

The combination of ARVs with cotrimoxazole used in chemoprophylaxis, potentiates certain adverse effects such as rashes; given the importance of cotrimoxazole in preventing opportunistic infections, we do not suggest reducing its use [25]. The socio-demographic, clinical and therapeutic characteristics of our patients did not interfere with the prevalence of adverse effects ($p>0.05$).

Conclusion

The prevalence of first-line ART adverse reactions is high with prevalence of neuropsychiatric and digestive disorders. These side effects are mostly mild and do not result in treatment changes.

There is no significant association between the sociodemographic, clinical and therapeutic parameters studied and the occurrence of adverse effects. It is therefore necessary to ensure strict monitoring of adverse effects in any PLHIVs treated with ARVs.

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