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Biological effects of two antiretroviral tritherapy (stavudine-lamivudine-nevirapine and emitricitabine-tenofovir-efavirenz) in patients HIV positive in Abidjan (Côte d'Ivoire)

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Abstract

To better understand the effects of antiretroviral tritherapy on local population in Abidjan, a descriptive study was conducted on two therapeutic combinations (Stavudine-Lamivudine-Nevirapine and Emitricitabine-Tenofovir-Efavirenz). The patients studied were selected from people infected with HIV, who started treatment at National Center of Blood Donors in Abidjan, Côte d'Ivoire. These patients received regular treatment for 36 months, blood samples were taken every 6 months, clinical and laboratory assessments were performed. All patients were infected with HIV-1 type. Biological parameters analyzed showed positive impact of the treatment characterized by the increase of the number and the percentage of CD4+. The value of the number and the percentage of CD4 at the end of the treatment were around 400cells/mm3 and 35% respectively. The treatment did not show toxic effect on the liver and the kidney measured through the rate of creatinine, transaminases (TGO, TGP). The glycemy of the patients was normal without any significant modification. The clinical parameters confirm the positive impact of the treatment. Indeed, the Body Mass Index (BMI), the Brachial Perimeter (BP) and the Karnofsky Index (KI) were in the normal ranges. There is no significant difference between the two therapeutic combinations (Stavudine-Lamivudine-Nevirapine and Emtracitabine-Tenofovir-Efavirenz). These positive effects could explain the use of these therapeutic combinations in the first line treatment of HIV positive patients in the National centre of blood donors in Abidjan.

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Introduction

Since the discovery of the human immunodifiency virus (Barré-Sinoussi *et al.*, 1983 ; Barré-Sinoussi *et al.*, 1985 ; Miedema, 2008 ; Vahlne, 2009 ; Agrawal *et al.* 2010) the HIV-1 and HIV-2 the itiological agents of aids have been rapidily spreading in many countries. Despite the importance of the work done and the quality of the knowlegde accumulated, aids remains an universal fear subjet and Subsahara Africa is one the region which is mostly affected by HIV (ONUSIDA, 2009).

In the absence of curative treatment, antiretroviral therapy has emerged as an effective tool for saving lives. ARV treatment today remains the best choice for people living with HIV. Currently, therapeutic treatment of AIDS has mainly relied on the four types of anti-HIV/AIDS drugs: the viral reverse transcriptase (RTase) inhibitors that include nucleoside and nonnucleoside type RTase inhibitors (King *et al.*, 2002; Feng *et al.*, 2009), protease inhibitors (Dierynck *et al.*, 2007), integrase inhibitors (Blanco *et al.*, 2011) and entry inhibitors (Ji *et al.*, 2009). Availability of free antiretroviral drugs to HIV infected individuals in poor countries has provided a new opportunity of life to these patients. Treatment of HIV infected patients with currently available highly active anti-retroviral drugs though successful in reducing the burden of the disease but is associated with various side effects, including emergence of drug resistant HIV strains (Lange, 1995; Dybul *et al.*, 2002; Hofman and Nelson, 2006; Agwu *et al.*, 2008; Este and Cihlar, 2010). Hence, it is imperative to better understand the biological and clinical effects of these molecules in Côte d'Ivoire where local data about the effects of drugs manufactured in developed countries are lacking. Therefore, this study has been undertaken to assess the effects of two first lines ARV (Stavudine - Lamivudine - Nevirapine and Emitricitabine-Tenofovir-Efavirenz) in local patients HIV positive of the National Centre for blood donors in Abidjan-Côte d'Ivoire. This study has also been conducted to compare the biologic effects of these two therapeutic combinations.

Material and methods

Sample constitution

The study involved patients infected with HIV, who started tri-therapy at National Center of Blood Donors in Abidjan, Côte d'Ivoire. The inclusion and exclusion criteria for the constitution of the sample were as below: adult patients (with at least 16 years) infected with HIV, female and male, who started for the first time tri-therapy at the center (Inclusion criteria). HIV patient, less than 16 years or adult, female or male, untreated were excluded. 75 patients meeting the inclusion criteria, in whom the initial systematic biological assessment was made, were selected.

Treatment

During 36 months, selected patients received regular treatment (Table 1 and 2) of first-line ARV. The first group received the combination constituted by D4T-3TC-NVP and the second group received FTC-TDF-EFV. They received a laboratory monitoring during the treatment. Every six months blood samples were taken for biological analysis.

HIV detection

The DETERMINE (Unipath Limited, UK), a chromatographic immunoassay, was used for the qualitative detection of anti HIV 1 and anti-HIV 2 antibodies. The blood is deposited in the drop zone of the sample provided on the strip. If the anti-HIV 1 and 2 antibodies are present, it's formed an antigen-antibody complex which is materialized by the formation of a red line; the test is positive. In the absence of anti-HIV 1 and HIV 2 antibodies, the red line is not formed and the test is negative. A control bar is included in the system to ensure the validity of the test (Pavie *et al.*, 2010). Confirmation of the result is made by the STAT-PAK (Clearview, USA) HIV 1 and 2 test, according to a similar procedure (Louie *et al.*, 2008).

The discrimination between HIV 1 and HIV 2 is performed by GENIE III (Bio Rad, USA) test. GENIE III is a chromatographic immunoassay, based on the specific detection of anti-HIV 1 and anti-HIV 2

antibodies by antigens. The strip comprises three reading zones materialized by the letter C (Control), the number 1 (HIV 1) and number 2 (HIV 2). Filing procedures and migration of the sample are similar to those of STAT-PAK. The sample contains HIV 1 or HIV 2 or both types of virus, if the red lines appear in zones 1 or 2, or 1 and 2 (Amadou *et al.*, 2005).

CD4+ count

CD4+ count is done using a flow cytometer (GUAVA AUTO Technologies, USA). The Guava measures the total lymphocytes (CD4+) and its percentage in the blood. Whole blood is collected in special tubes containing an anticoagulant (EDTA). The samples were then thoroughly homogenized using a Bloodmixer before being introduced into the apparatus. When reading the results, the system determines the number and the characteristics of the cells. Two control tests are performed (Nkwanyana *et al.*, 2009).

Biochemical analysis

A fully automate analyzer was used to measure the biochemical parameters. Blood samples were collected in plain tubes without anticoagulant and centrifuged. The sample is decanted 5 to 10 minutes and the serum is collected for analysis. Fully performs the biochemical analysis, such as the determination of creatinine and transaminases (OGT, PGT) and glycemy.

Clinical analysis

The Karnofsky index (KI) is an indicator of overall health status that is similar to a synthetic scale of quality of life. The KI measured on a scale from 0 (death) to 100% (complete autonomy), patient functional dependence as the help he needs to gestures of everyday life (personal needs, dressing etc.) and medical care. This parameter is determined by the medical team of Centre Médical de Suivi des Donneurs de Sang (CMSDS). Body mass index (BMI) is used to assess the risk of diseases associated with an excess or a deficiency in weight. It is calculated using the formula: $BMI=W(Kg)/H(m)^{2.}$ The weight (W) and height (H) are measured in each patient's passage at CMSDS. The Brachial Perimeter is the arm circumference in millimeters. It is measured in the left arm halfway between the tip of the elbow (Olecranon) and the tip of the scapula (Acromion). The arm should be relaxed.

Statistic analysis

The processing of data was performed using Statistica Software version 10. The results were expressed as mean±SD (standard deviation). All the graphs were made by Graphpad Prism 5. The Student's t test was used to compare the averages. The test was considered significant at a value of $p<0.05$.

Results

Effects of the treatment on the number of CD4

CD4 cells are the primary targets of HIV. Thus, the number of CD4 lymphocytes in 1 mm^3 of blood reflects the patient's immune status and consequently the effect of ARV treatment. The specific effect of the treatment with ARV (Fig. 1) gives the following results:

1. The number of CD4 is at a low level of 170.44±16 cells/mm3 at the beginning of the treatment. Under the action of D4T-3TC-NVP, the number of CD4 undergoes an important increase of 146.80 % and reaches 420±41 cells/mm^3 after 12 months. From the 12^{th} month until the 36^{th} month, the values tend to stabilize around 400 cells/mm^3.

Table 1. Therapeutic scheme.

Therapeutic combinations	Sample	Therapeutic strategy	ARV Class combination
D4T-3TC-NVP	58	1^{st} line	2 INTI/1 INNTI
FTC-TDF-EFV	17	1^{st} line	2 INTI/1 INNTI

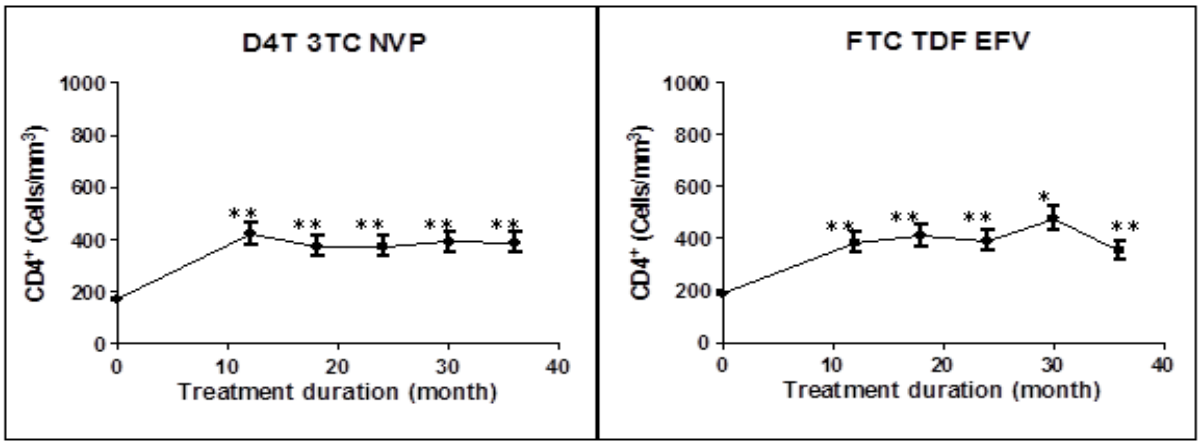
2. The treatment with FTC-TDF-EFV gives variations in the number of CD4 similar to those obtained with the DT4-3TC-NVP.

Table 2. Molecules used for the constitution of the therapeutic scheme (WHO, 2006 modified).

Generic names	Mechanism of action	Dose administrated
Stavudine (D4T)	INTI	40mg, 2X/day
Lamivudine (3TC)	INTI	300mg/day
Nevirapine (NVP)	INNTI	200mg/day during 14 days and 200mg, 2X/day
Emtricitabine (FTC)	INTI	200mg/day
Tenofovir (TDF)	INTI	300mg/day
Efavirenz (EFV)	INNTI	600mg/day

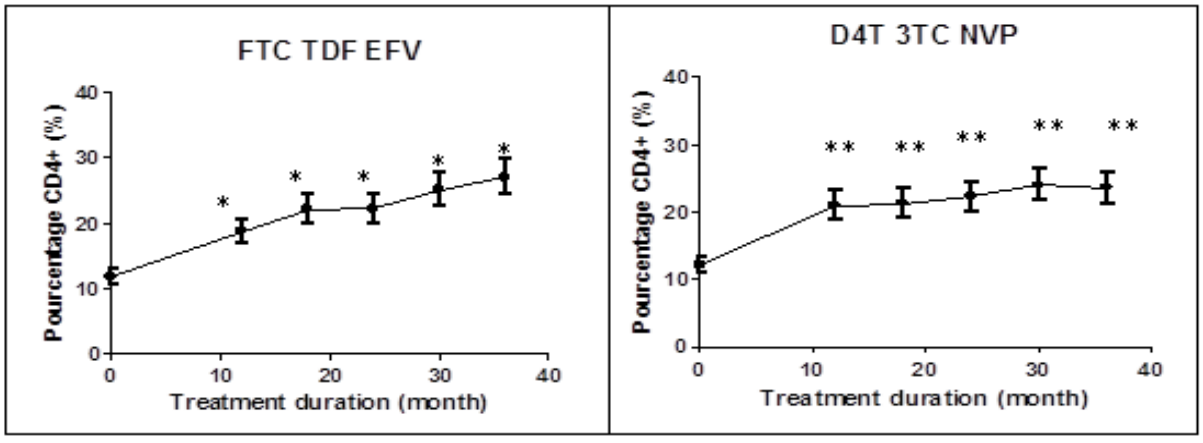
Effects of the treatment on the percentage of CD4

The treatments induced a significant effect on the percentage of CD4 resulting in a significant increase. Thus, after 12 months the increases obtained are 73.41 % and 58.92 % respectively for D4T-3TC-NVP and FTC-TDV-EFV. From the 12th month, the increases caused by these two therapeutic combinations are similar and progressive (Fig. 2).



** : P<0,01 ; * : P<0,05.

Fig. 1. Effects of the treatment on the number of CD4.

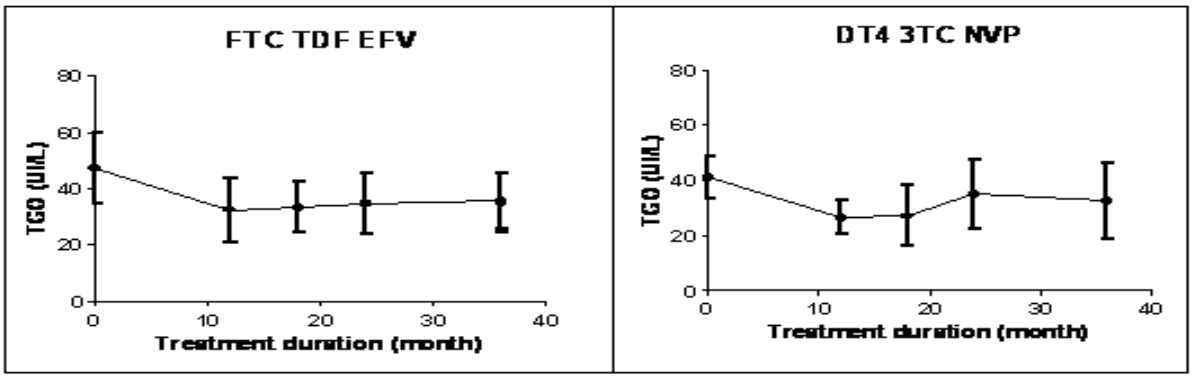


** : P<0,01 ; * : P<0,05

Fig. 2. Effects of the treatment on the pourcentage of CD4.

Effects of the treatment on the Oxaloacetic Glutamic Transaminases (OGT)

D4T-3TC-NVP and FTC-TDF-EFV induce in first time a non-significant decrease in the rate of OGT and then maintain this rate without significant change until the 36th month of treatment (Fig. 3).

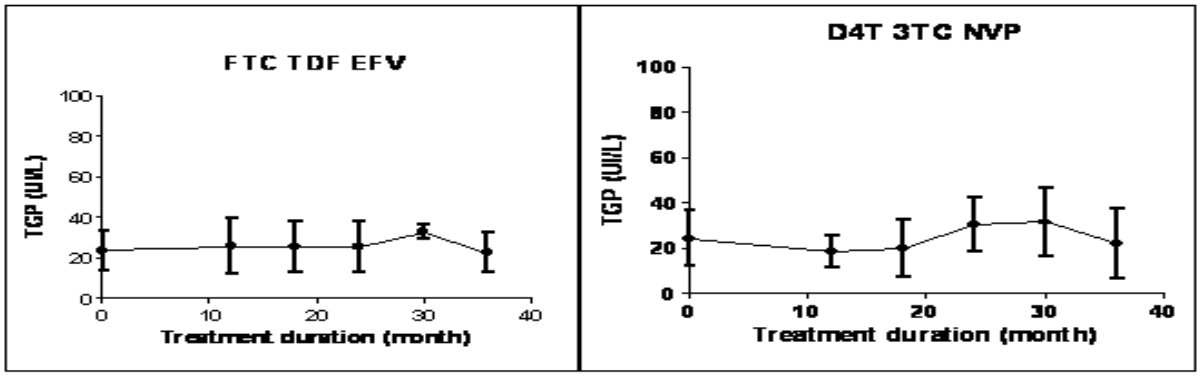


* : P<0,05

Fig. 3. Effects of the treatment on the rate of Glutamic Oxaloacetic Transaminases.

Effects of the treatment on the Pyruvic Glutamic Transaminases (PGT)

Even if, the analysis shows some differences, globally the profiles of the rate of PGT are similar with the two treatments D4T-3TC-NVP and FTC-TDF-EFV. Indeed, regardless of the molecules used, an increase appears to 30th month of treatment followed by a decline bringing the PGT value below the value at the initiation of the treatment (Fig. 4).



* : P<0,05

Fig. 4. Effects of the treatment on the rate of Glutamic Pyruvic Transaminases.

Effects of the treatment on the rate of creatinine

The treatment with D4T-3TC-NVP and FTC-TDF-EFV maintains creatinine levels in a range of 10 to 12 mg/l, from month one to month 36 without any significant change (Fig. 5).

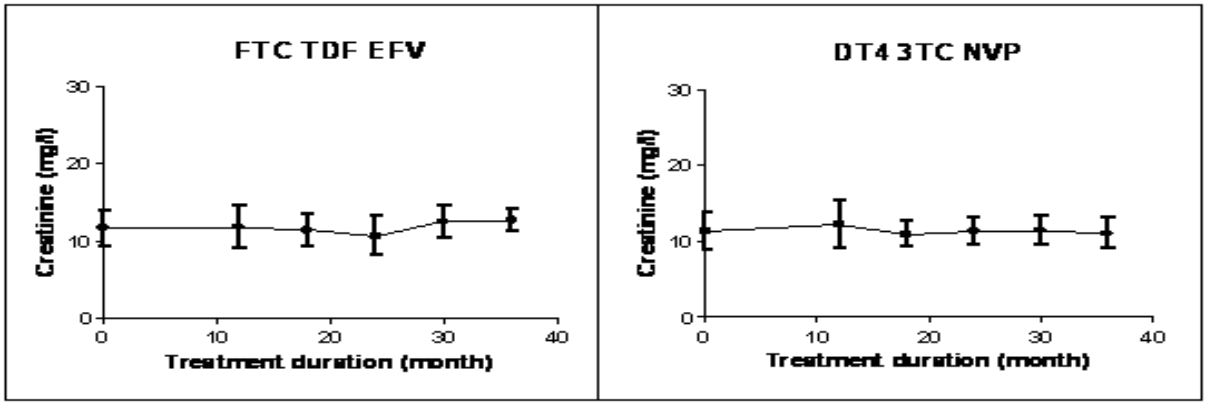


Fig. 5. Effects of the treatment on the rate of creatinine.

Effects of the treatment on the glycemy

In all patients, blood sugar remains substantially constant below 1g/l during the treatment with D4T-3TC-NVP and FTC-TDF-EFV (Fig. 6).

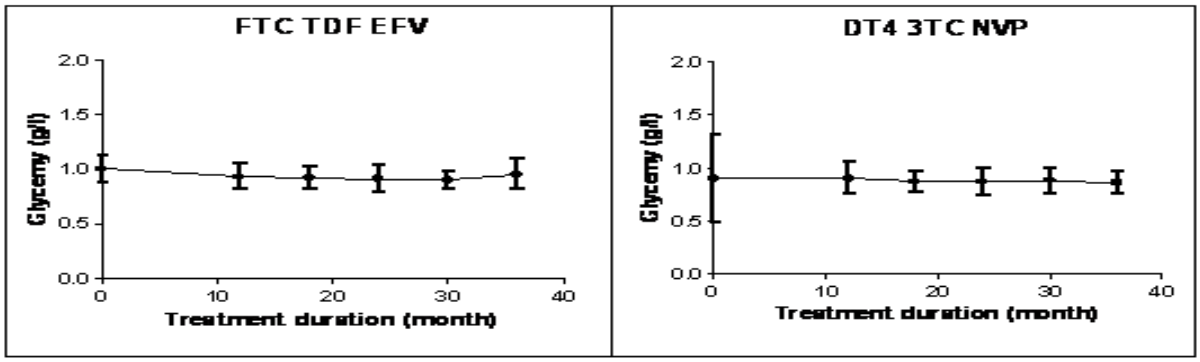


Fig. 6. Effects of the treatment on the glycemy.

Effects of the treatment on the indix of KARNOSFKY

The Karnofsky index denotes the patient's ability to be independent or not. In all patients, the Karnofsky Index remains constant around 100 % since initiation of treatment until the 36th month. The effect of the treatment, thus, results in maintaining the Karnofsky index within normal values (Fig. 7).

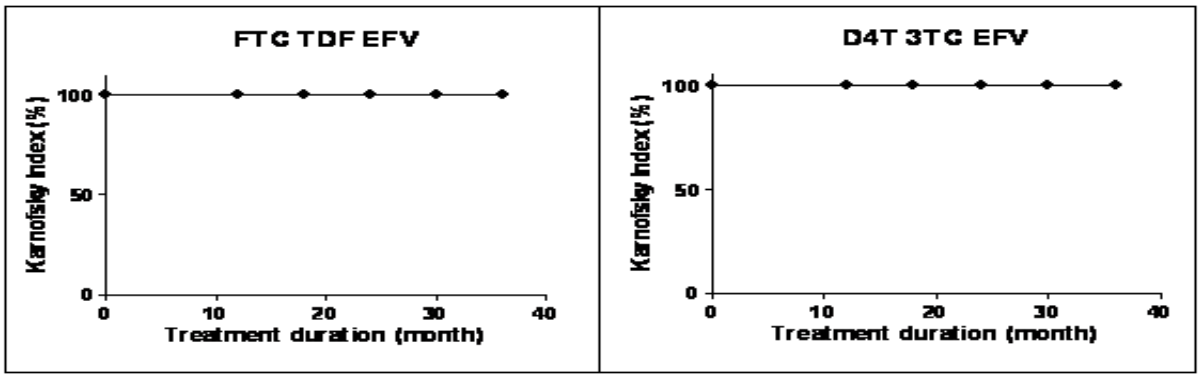


Fig. 7. Effects of the treatment on the Indice of Karnofsky.

Effects of the treatment on the Body Mass Index (BMC)

The body mass index reflects the physical condition of a person. The average value of this index among all patients varies between 21 and 24 Kg/m² (Fig. 8). The different treatments of ARVs administered do not specifically influence the evolution of this index which remains in this range until the 36th month of treatment (Fig. 8).

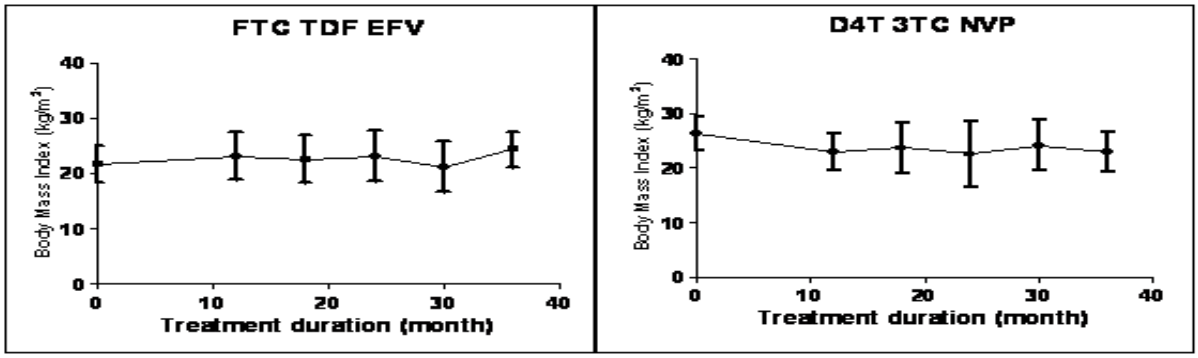
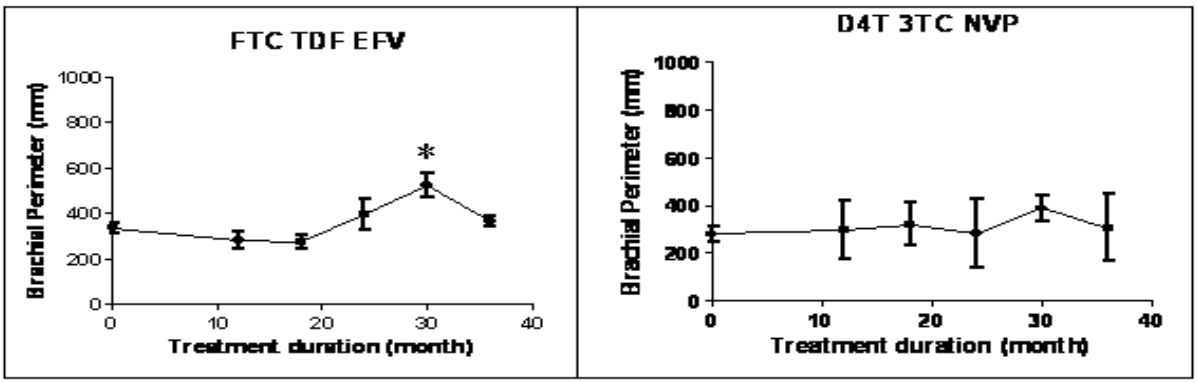


Fig. 8. Effects of the treatment on the Body mass Indice.

Effects of the treatment on the Brachial Perimeter

Although usually used in children, Brachial Perimeter is used to measure the physical condition of HIV positive patients. In all patients under ARV treatment, the average value of Brachial perimeter increases gradually and significantly (P <0.05) during the treatment. Each combination results in a gradual and significant increase (P < 0.05) of PB in time. These increases are respectively 6.27 %, 14.36 %; 6.63%; 38.72% and 8.84% for M12, M18, M24, M30 and M36, for DT4-3TC-NVP (Figure 9) and 15.79%; 18.76%; 17.37%; 55.86% and 8.87% at M12, M18, M24, M30 and M36, for TDF-FTC-EFV (Fig. 9).



* : P<0,05

Fig. 9. Effects of the treatment on the Brachial Perimeter.

Discussion

HIV is a retrovirus that preferentially attacks the immune system including CD4 cells. To measure the impact of treatment with ARVs, it is essential to determine the effects of these molecules on the number and percentage of lymphocytes in the blood of patients. Indeed, it reflects the patient's immune status. The analysis of the CD4 showed a gradual increase. Indeed, CD4 count reached 400 cells/mm^3 after 36 months of treatment. For all patients, the number and percentage of CD4 increase significantly under the effect of ARVs (Stavudine-Lamivudine-Nevirapine and Emitricitabine-Tenofovir-Efavirenz).

Our results are similar to those obtained by several authors (Krou *et al.*, 2012; Tovi *et al.*, 2014). The treatment showed an immune restoration and more control of viral replication (Fener, 2011). Indeed, in the body's defense system, the activated CD4 lymphocyte is not only necessary to boost a humoral response, but also essential to induce the differentiation and proliferation of CD8 cells, the effectors of cytotoxicity. These CD8 are essential to the defense against infections. All these results seem to also suggest that efficacy of the treatment is relatively limited in the context of immune restoration of these ARVs in our experiment. Indeed, although the number and percentage of CD4 show satisfactory growth, the notion of therapeutic success, defined as a CD4 count above 500 cells/mm^3 after 24 months of treatment, can not be immediately advanced. We note, indeed, that it is only after 36 months of treatment that the rates measured in our experiments reach the lower limits of standards, set at 400 cells/mm3 and 35% respectively.

In most patients, the CD4 count increases after starting treatment with immune restoration. Even patients whose CD4 counts below 10 cells/mm^3 before starting treatment may show a restoration of CD4 if enough time is given. In some patients also CD4 never exceed 200 cells /mm^3; they always remain severely immunocompromised (OMS, 2006).

There is also a delay in the onset of efficacy that could be justified in two ways: In the study of Krou *et al.* (2012) as in ours, patients began treatment late, with low levels of CD4 rates (200 cells/mm^3), while the new WHO recommendations advocate the initiation with a CD4 count below 350 cells/mm^3. According to

this recommendation, early initiation has the advantage of low morbidity of patients, mortality and transmission (TEMPRANO-ANRS 12136 trial, 2010). All patients treated are naive of ARV, their organizations need a necessary adaptation to these drugs before optimizing their effect, this can also explain the delay observed between the beginning of the treatment and the appearance of the effects.

The Nucleoside Reverse Transcriptase Inhibitor (NRTI) such AZT exerts a competitive inhibition of the activity of the reverse transcriptase, thus preventing the destruction of the CD4 lymphocyte and infection of new cells (Mitsuya *et al.*, 1985; Yarchoan *et al.*, 1986), where increasing the number and the percentage of these cells. All NRTIs used in our study, namely Lamivudine, Stavudine, Emtricitabine and Tenofovir act according to a mechanism similar to that of AZT (Basson, 2005; Germanaud *et al.*, 2010) by blocking the activity of reverse transcriptase by a competitive inhibition.

The Non-nucleoside reverse transcriptase inhibitors (Nevirapine or NVP, or EFV Efavirenz) do not compete with the viral genome to the active site of the reverse transcriptase; these molecules bind to amino acid residues of the enzyme, near the catalytic site of which they modify the structure, making the enzyme inactive (Germanaud *et al.*, 2010). This is a non-competitive inhibition of the enzymatic activity of the reverse transcriptase. Blocking the infection by the different treatments did not affect the functioning of vital organs of the body of the patients. The hepatic, renal and metabolic functions of the patients are stable resulting in rate of transaminases, creatinine and glucose in the standard range. In the literature, it is nevertheless described the existence of liver and kidney damage usually associated with taking ARVs.

All classes of ARVs can induce hepatotoxicity (Kontorinis and Dieterich, 2003). We know for example hepatotoxicity of Nucleotide Reverse Transcriptase Inhibitors described by Gervais (2009). For Ollivon (2012) most likely ARVs induce liver abnormalities are NNRTIs and IP, as these drugs are metabolized primarily by the liver. In this class of ARVs, Gervais (2009) described the hepatotoxicity of Efavirenz and Nevirapine. Similarly, according Ollivon (2012), people living with HIV are 30-40% significant risk of steatosis, the NRTI could be the cause.

The absence of this toxicity in our study could be justified by the fact that patients in our study were well tolerated drugs that have been prescribed. However this hypothesis is to be taken with caution because, according to this different authors (Gervais, 2009; Ollivon, 2012), liver diseases are often silent and symptoms are slow to appear. They are often difficult to identify. Therefore in patients with metabolic disorders and an increase in transaminases, it is recommended to do additional tests such as ultrasound, liver biopsy, etc.

The published data also tell us that antiretroviral drugs have nephrotoxic potential (Izzedine *et al.*, 2005). Some ARVs in fact, can cause tubulopathy, a kidney disease that can lead to severe kidney failure in some patients (Traba-Villameytide and Fernandez-Guerrero, 2004; Harmouche *et al.*, 2005; Lazon *et al.*, 2007; Podsadecki *et al.*, 2007; Mocroft *et al.*, 2010; Ondounda *et al.*, 2010; Scherzer *et al.*, 2012). While renal toxicity of ARVs is well documented, our results reveal that after 36 months of treatment, renal function is stable in patients. The stability of the renal function was also ascertained by Leport *et al.* (2014) in study in HIV patients treated with indinavir and tenofovir. These authors also demonstrated the existence of factors associated with renal impairment. These factors are typically, sex, age, BMI, blood pressure (hypertension). It is therefore necessary to use the appropriate formulas to make an accurate diagnosis.

One could also assume that our patients were free of all other risk factors for renal impairment as dehydration, preexisting renal impairment and co-prescription of nephrotoxic drugs. However, if the proper functioning of their kidneys is a sign of effectiveness of treatments, this does not exclude to

keep vigilance in patients by regularly monitoring this function, adjusting dosages and eliminating as much as possible, risks of renal disease.

Carbohydrate metabolism was assessed by measuring blood glucose. The results show a normal blood sugar levels for all treatments of ARV. Chirouze and Hoen (2006) showed that after 1 and 3 years of treatment, the risk of diabetes increased by 4 and 9% respectively in men and 2 to 11% in women.

The clinical aspect was evaluated by measuring the Karnofsky Index, Body Mass Index and Brachial Perimeter or arm circumference. During the 36 months of the study, the Karnofsky index remained unchanged. Thus, the average value of this index for all patients remains around 100% without significant change. The optimal level of Karnofsky index shows that patients have no signs of illness and can lead a normal life. This is a good clinical condition, which is a reflection of the absence of toxicity to vital organs.

BMI in diagnosis is a strong and independent predictor of survival in patients infected with HIV in West Africa. In the absence of clinical support and sophisticated laboratory, BMI could also play a useful role in decision guide for when to initiate antiretroviral therapy (Van der Sande *et al.*, 2004). Linear regression showed a small, but high and significant correlation between baseline BMI and baseline CD4 count (Van der Sande *et al.*, 2004). Changes in BMI also shows that over the duration of treatment, patients kept a good corpulence accordance with WHO standards (18.5 <BMI <25). The characteristic feature is that no loss of weight was observed. People living with HIV are often threatened the "wasting syndrome," which is defined as a loss of more than 10% of body weight. In view of these results, one could assume that the weight balance of the patients is the fact of a good socio-emotional balance, along with a good tolerance for drugs that have led to any symptoms or side effects that would make the act of eating difficult. This is justified by the satisfactory development of Brachial Perimeter, which confirms the absence of emaciation and malnutrition in patients. BMI and BP therefore show good nutritional status of patients on ARV treatment. Unlike our study, a US research on 363 patients from two medical cohorts (Crum-Cianflone *et al.*, 1992), showed a generalized overweight problems in HIV-positive: 63 % were overweight, 46% overweight (25 < BMI < 29.5) and 17% where obese (IMC≥30). This study shows that even among patients with AIDS reported, 29% are overweight or obese.

Conclusion

The biological parameters analyzed showed positive impact of the treatment characterized by the increase of the number and the percentage of CD4+. The treatment did not show toxic effect on the liver and the kidney measured through the rate of creatinine, transaminases (TGO, TGP). The glycemy of the patients was normal without any significant modification. The clinical parameters confirm the positive impact of the treatment. Indeed, the Body Mass Index (BMI), the Brachial Perimeter (BP) and the Karnofsky Index (KI) were in the normal ranges. There is no significant difference between the two therapeutic combinations. These positive effects could explain the use of Stavudine-Lamivudine-Nevirapine and Emtracitabine-Tenofovir-Efavirenz in the first line treatment of HIV positive patients in the National centre of blood donors in Abidjan.

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