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Biological effects of antiretroviral drugs in patients VIH positive of the national centre of blood donors in Abidjan (Cote d'Ivoire) : gender and age groups analysis

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Abstract

HIV is a dynamic field, it is crucial to understand the latest advances in ARV therapy. Data regarding new drugs and their combinations continue to emerge, changing standards of practice. In order to assess the effects of antiretroviral drugs on the local population, a descriptive study was conducted on seven therapeutic combinations. The patients studied were selected from the patients 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 globally by the increase of the number and the percentage of CD4. The analysis according to the gender and the age groups didn't show a marked difference. 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 and transaminases (TGO, TGP). The gender and the age groups didn't have any influence on these parameters. These positive effects could explain the use of these therapeutic combination in the treatment of HIV positive patient in the National centre of blood donors in Abidjan.

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Introduction

The control of viral diseases has been the subject of intense scientific endeavour, with special attention being devoted to those having retroviruses as etiological agents, including acquired immunodeficiency syndrome (AIDS) (Abad *et al.*, 2002). 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 non-nucleoside type RTase inhibitors (Feng *et al.*, 2009; King *et al.*, 2002), 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 lease of life to these patients. Treatment of HIV infected patients with currently available highly active anti-retroviral (HAART) drugs though successful in reducing the burden of the disease but is associated with various side effects, including emergence of drug resistant HIV strains (Dybul *et al.*, 2002; Hofman and Nelson, 2006; Este and Cihlar, 2010; Lange, 1995; Agwu *et al.*, 2008). It is also known that women are more affected than men and the age groups show differences in the infection rates. Hence, it is imperative to better understand the biological 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 first line ARV in local patients HIV positive of the National Centre for blood donors in Abidjan-Côte d'Ivoire, analyzing the data under the gender and the age groups aspects.

Materials 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 (Exclusion criteria). 321 patients meeting these 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. They received a clinical and laboratory monitoring during the treatment. Every six months blood samples were taken for biological analysis.

VIH 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 (TGO, TGP).

Statistical analysis

The processing of data was performed using Statistica Software version 10. The results were expressed as mean±SD (standard deviation). 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 on the number of CD4

The average value of the number of CD4 of all patients treated with ARV treatment showed a gradual increase. Initially low, around 200 cells/mm3, the rate was approximately 300 cells/mm^3 in the 12th month of the treatment indicating a significant increase of 74.82% ($P<0.05$). This increase was maintained even if it was in smaller proportions until the 36th month (Figure 1). The number of CD4 on the 36th month was around 400 cells/mm^3. The gender analysis gave a similar trend among women (72.76%) and men (82.07%). These values were also in the same ranges as those measured in all patients (Figure 2). In terms of age groups, if there was a similarity in the development of young people (17-35 years) and adults (36-50 years), with a respective increase of 77.43% and 78.88 % within the first 12 months, however, it existed a marked difference in the shape of the curve of the elderly (50 years). Indeed, if a substantial and significant increase was noted after 12 months (36.52%), from that date, a gradual fall in the average value of the number of CD4 were noted until the 30th month. An increase was noted, however the 36th month (Figure 3). Overall, the different measured values remained above the initial value which was about 250 cells/mm^3.

Table 1. Therapeutic Scheme.

Therapeutic combinations	Sample	Therapeutic strategy	ARV class Combination
AZT-3TC-EFV	53	1st line	2 INTI/INNTI
AZT-3TC-NVP	149	1st line	2 INTI/INNTI
AZT-3TC-NFV	17	1st line	2 INTI/IP
AZT-3TC-LOP-RIT	17	1st line	2 INTI/IP
DT4-3TC-EFV	10	1st line	2 INTI/INNTI
DT4-3TC-NVP	58	1st line	2 INTI/INNTI
FTC-TDF-EFV	17	1st line	2 INTI/INNTI

Effects on the percentage of CD4

The average value of the percentage of CD4 lymphocytes measured in all patients on ARV treatment has gradually increased during treatment significantly. The increases obtained were 34.90%, 38.60%, 50.41%, 55.07% and 54.30% respectively after 12, 18, 24, 30 and 36 months (Figure 4). The analysis of these results by gender showed that the percentage values, both in women and in men, have evolved in the same proportions. This variation was

similar to that recorded in all patients regardless of gender (Figure 5). The analysis by age groups induced results similar for all age groups; however, younger patients showed a significant increase compared to the initial value. In addition, in the elderly, we noted a fall in the 30th and 36th month even if it was not sensitive and did not leave the interval values. The values obtained after the fall were all greater than the initial value (Figure 6).

Effects transaminases Glutamic Oxaloacetic (TGO)

The average value of this parameter in all patients was about 45UI/L at the beginning. After 12 months this parameter showed a significant decrease (28.14%). The new value was maintained without significant change until the end of treatment (**Figure 7**). The gender analysis showed that, this parameter had a similar trend in women and men with a decrease after 12 months of 14.19% and 44.95 respectively (Figure 8). Analysis by age group showed that youth and adults had a similar evolution and comparable to those of all patients taken together (Figure 9). Patients of 17-35 years and those aged 36-50 years showed a decrease of the rate of TGO of 17.90% and 39.25% respectively. In patients older than 50 years, the treatment did not induce any significant change on the rate of TGO (Figure 9).

Table 2. Molecules used for the constitution of the therapeutic scheme.

Generic names	Mechanism of action	Dose administrated
Azidovudine (AZT)	INTI	250mg 2X per day
Lamivudine (3TC)	INTI	150mg 2X per day
Efavirenz (EFV)	INNTI	600mg per day
Nevirapine (NVP)	INNTI	200mg/day during 14j and 200mg 2X per day
Nelfinavir (NFV)	IP	1250mg 2X per day
Lopinavir LOP	IP	Capsule : 133,3mg/day ; Tablet : 200mg/day
Ritonavir (RIT)	IP	Capsule : 33,3mg/day ; Tablet ; 50mg/day
Stavudine (D4T)	INTI	40mg 2X per day
Emtricitabine (FTC)	INTI	200mg per day
Tenofovir (TDF)	INTI	300mg per day

Effects on transaminases Glutamic Pyruvic (TGP)

The average values of the rate of TGP at the beginning of treatment were around 30UI/L. This value remained unchanged during the first 24 months of treatment. A significant increase ($P< 0.05$) occurred at the 30th month of treatment followed by a decrease after 6 months, so that after 36 months of treatment the average value of TGP was less than his value at the initiation of treatment (Figure 10). The gender analysis showed that changes in the rate of TGP in women as in men were similar to that of all patients on ARV treatment (Figure 11). Taking into account age groups, young people and adults showed a similar profile with regard to the rate of TGP. This profile was also similar to that of patients taken together (Figure 12). In people over 50 years a gradual increase in TGP until 30th month of treatment has been noted. A decrease occurred in the 36th month bringing the rate of TGP to a value similar to that measured at the initiation of treatment (Figure 12).

Effects on creatinine

The mean value of serum creatinine of all the patients was around 14mg/l which is the upper limit of the standard. This parameter did not change significantly throughout the 36 months of treatment (Figure 13). The analysis by gender showed that serum creatinine level in women at the initiation of treatment was at 11mg/ml. This rate did not change during the treatment (Figure 14). Among men, the rate at the initiation of treatment was measured at 17.51mg/ml. This value dropped by 22.90% after 12 months of treatment and was maintained without any great change throughout treatment (Figure 14). Analysis by

age groups showed that in young and elderly this parameter was similar to the development of women, that is to say without any great change throughout treatment (Figure 19). The evolution of this parameter even among adults (36-50 years) was similar to that of men. Indeed, at the initiation of the treatment, the serum creatinine was measured at 15mg/ml. After 12 months of treatment, this value fell to 17.84% and remained at this new value until the end of treatment without significant change (Figure 15).

Discussion

HIV is a retrovirus that preferentially attacks the immune system such as lymphocytes. To measure the impact of treatment with ARVs, it is important to determine the effects of these molecules on the number and percentage of CD4 in the blood of patients.

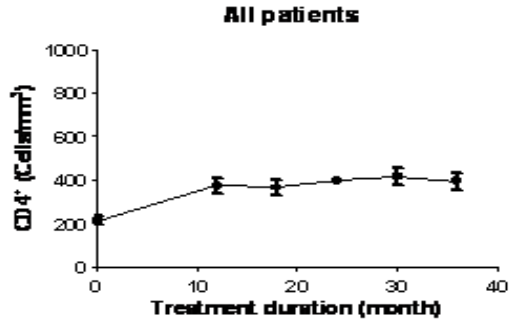

Fig. 1. Global effects on the number of CD^{4+}.

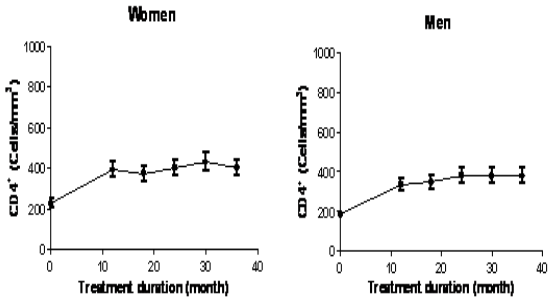

Fig. 2. Gender analysis of effects of the nomber of CD^{4+}.

The global analysis of CD4 showed a gradual increase of the number. Indeed, with 200cellules/mm^3 at the beginning of the experiment, the number of CD4 reached 400cellules/mm^3 after 36 months of treatment. For all patients, the number and percentage of CD4 increased significantly.

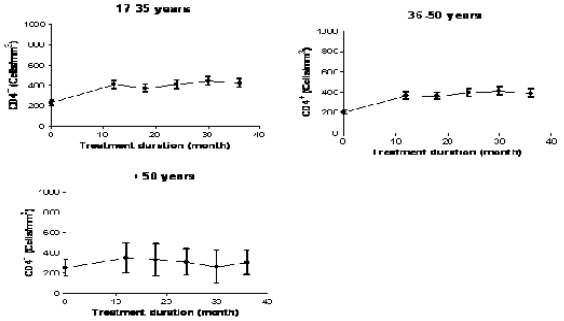

Fig. 3. Age groups analysis of the effect on the number of CD^{4+} ** : P<0,01 ; * : P<0,05.

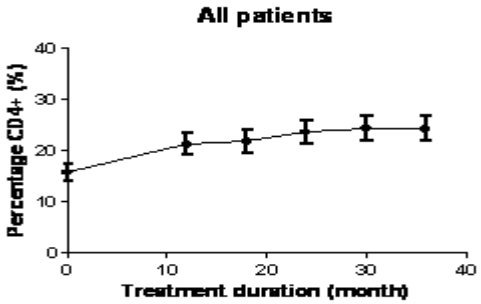

Fig. 4. Global effects of the treatment on the percentage of CD4+.

The analysis by gender and age group did not significantly change the nature of this development in the number of CD4 even if the curve in the elderly showed a gradual fall between the 10^{th} and 30^{th} months of treatment.

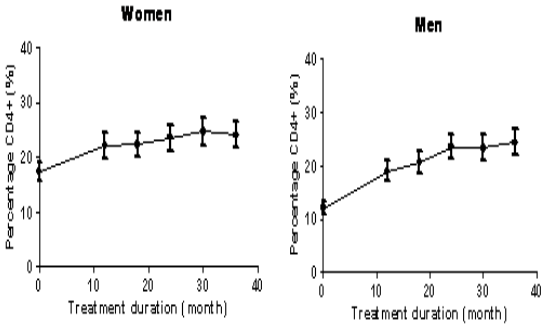

Fig. 5. Gender analysis of the effects on the percentage of CD4+.

Globally, the treatment showed an immune restoration, in addition to the control of viral replication (Fener, 2011). Indeed, in the defense system of the body, activated CD4 lymphocyte is not

only necessary to amplify a humoral response, but also essential to induce the differentiation and proliferation of CD8 lymphocytes, which are cytotoxicity effectors. These CD8 lymphocytes are essential for the defense against infections.

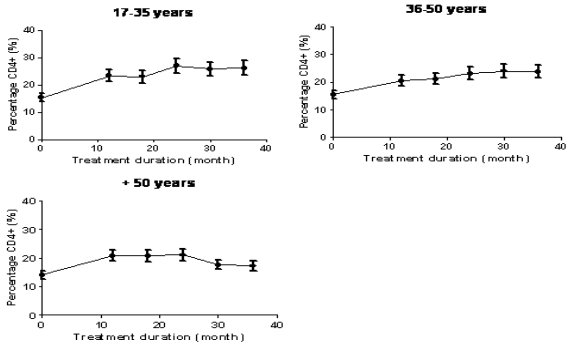

Fig. 6. Age groups analysis of the effects the percentage of CD4+** : P<0,01 ; * : P<0,05.

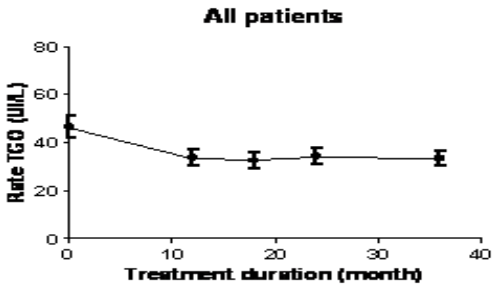

Fig. 7. Global effects on the Transaminases Glutamic Oxaloacetic.

Indeed, although these parameters are experiencing satisfactory progress, the concept of therapeutic success, defined as a CD4 count greater than 3500cellules/mm3 after two years of treatment, can't be immediately advanced. We note that in fact it is only after 36 months (three years) treatment that the rates reach their lower standards thresholds set at 35% and 400Cellules/mm3.

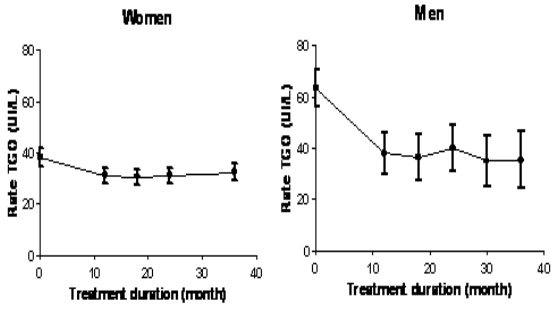

Fig. 8. Gender analysis of the effects on the Transaminases Glutamic Oxaloacetic.

In patients infected with HIV-1, there exists a significant and steady decline in CD4 lymphocytes (helper/inducer) that correlates with progression to disease. The steady decline in CD4 cells is related to the trophism of HIV-1 for the CD4 receptors. The percentage as well as the total numbers of CD4 lymphocytes in the peripheral blood of patients infected with HIV is one of the parameters to monitor prognostically (Bot *et al.*, 2007).

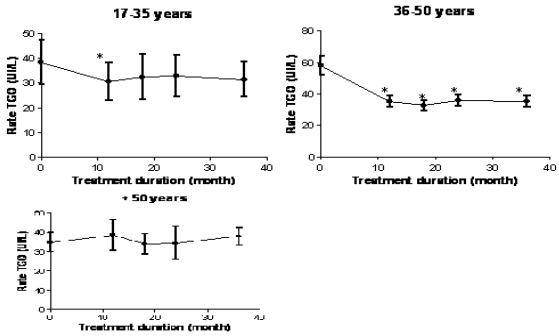

Fig. 9. Age groups analysis of the effects on the Transaminases Glutamic Oxaloacétic* : P<0,05.

The ARV drugs used in the context of our study are grouped into three major therapeutic classes. The Nucleoside Reverse Transcriptase Inhibitors (NRTIs), the Non-nucleoside inhibitors of reverse transcriptase inhibitors (NNRTIs) and the Protease Inhibitors (PIs).

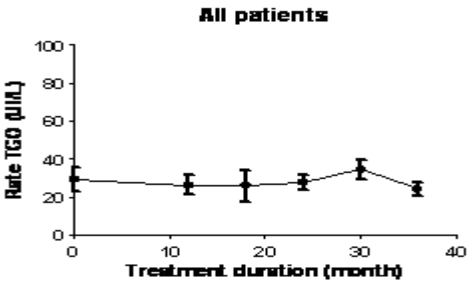

Fig. 10. Global effects on the Transaminases Glutamic Pyruvic.

The immune restoration observed in our study is equivalent in older than in younger subjects. It is however acknowledged that the age (over 50 years) and the male gender are associated with poorer immune reconstruction (Sahali *et al.*, 2011). The older patients will increase their CD4 less than younger patients. Indeed, the regeneration of the immune system decline with the age. This is due to the

decrease in the tissue necessary in the production of CD4. The HIV infection progresses rapidly to AIDS when the patient is aged (Babiker *et al.*, 2001).

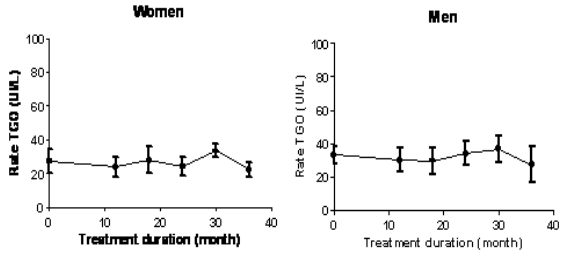

Fig. 11. Gender analysis of the effects on the Transaminases Glutamic Pyruvic.

The blockage of the infection by the various treatments did not affect the functioning of vital organs in the body of patients such as the kidney and the liver. All the therapeutic combinations showed global positive action on hepatic and renal function of patients through the evolution of the transaminases (TGP, TGO) and the rate of the creatinine which were in the standard range.

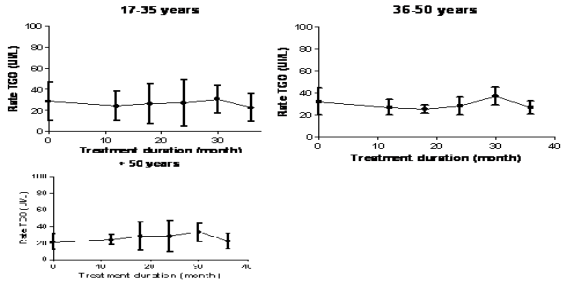

Fig. 12. Age group analysis of the effects on the Transaminases Glutamic Pyruvic.

In the literature, it is nevertheless described the existence of hepatic and renal impairment usually associated with taking antiretroviral drugs. Indeed, it is not uncommon to observe abnormalities in liver function among people living with HIV under ARV treatment. All classes of ARVs may induce hepatotoxicity (Kontorinis and Dieterich, 2003).

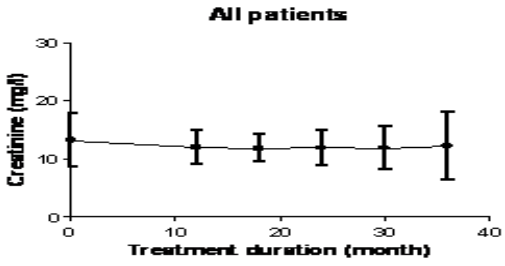

Fig. 13. Global effects on the rate of creatinine.

The literature data also tell us that antiviral drugs have a nephrotoxic potential (Izzedine *et al.*, 2005). Some antiretrovirals effect can cause tubulopathy, a kidney disease that can lead to severe renal failure in some patients (Mocroft *et al*, 2010). This is the case of the Fanconi syndrome , a disorder of proximal tubule of the kidney, due to the toxicity of tenofovir (Harmouche *et al*, 2005; Ondounda *et al.*, 2010), although studies of the renal toxicity of this molecule seem discordant (Scherzer *et al.*, 2012). Stavudine and Lamivudine are also implicated in this condition. Stavudine for example, generates neuropathies and sometimes severe mitochondrial toxicity, which causes toxicity in the longer term (Lazon *et al*, 2007; Podsadecki *et al*, 2007).

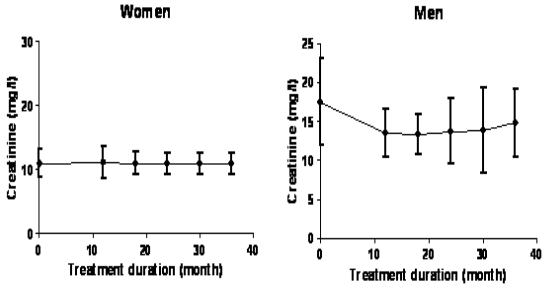

Fig. 14. Gender analysis of the effects on the rate of creatinine.

The main results of our study showed that the therapies positively affect the number and the percentage of CD4 but the gender and the age groups didn't really change these results even if on the patients of 50 years and more the treatment seems less effective than the other groups. This study therefore confirms the choice of these therapies in the National Centre of Blood donors to treat people infected with HIV with any consideration of the gender and the age groups.

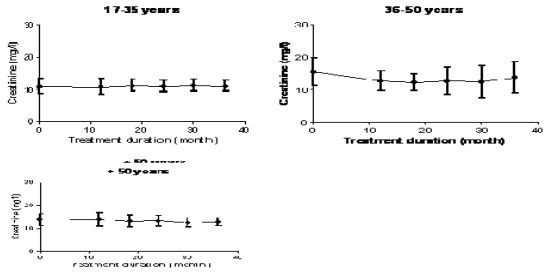

Fig. 15. Age groups analysis of the effects on the rate of creatinine.

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