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INCIDENCE OF ANEMIA INDUCED BY ZIDOVIDUNE IN GOMA TOWN, DEMOCRATIC REBUPBLIC OF THE CONGO

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A B S T R A C T

Introduction: The zidovudine (ZDV) is one of the preferred nucleoside reverse transcriptase inhibitor in the first line antiretroviral treatment in DR Congo. It is known to be associated with life threatening toxicity such as anemia. For this reason, in the Democratic Republic of Congo (DRC), the national program has a tendency to gradually replace this molecule by tenofovir. Yet, its therapeutic efficacy is fully demonstrated but not many studies have been carried out in the country in order to assess the factors associated with this toxicity. This study was aimed at determining the prevalence of anemia induced by ZDV to HIV infected patients under therapeutic regime containing this antiretroviral also to find out the factors which favour the induction of that anemia.

Methods: This study was conducted in the two major health facilities in support of HIV infection in the city of Goma. Patients were treated according to the National program guidelines of the DRC to Fight against HIV (PNLS).

Patients (N = 685) with hemoglobin (Hb) > 8 g/dL were submitted to a diet containing ZDV. Anemic patients developing anemia (< 8 g/dL) with other causes of anemia were excluded from the cohort. Correlation of baseline characteristics of the sample study population (age, gender, hemoglobin levels, weight, CD4 counts and WHO clinical stage) with risk of developing anemia was also calculated.

Results: One hundred and one patients or 16.1% on ZDV regimen developed anemia with a rate of hemoglobin (< 8 g/dL). Men were more thin-skinned to develop anemia with a sex ratio of 3.4 for males 17.3% and females 16.9%. The low average weight (46 ± 8.02), the mean CD4 count below 200 /µL (117 ± 77.4) at the beginning of treatment, the diet with ZDV in first intention (73.3%) were incriminated in the occurring of anemia induced by ZDV. Age, clinical stage of the disease according to WHO and the hemoglobin at treatment had no connection with the development of anemia.

Conclusion: The high incidence of anemia caused by ZDV in this study indicates that patients with a low average weight, a CD4 count below 200 /µL early treatment should benefit from closer monitoring. A regimen with ZDV in second line will minimize the risk of anemia induced by ZDV.

INTRODUCTION

Described in 1983 by Luc Montagnier and al at the Pasteur Institute, the acquired immunodeficiency syndrome (AIDS) has become a major public health problem [1]. In 2007, 33 million people were living with human immunodeficiency virus (HIV) and 33, 4 in 2010. The annual number of new HIV infections declined from 3.million in 2001 to 2,600,000 in 2010 [2].

Treatment with antiretroviral (ART) associated in developed countries, which has already begun since 1987, the marketing of zidovudine significantly lowers morbidity and mortality due to HIV [3]. Thanks to these therapies, people with HIV infection maintained a satisfactory health status that allowed them to lead more productive and less dependent life. However, because of the high cost of these drugs in developing countries, the majority of people living with HIV (PLHIV) had no access to treatment. In 2002, developed countries which accounted only 5% of PLHIV had 70% of them under antiretroviral therapy whereas with 70% of PLHIV in sub-Saharan Africa, only 4% were treated by the ART [4].

Thanks to the efforts of governments, Non-Government Organizations, United Nations agencies, antiretroviral therapy price dropped significantly to access to treatments in resource-limited countries [5]. The number of new infections together with deaths, have decreased thanks to universal access of antiretroviral treatment together this therapy that has favorably changed the prognosis and course of HIV disease [6]. In fact, according to WHO, l3 million PLHIV are under antiretroviral treatment worldwide, including 11.7 in low-income countries. As for the Democratic Republic of Congo (DRC), the situation remains particularly critical of PLHIV despite advances at world stage. For example, the National

program guidelines of the DRC to Fight against HIV (PNLS) estimated in late 2013, the number of PLHIV in 1.3 million the number of PLHIV whose 350,000 needed antiretroviral treatment while only 44,000 benefited from this treatment. This corresponds to a coverage rate of 14% ART either one of the lowest in the world [7]. Moreover, despite a lot of benefits they bring, antiretroviral drugs can have a lot of side effects. For example, nucleoside inhibitors of reverse transcriptase can cause among other things, neuropathy, lactic acidosis, anemia and hepatitis; while nucleoside inhibitors are associated with allergies, hepatitis and psychiatric disorders. As for protease inhibitors, undesirable effects consist lipodystrophy, dyslipidemia, glucose intolerance or diabetes mellitus, digestive disorders, kidney stones and failure [8]. Furthermore, in accordance with the recommendations proposed by the WHO in low-income countries, zidovudine, a nucleoside reverse transcriptase inhibitor, is one of the most prescribed first-line antiretrovirals in the DRC. Yet, that antiretroviral treatment although very effective, is also associated with a risk to patients develop adverse effects, the most formidable myelotoxicity is manifested by, among other things, and anemia occurred which sometimes requires stopping zidovudine and substitute with another antiretroviral [9]. However, anemia having several causes and HIV infection being a defect, anemia to PLHIV is not necessarily related to zidovudine. Thus, a study carried out in Uganda revealed that up to 40% of PLHIVs developed anemia during the disease whereas the frequency of anemia attributed to zidovudine varies from 2 to 36% according to the study and to countries [10]. The causes of this variation are not well known. However, they criminalize certain socio-demographic factors of patients (age, nutritional status, sex) and clinical (clinical stage early in treatment, certain medications, associated pathologies) that vary from one part of a group of patients and the other on the other hand from one country to the other [11,12]. Indeed, several studies have shown that the side effects of antiretroviral in general and in particular zidovudine rampant especially in areas of the world where sanitation, hygiene and nutrition are becoming unacceptable [11, 13]. For the DRC in general and the East of the country in particular, very few studies have been devoted to the issue while rehearsing wars, resulting in not only the disruption of living conditions but also the fragility the health system would favor certain factors associated with anemia induced by zidovudine such as delayed access to treatment and thus a treatment beginning at an advanced stage of infection, malnutrition, and thus a low weight at the beginning treatment. In view of the preceding ideas, the DRC through the PNLS is now envisaging to leave out zidovudine as first line treatment and to replace to by tenofovir. And among the reasons mentioned, besides the bond issue appears first that of anemia related to this product. Note that few studies were conducted in the DRC and especially in unstable regions of the east of the country.

This study was aimed at determining the incidence to ZDV induced anemia in HIV infected patients initiated to ZDV containing antiretroviral therapy regimen and also to evaluate the correlation between this complication and some socio-demographic and Biologic features in Service of HIV patients followed up in the General Hospital of Virunga (HG Virunga) and those of the Provincial Hospital of North-Kivu (HPNK).

MATERIALS AND METHODS

FRAMEWORK OF THE STUDY

This study was carried out in the two major health facilities in support of HIV infection in the City of Goma. In both health facilities, there is a department responsible for the management of all people living with HIV/AIDS named service of HIV (SHIV). This is the SHIV of General hospital of North-Kivu and that of the HG of Virunga.

MATERIEL

The study focused on 101 patients with anemia due to zidovudine which 71 male and 30 were female with an average age of 33.45±7.18 years old. The control population was 526 patients without anemia but is treated by the same molecule whose 409 male and 177 female with an average age of 34.6 ± 4 years old.

METHODS

This is a descriptive cross-sectional study. It was to restore the biological and clinical history of patients followed up in the service. It covered a couple years' period from 1st January 2013 to 31st December 2015. The pieces of information were collected from patient records. The HIV infection was confirmed using two diagnostic tests according to the national protocol, namely Determine coupled to Unigold. Socio-demographic data, weight, WHO clinical stage and CD4 count in HIV positive patients were registered. The treatment was initiated, as per national guidelines in DRC, according to which fixed dose combination of two NRTIs (zidovudine/stavudine + lamivudine) and one NNRTI (nevirapine/efavirenz) is recommended. zidovudine was prescribed if the hemoglobin was more superior than 8 g/dL and stavudine based regimen was started if the hemoglobin was < 8 g/dL. Were included in the study, all patients older than 15 years receiving the combination containing the zidovudine. The hemoglobin Control was performed at baseline and then every 3 months. Anemia related to zidovudine has been defined as any fall in hemoglobin < 8 g/dL to patients under therapy zidovudine and a subsequent increase in hemoglobin levels at stopping therapy. All patients who developed an anemia have been placed under a based therapy upon the tenofovir. The presence of opportunist infections in particularly intestinal infections and other conditions, which could lead to anemia, were excluded. The history of ingestion of drugs such as non-steroid anti-inflammatories was recorded. The menstrual disorders to women and hemorrhoids have been noted as well. Direct examination of stool in search for cysts has been done. To exclude other hematological disorders, besides the hemoglobin rate, the reticulocyte rate have bone to patients who could let it themselves. Patients with anemia signs linked to other causes were not included in the group of anemia related to ZDV. The prevalence of anemia induced by zidovudine has been calculated on the following parameters: the initial weight, age, sex, hemoglobin rate, CD4 count and WHO clinical stages. The follow up period, during which the patient was considered at risk, started the day of the initiation treatment at the zidovudine till the date of the anemia development. Ethically, the identity of every patient was hidden.

Statistical Analysis

Data were analyzed using software SPSS (version 16, SA). Unpaired 't' test was used to find out the difference among mean values of the numerical variables at baseline among patients who developed zidovudine induced by anemia (group 1) through those which did not develop anemia (group 2). Chi-square test was used to find out the significant association for qualitative variables used. Multivariate and univariate analyses were done to know the risk factors to develop anemia to the baseline characteristics.

RESULTS

Demographic and clinical data of patients are presented in Table I below. It presnts the characteristics of patients on zidovudine therapy who developed anemia (group 1) to those who did not develop anemia (group 2).

Table I Comparison of baseline of demographic and clinical data

Variables	Groupe 1 (n=101)	Groupe 2 (n=526)
Age, Year	33.45±7.18	34.6 ± 6.44
Male / Female	71/30	409/177
Weight in kg	46.2 ± 8.02	47.6 ± 9.52
WHO clinical stage:		
I	26 (15,5)	142 (84.4)
II	23 (15.2)	128 (84.8)
III	36 (18.1)	163 (81.9)
IV	66 (51.4)	43 (48.6)

These results show that the incidence of anemia is higher in the population with the following characteristics: an average age of 33.45 ± 7.18, the sex ration of 2.37 with a predominance to men 17.3% to that of women 16.9%, an average weight of 46.2 ± 8.02 kg, patients who started treatment in stage 4 of the disease according to the WHO 51% of cases.

In Table II, we present the biological characteristics of the patients under the regime of ZDV group1 (who developed anemia > grade 1) compared to group 2 (who did not develop anemia).

Table II Distribution of comparative biology basic of patients

Variables	Groupe 1 (n=101)	Groupe (n=526)
Hb (g/dL)	9.66 ± 1.57	11.07 ± 1.56
CD4/mm3	117.9 +77.4	116.20 +67.5
<50	26 (18.7%)	113 (81.3%)
50-100	24(16%)	126 (84%)
101-200	35 (13.1%)	233 (86.9%)
>200	16 (22.9%)	54 (77.1%)

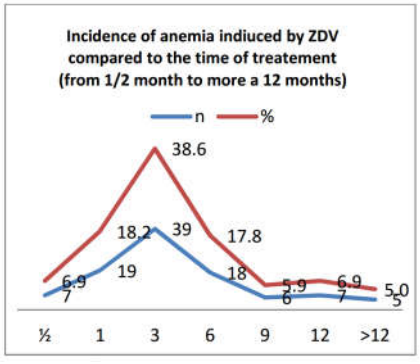

Figure N° 1 Incidence of anemia with time

These results show that the incidence of anemia is higher in the population with the features: a hemoglobin (g/dL) of 9.66 ± 1.57, the mean CD4 count of 117.9 +77.4. This figure N° 1 shows the incidence of anemia with time.

The results show that the incidence of anemia is important in the first 9 months on ZDV treatment regime with a greater proportion around the third month of treatment (38.6).

At the Table IV, we present the anemic patients by gender in relation to the onset of anemia according to the group having been treated by ZDV regimen in first intention (ZDV1) and those having been treated by ZDV in second intention (ZDV 2).

Table IV Comparative distribution off patients by gender

Gender	ZDV in 1st intention	ZDV in 2nd intention	TOTAL
Man	51(71,8)	20(28,2)	71
Woman	23(76,7)	7(23,3)	30
TOTAL	74(73,3)	27(26,7)	101

The frequency of anemia was higher to patients who were treated by the regime with ZDV in first line (ZDV1) 73.3% against those who were treated with ZDV in second line (ZDV2) 27%.

Discussion Demographic Characteristics And Clinical Basic Treaty Patients Under The Scheme Zdv

These results show that the occurrence of anemia is higher in the population having the following characteristics: mean age 33.45 ± 7.18, a sex ratio of 3.4 with a predominance to males to that of 17.3% women 16.9%, an average weight of 46.2 ± 8.02, patients who begin treatment at the stage 4 of the disease according to WHO. These results are close to those found in Ethiopia and Habtamu Hayleselasié who found that age was a major risk factor with a predominance in the range of 30 to 35 years and that this risk increased for each year of over 1.4% [8]. However, Agwaral stipulates that under normal conditions of taking over and to patients with a good nutritional status at the beginning, the age at start of treatment is not a preacher factor of anemia related to ZDV [6]. In this study the prevalence of anemia is to the male population, one should note that women who developed anemia under ZDV to whom bleeding has been reported were automatically excluded from this study. Akndral S *et al* has showed that anemia associated with ZDV appears with a slight superiority in the male sex (22.7%) to that of females (21.4%). These results are contradictory to those found in Nigeria by Emeka *et al*, in which the prevalence of anemia induced by ZDV was the same as in men and women. However, they oppose what Agwarwal found in these studies in India that female PLHIV developed more over the ZDV-induced anemia than men [5, 13, 14]. The wonder Indian scientist had thought that menstrual blood whose are subject women would be the basis of this variation.

The weight of patients

The results of this study showed that the average weight of 46.2 ± PLHIV 8.02 most affected by anemia caused by ZDV. These results are similar to those found in Lesotho by Adebanjo Lesotho in which the weight plays an important role in the tolerance of antiretrovirals. According to his studies, low-weight individuals respond poorly to ARVs and knew of earlier adverse reactions and more severe than their

normal-weight counterparts in early treatment [15]. This can be partially explained by the fact that low weight PVVs are already weakened by poor nutritional status, and therefore susceptible to the effects of any toxic agent. And the absence of anemia in PLHIV with weight greater than 71 kg proves relatively resistance of these individuals with respect to the toxicity of ZDV. Indeed a good nutritional status is proof of a strong enzymatic machinery against various toxic agents. Thus, several studies have shown that the side effects of antiretrovirals in general and zidovudine particularly rampant and especially more severely in areas of the world where sanitation, hygiene and nutrition brief the living conditions are more unacceptable [5, 6, 16].

Moment onset of anemia due to ZDV

The results showed that anemia appeared especially in the interval of time between 3 and 6 months of treatment to zidovudine (38.6%). These results partially contradict those found in Nigeria by Emeka *et al*, in which anemia appeared mostly in the first year but with a predominance in the first 3 months. However, we can't be too much worried because even though facing different populations in different places and times, one thing connects our results i.e. anemia occurred mostly in the first half of treatment [17]. In addition, the frequency of anemia is higher to patients who were treated by the regime with ZDV as first line (ZDV1) 73.3% against those who have been treated with ZDV in second line (ZDV2) 27%. During the course of patients on HAART/ZDV, we observed two models in the development of anemia: 71% of patients have made a low progress in hemoglobin, and 29% of patients had a fall brutal hemoglobin. In most of patients (67%), there was a strong recovery in hemoglobin levels after discontinuation of zidovudine in a month.

Several studies have shown that the prevalence of anemia decreased to patients who started on ZDV regimen as second-line, especially beyond 6 months in comparison to the previous treatment makes a diet either tenofovir or stavudine [17, 18, 19, 20]. Risk factors for anemia due to zidovudine reported in various studies include advanced HIV / AIDS, a low CD4 counts at initiation of treatment, low body weight and low baseline hemoglobin [19]. But in this cohort, we have not found the WHO clinical stage, as a risk factor for anemia caused by ZDV, but low baseline Hb was a factor significant risk to the development of anemia.

Clinical stages of the disease, according to WHO

Compared to clinical Stage of the disease according to the WHO, patients who begin treatment in stage 4 of the disease according to WHO more developed anemia (51.4 % of cases). These results contradict those found in Benin by Barbarossa that anemia ZDV was more found to PHAs who were already at stage 3 or 4 at the beginning of treatment. Furthermore, Van der Werf MJ and al showed at the end of his research in India as the clinical stage according to the WHO, was not a preacher of anemia factor [19]. These differences are partly explained by the fact that these wonders in medicine included in their methodology to data from the histological analysis of possible damage caused by ZDV. This allowed them to include in their research all patients even those with prolonged fever and / or chronic diarrhea. For, indeed the risk for them to confuse anemia related to ZDV and anemia due to these disorders mentioned above was minimized [5, 11]. As for us, in view of preventing any eventual confusion we have completely excluded from our study all subjects with prolonged fever and / or chronic diarrhea, which may explain this difference.

Biological Carasteristics of Patients

The hemoglobin level at the beginning of the treatment

These results demonstrated that patients with a hemoglobin (g/dL) average of 9.66 ± 1.57 were the most likely to anemia. These results do not contradict those of sali F *et al* and those of al Curkendall SM according to which a normal hemoglobin at treatment initiation in no savings no induced anemia ZDV. Moreover, according Agwaral basis of hemoglobin and age at start of treatment are preachers factors of anemia associated with ZDV [6, 20, 21].

The CD4's rate at the beginning of treatment

The mean CD4 count is goshawks of 117.9 +77.4. These results are similar to those observed by Huffam S *et al* in Ethiopia, who had proved that anemia associated with ZDV, was more prevalent to patients with a CD4 count below 200 [22]. Several studies show that at an advanced stage of the disease, the HIV virus as well as other opportunistic viruses by their tropisms stem cells in the bone marrow cells, to expose these cells to a fragile compared to hematopoiesis in its entirety. In countries with limited resources, a lot of patients start antiretroviral therapy when the CD4 late especially when the rate is less than 200/µL [13, 14, 15, 16]. From this, we can say that a large number of cases of anemia related to ZDV is linked to a late start of treatment, which shows that the awareness for early initiation of antiretroviral therapy will let exploit this molecule with more security [23].

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