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Scientific Research

Immunovirologic Evaluation of Triomune (Lamivudine, Stavudine and Nevirapine) Antiretroviral Therapy in First Line HIV-1 Adult Patients in N'Djamena, Chad

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Abstract

Contexte: The fight against HIV/AIDS epidemics is one of the greatest challenges of this century. The epidemic affects generally under-developed countries, and Sub-Saharan Africa are the most concerned. The combined marketed form known as Triomune was used as first-line treatment in several sub-Saharan African Countries (60% of VIH infected people), including Chad. However, no evaluation has been done for that treatment in the country. Objective: To evaluate the efficacy and safety immuno-virological of Triomune at the General Hospital in N'Djamena/Chad. Methods: 48 HIV-1 positive patients eligible for ARV treatment were enrolled in our study, and they have been then followed for 8 months. We have measured in these patients the CD4 cell count before treatment and at the 8th month of treatment. After 8 months of treatment, we have also evaluated the Lymphocyte T CD4 and the plasma viral load (VL). Comparisons of means of CD4 lymphocytes and plasma CV (≥1000 copies/ml) were used to define treatment failure. Results: 48 patients were under Triomune regime. The average CD4 count was decreased from 462 ± 179.22 [56 - 981] cells/mm^3 before treatment to 327.23 ± 153.77 [10 - 1008] cells/mm^3 at the 8th month of treatment. The mean plasma viral load for patients was 66008.62 copies/ml. The failure rate to Triomune was 43.75% (21/48). Conclusion: Aside from the side effects already described for Triomune, our study reveals a high treatment failure rate. Hence, there is the need of regular revisions

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of therapeutic regime administer in the first intention.

Keywords

Plasma, Viral Load, Triomune, Antiretroviral Therapy, Virological Failure, ARVs, HIV-1, First Line

1. Introduction

Although the number of deaths due to Human Immunodeficiency Virus (HIV) infection in Sub-Saharan Africa has decreased by 32% from 2005 to 2011 [1], the continent still accounted for 70% of total deaths in 2011. HIV infection remains to be a very devastating pandemic this day. Sub-Saharan Africa pays the heaviest price. In 2011, the number of people living with HIV worldwide was estimated to 34 million [31.4 - 35.9], of which nearly 70% were living in sub-Saharan Africa, a region that accounts for 12% of the world population [1].

As in other countries south of the Sahara, Chad is a country where the HIV epidemic is responsible for a high morbidity and mortality. According to recent seroprevalence survey of 2005, the prevalence among the Chadian population aged from 15 to 45 years, estimated at 7 million, was 3.3% [2].

In Chad, the variant of HIV circulating since the advent of AIDS is HIV-1. Only the group M with 4 subtypes (A, D, F and G) and 3 recombinants (CRF01-AE, CRF02-AG and CRF11-cpx) is predominantly found. Group O is in minority and N is not yet detected. HIV-2 also has not yet been found in Chad [3] [4].

Rates of drug resistance in patients receiving Antiretroviral Therapy (ART) in sub-Saharan Africa have shown a large variation. These rates are reported in the range of 3.7% to 49% after 24 to 163 weeks of treatment [5]. In Chad, a 2009 study of 88 patients at the National Reference General Hospital indicates a 64% treatment failure rate of first-line ARV [6].

Since 2007, the Chadian government has introduced free ARV and any additional tests related to AIDS. Since then, a treatment protocol based on triple therapy has been established. It was mainly with Triomune (Cipla, India) which is a combination of 3 molecules in a fixed dose (FDC, fixed-dose combinations), all inhibitors of Reverse Transcriptase (RT): 2 Nucleosidic (Stavudine-d4T and Lamivudine-3TC) and 1 Non-Nucleosidic inhibitor (Nevirapine-NVP). This combination has been marketed since 2000 and recommended by the World Health Organization (WHO) for countries with limited resources due to its availability and its heat-resistant [7]. However, the genetic barrier for Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) is very low. Indeed, one single mutation (K103N or Y181C) is enough to destroy their effectiveness [7].

Triomune is easy to take for patients and has long been the most widely used combination therapy as first-line in resource-limited countries including Chad.

Recent studies have indicated that treatment failures were incorrectly diagnosed in many patients and that they had unnecessarily prescribed to these patients' second-line ARV drugs [8]. To assess the therapeutic failure, WHO recommends measuring changes in the rate of CD4+ T cells every 6 months for monitoring patients on ART in resource-poor countries, where the measurement of viral load (VL) is not routinely available [9].

The objective of this study is to evaluate the efficacy and immuno-virological safety of Triomune in the General Hospital of N'Djamena/Chad.

2. Methods

The study was conducted from September 1, 2010 to June 31, 2011 (10 months). This is a prospective cohort of patient monitoring. We included in the study, all HIV-1 positive patients eligible for ARV treatment of both sexes, followed at the Department of Infectious Diseases at the National Reference General Hospital. These patients were receiving ARV and were followed for 8 months.

Forty-eight patients (28 women and 20 men) were enrolled in this study. All patients gave their consent after being informed of the objectives of the study and its importance. A standardized questionnaire was administered to gather demographic information.

A sample of venous blood was collected on EDTA two tubes of 4 ml each. Both tubes are agitated gently to mix the blood with the anticoagulant. The blood is centrifuged for 10 min at 2000 tg. Plasma was aliquoted into 3 cryotubesof 2 ml (2 - 3 cryotubes were used according to the volume of plasma). They were then put in a box

and stored at −80˚C until transportation to the AIDS Reference Laboratory (LRS) of the Centre Hospitalier Universitaire de Liège (CHU-Lg) in Belgium for the measurement of Viral Load (VL).

At the National Reference General Hospital in N'Djamena (Chad), CD4 lymphocytes were measured before initiation of treatment in all patients by FACS Count (Becton Dickinson Immunocytometry Systems, USA). A second measurement was done after 8 months of treatment.

At the CHU-Lg LRS, VL measurement was done on the automated m2000 system (m2000sp for processing samples and m2000rt for amplification and detection) on all samples using Abbott Real Time HIV-1 *in vitro* test version Ref 2G3190. Comparisons of means of CD4 lymphocytes and plasma CV (≥1000 copies/ml) were used to define treatment failure. The data were processed with Microsoft Excel 2011 and EPI INFO (version 3.3.2) software using the Chi^2 test. A difference of $p < 0.05$ was considered significant.

3. Results

Forty-eight (48) patients under the Triomune regime were included in the study. There were 28 women (58.33%) and 20 men (41.66%). The average age of our patients was 41 years with 83 years for the oldest and the youngest 23 (**Table 1**).

The average CD4 lymphocytes at the initiation of treatment (J1) was of 462 ± 179.23 [56 - 981] cells/mm^3 and at 8 months was 327.23 ± 153.77 [10 - 1008] cells/mm^3. The medians CD4 were of 432 cells/mm^3 at J0 and 298.5 cells/mm^3 at 8 months (**Table 2**).

Thirty-nine patients (81.25%) were in poor adherence as notified by the attending physician, 2 (4.17%) have reported a discontinuation for at least one month, another one (2.08%) stopped taking his medication for one month after the onset of side effects, 6 (12.5%) had a CD4 cell count oscillating at the end of several steps between the 1st and 8th months. Over 81% of patients treated with Triomune were in poor compliance during our study.

Twenty-one patients (43.75%) had a plasma CV ≥ 1000.00 copies/ml after 8 months of treatment with the Triomune. The immuno-virological failure rate with Triomune was 43.75%.

Among the 48 patients, viral load was measured in 25 of them before intiation of treatment. The average VL measured at 8 months of treatment was 66008.62 [1304 - 366,256] copies/ml (**Table 3**).

Table 1. Range of age within the sex.

Range of age	Female	Male	Total
23 - 30	03 (10.7%)	00 (00%)	03 (06.3%)
31 - 40	16 (57.1%)	06 (30%)	22 (45.8%)
41 - 50	08 (28.6%)	09 (45%)	17 (35.4%)
51 - 60	00 (00%)	04 (20%)	04 (8.3%)
>60	01 (03.6%)	01 (05%)	02 (4.2%)
Total	**28**	**20**	**48**

Table 2. Values of LT CD4.

CD4 Values (Cells/mm^3)	**1st Values (J0)**	**2nd Values (M8)**
<200	2 (4.2%)	14 (29.2%)
200 < x < 500	28 (58.3%)	26 (51.2%)
>500	18 (37.5%)	8 (16.6%)

Table 3. Values of viral load.

Viral Load (Copies of RNA/ml)	**1st Values (J0)**	**2nd Values**
<1000	15 (60.0%)	27 (56.25%)
>1000	10 (40.0%)	21 (43.75%)
n	25	48

4. Discussion

This study aimed to determine the treatment failure rate of Triomune administer to People living with HIV (PLHIV), followed at the Infectious Diseases department of the National Reference General Hospital. The failure rate to Triomune in this study was 43.75%. This rate seems to us to be very high in a country where ARVs were subsidized by the state for PLHIV at the time of study. Koyalta *et al.* published in 2009, a rate of treatment failure of first line by 64% of 88 patients followed in N'Djamena [6]. This difference may be due to different modes of recruitment and different study periods.

Over 81% (39/48) of patients were in poor compliance, it may also encourage the emergence of drug resistance which is low genetic barrier to the example of inhibitors non-nucleoside reverse transcriptase inhibitor (NNRTI: Nevirapine, Efavirenz). One mutation such as K103N or Y181C for this group can cause a total and irreversible resistance [7].

This high failure rate may be explained by, among other, the poor adherence to treatment observed in recent years. Poor adherence may have various reasons related to the patient, their environment and the molecule used or health stakeholders. Some patients skip drug intakes, forgetfulness or neglect, which can promote the emergence of HIV resistance to treatment. Others go to traditional healers and marabouts who believe that healing is possible through traditional medicine. It should be noted that this practice is not without consequences as it contributes to the deterioration of the health status of patients who are often subject to many opportunistic infections.

At the time of the study, Triomune was wildly used [10]. It was phased out in the country, in accordance with WHO recommendations, because of its many debilitating side effects (mainly neuropathy, lipodystrophy and glucose disorder) [11] and/or peripheral neuropathy and toxicity [12]. Currently, the new recommendations of therapeutic regimens for countries with limited resources are used in a first line 2 nucleosidic inhibitors (Zidovudine + Lamivudine, Tenofovir + Lamivudine, Tenofovir + Emtricitabine) and 1 NNRTI (Efavirenz or Nevirapine) [13]. These recommendations were adopted by the National Programme for the Fight against AIDS in Chad.

5. Conclusion

The failure rate to Triomune at the National General Reference Hospital (HGRN) was 43.75% (n = 48). To better appreciate this failure rate and highlight the subtypes in question, we will suggest that a large scale study be conducted in all major cities of the country where there are centers of support for People Living with HIV. However, regular laboratory monitoring and patient's education on adherence would be in our opinion a panacea in the fight against AIDS in a country where resources are limited and many patients are illiterate. The difference is not significant between the failure rate and sex ($p < 0.05$). In the light of these finding, we recommend that the National Program stop the use of Triomune for HIV infected patients in Chad.

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Potential Conflicts of Interest

All authors declare that there is no conflicting interest.

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