Original Article

EFFICACY OF HIGHLY ACTIVE TRIPLE ANTIRETROVIRAL THERAPY IN PREVENTING MOTHER-TO-CHILD HIV TRANSMISSION IN THE UNIVERSITY TEACHING HOSPITALS IN YAOUNDE, CAMEROON.

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ABSTRACT:

Paediatric HIV-infection rates remain high in Cameroon in spite of the various existing preventive strategies. This study will provide scientific evidence that HIV-infected pregnant women receiving highly active triple antiretroviral therapy would be expected to have significantly lower viral loads and a lower risk of HIV mother-to-child transmission (MTCT) without scheduled Caesarean section. We enrolled 90 newly diagnosed HIV-infected pregnant women who accepted to participate in the study from the 4 Teaching Hospitals in Yaoundé between January 1, 2006 and December 31, 2008. In addition to routine antenatal care, they received two types of potent triple antiretroviral regimens depending on their initial CD4 counts. Drug efficacy and safety were assessed by CD4 count, viral load, liver enzymes level, fasting blood sugar level, blood urea and haemoglobin concentration level before and after treatment and the paediatric seroprevalence rate. Highly active triple antiretroviral therapy was associated with maternal immunological improvement, statistically significant reduction of maternal viral load ($P< 0.05$) with resultant low paediatric HIV infection rate (1.1%) and minimal maternal biological impairment. Short courses of highly active triple antiretroviral therapy to prevent HIV MTCT is therefore not only efficacious compared to other treatment options like monotherapy, bitherapy, and bitherapy associated with scheduled caesarean section, but also safe and should constitute the mainstay intervention strategy.

KEY WORDS: HIV MTCT- Triple antiretroviral therapy- Adverse effects - Paediatric HIV infection rate.

L'EFFICACITE DE LA PREVENTION DE LA TRANSMISSION MERE-ENFANT DU VIH PAR LA TRI-THERAPIE ANTI-RETROVIRALE DANS LES HOPITAUX UNIVERSITAIRES DE YAOUNDE, CAMEROUN.

RESUME:

Le taux d'infection pédiatrique du VIH demeure élevé au Cameroun malgré les nombreuses mesures préventives existantes. Le but de cette étude était de prouver que les femmes enceintes séropositives recevant une trithérapie anti-rétrovirale auraient une charge virale significativement plus faible avec en conséquence un moindre risque de transmission mère-enfant (TME) du VIH, même en l'absence de la réalisation d'une césarienne élective. Quatre vingt dix femmes enceintes infectées par le VIH et qui avaient accepté de participer entièrement à l'étude ont été recrutées dans les 4 hôpitaux universitaires de Yaoundé entre le 1er janvier 2006 et le 31 décembre 2008. Elles avaient reçu l'un des 2 protocoles de trithérapie antirétrovirale en fonction de leur taux de CD4 initial, en plus des soins prénataux de routine. L'efficacité et la tolérance des médicaments étaient évaluées par le dosage du taux de CD4, la charge virale, le taux des enzymes hépatiques, la glycémie à jeun, l'urée sanguine, le taux d'hémoglobine, ceci avant et après le traitement ainsi que le taux de séroprévalence pédiatrique. La trithérapie antirétrovirale était associée à une amélioration du statut immunologique maternel, une réduction considérable de la charge virale maternelle ($P< 0.05$) avec une baisse conséquente du taux d'infection pédiatrique du VIH (1.1%) et une légère perturbation des paramètres biologiques maternels. Les cures courtes de trithérapie antirétrovirale pour la prévention de la TME du VIH sont non seulement efficaces par rapport aux autres options thérapeutiques (monothérapie, bithérapie ou bithérapie associée à la réalisation de la césarienne élective), mais aussi mieux tolérées et devraient par conséquent constituer la stratégie interventionnelle principale.

MOTS CLES: TME du VIH- Trithérapie antirétrovirale- Effets secondaires- Taux d'infection pédiatrique du VIH.

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I- INTRODUCTION

Mother-to child HIV transmission (MTCT) is the most common aetiology of paediatric HIV infection throughout the world [1]. The increasing number of infected women of childbearing age makes the prevention of MTCT a public health priority in many African countries where antenatal HIV seroprevalence ranges between 20 and 40% [2,3]. The virus may be transmitted during pregnancy, childbirth or breastfeeding [4]. Where no preventive measures are taken, the risk of paediatric HIV infection from the infected mother ranges from 15% to 25% in the industrialized countries and from 20 to 40% in the developing countries [2]. Cameroon government strategic plan for 2006-2010 concerning the prevention of MTCT has consisted of antiretroviral Nevirapine monotherapy or bitherapy (Zidovudine and Nevirapine) during pregnancy for women who are HIV positive or triple therapy for pregnant women with AIDS [5]. Such a therapeutic approach in Cameroon has significantly reduced perinatal transmission over the years from 40% to values ranging between 6-11% [3]. These values still remain extremely higher than the 2% vertical transmission rate in the industrialized countries where triple antiretroviral therapy, scheduled Caesarean sections and artificial feeding constitute the main intervention in preventing MTCT [6]. However, no definitive data are available regarding the risk of HIV transmission to the baby according to the mode of delivery among HIV infected pregnant women receiving potent antiretroviral therapy. In this study, we intended to provide evidence that HIV-infected pregnant women receiving highly active triple antiretroviral therapy without elective caesarean section which carries risk of increased morbidity and mortality can be expected to have significantly lower maternal viral load; with consequently a lower risk of MTCT.

II- MATERIALS AND METHODS

This prospective and descriptive study was enrolled at the 4 teaching hospitals (Central Maternity, University Teaching Hospital, General Hospital and Gynaecologic-Obstetric & Paediatric Hospital) in Yaoundé (Cameroon) from January 1, 2006 to December 31, 2008. Sociodemographic variables including the age, occupation, marital status, religion and regional origin were collected. Other covariates studied were the partner's serostatus, antiretroviral therapy protocol, baby's gestational age at birth, gender, birth weight, placental weight and serostatus. Maternal biological and immunological variables analyzed to evaluate drug efficacy and toxicity were the CD4 count, viral load (VL), fasting blood sugar (FBS), liver enzymes (SGOT, SGPT), blood urea, alkaline phosphatase (PAL) and haemoglobin concentration (Hb). A questionnaire containing the studied variables was filled for each patient. For each variable, the value before and after antiretroviral therapy were compared. All the patients underwent routine antenatal supervision, received haematinics and 3 doses of sulfadoxine-pyrimethamine tablets for malaria prophylaxis. Highly active triple antiretroviral therapy was provided free-of-charge from 28 weeks of gestation to one week post partum when participants were referred to the HIV/AIDS treatment centre at Yaoundé General Hospital for follow-up by one of the researchers. Patients with CD4 count below 250 cells/mm^3 received Nevirapine tablet 200mg twice daily, Lamivudine tablet (150 mg twice daily) and Zidovudine tablet (300 mg twice daily). Those with CD4 count above 250 cells/ mm3 received Lamivudine (150 mg tablet twice daily), Zidovudine (300 mg tablet twice daily) and Alluvia® (combination of Lopimavir and Retonavir) 2 tablets twice daily. This protocol was approved by the different hospital authorities.

During labour, vaginal disinfection with cyteal (hexamidine, chlorhexidine, chlorocresol) was carried out 4-hourly without rupturing the membranes artificially. Episiotomy, milking of cord blood, aspiration of the baby's upper respiratory airways and instrumental vaginal delivery were avoided as much as possible and Caesarean section was performed only for obstetric indications or when maternal viral load exceeded 1000 copies/ml. All newborns were bathed with diluted cyteal solution at birth and received nevirapine suspension, 2mg/kg in a single dose and zidovudine suspension, 4 mg/kg twice daily for 7 days. The babies were formula-fed and lactation was suppressed using bromocriptine orally for 10 days. For the early diagnosis of paediatric HIV infection, PCR assay, the cost of which was borne by the mother, was carried out on each baby 8 weeks after delivery at Centre Pasteur Yaoundé. The sensitivity and specificity of the real-time PCR assay were both 100%, with 95% confidence intervals of 93.7% to 100% and 98.3% to 100% respectively [7].

The prevalence of HIV infection in pregnant women in Cameroon is about 6%. The degree of precision of our study is 0.05 and the confidence interval is 0.05. By applying the Lorentz formula, our sample size should have at least 87 women. Consequently, we recruited cases in the 4 university hospitals for an optimal follow-up until our sample size was attained. All the data were analysed using SAS system for windows. Univariate

analysis was used to generate descriptive statistics and bivariate analysis to compare values of biological and immunological variables before and after treatment using Wilcoxon Signed-Rank Test for 2 dependent samples. The difference was considered significant for P-value less than 0.05.

III- RESULTS

HIV/AIDS is mainly a disease of the sexually active population with a mean age of 31.3 ± 4.7 years (Table I). Out of the 102 patients, 90 patients completed the study; 70% were married, 82.2% unemployed and 50% were Catholics. The majority of their partners (54.4%) were HIV seronegative and 34.4% were HIV infected giving a post-counseling voluntary screening rate of 88.9%. The remaining 11.1% had unknown HIV serostatus because they declined to do the test.

According to the treatment protocol, 70% of patients received Alluvia®, lamivudine and zidovudine (ALZ) combination while 30% had nevirapine, lamivudine and zidovudine (NLZ) combination. Almost all patients (97%) received treatment for at least 9 weeks (Table II). There was a significant reduction of viral load after treatment (Table III). However, one patient with an initial viral load of 139,928 copies /ml and a CD4 count level of 296 cells/ mm3 diagnosed HIV-infected at 34 weeks gestation was treated for only 2.5 weeks prior to delivery. Post treatment CD4 count was considerably improved to 331 cells/ mm3 while viral load was reduced to 530 copies /ml. Of the 90 patients, 89 delivered vaginally (Table IV). Only one patient underwent elective caesarean section for 2 previous sections. The average birth and placenta weights of the 90 apparently healthy babies were 3242 ± 238 gm and 600.0 ± 152.0 gm respectively. Biochemically, no significant difference was observed in the fasting blood sugar and SGOT values before and after treatment ($P > 0.05$) except for SGPT ($P < 0.05$) suggesting viral or chemical hepatitis. Alkaline phosphatase values were significantly increased ($P<0.05$) following treatment but renal function results and haemoglobin values were not significantly affected by treatment ($P > 0.05$). Out of the 90 babies, only 1 was infected giving a paediatric infection rate of 1.1%.

Table I- Distribution of the 90 patients according to age, marital status and partner's sero-status.

	No	Frequency %
AGE (years)		
20-25	15	16.7
26-31	22	24.4
32-37	48	53.3
38-43	5	5.6
Total	**90**	**100**
MARITAL STATUS		
Married	63	70.0
Unmarried	17	18.9
Cohabitation	9	10.0
Widow	1	1.1
Total	**90**	**100**
PARTNERS HIV SEROSTATUS		
HIV positive	31	34.5
HIV negative	49	54.4
Unknown	10	11.1
Total	**90**	**100**

Table II- Distribution of the 90 patients according to treatment protocol.

	No	Frequency (%)
Treatment protocol		
NVP+LAM+AZT	27	30
ALU+LAM+AZT	63	70
Total	**90**	**100**
Duration of treatment (weeks)		
<3	1	1.1
9-10	20	22.2
11-12	59	65.6
13-14	9	10.0
Total	**90**	**100**

Table III- Biological and immunological variables of the 90 patients.

Variable	No	Mean	SD	Minimum	Maximum	P-value
Pre-CD4 (cells/mm3	90	296.5	180.4	12	547	
Post CD4	90	345.3	115.2	171	546	0.10
Pre VL (copies/ml)	90	79581.5	124.0	49	338042	
Post VL	90	224.8	329.7	49	1000	0.0039*
Pre FBS (mg/dl)	90	71.78	10.51	61.0	90.0	
Post FBS	90	66.6	9.98	47.0	77.2	0.1719
Pre SGOT (iu/l)	90	29.82	11.44	5.0	45.0	
Post SGOT	90	26.0	9.19	10.00	40.0	0.6250
Pre SGPT	90	21.72	10.49	7.0	34.5	
Post SGPT	90	13.94	5.87	6.50	24.0	0.0078*
Pre PAL (U/l)	90	148.8	97.79	38	267.0	
Post PAL	90	187.17	92.4	63.5	316.0	0.0039*
Pre Urea (mg/dl)	90	14.69	5.68	7.0	26.0	
Post Urea	90	13.79	4.46	8.0	22.10	0.3828
Pre HB (gm/dl)	90	10.84	0.64	9.88	11.70	
Post HB	90	10.9	0.91	8.88	12.0	0.6406

* Statistically significant

Table IV- Distribution of the 90 patients according to gestational age at delivery, mode of delivery and baby's serostatus

	No	Frequency (%)
Gestational age at birth (weeks)		
<37	2	2.2
37-42	88	88.8
Total	**90**	**100**
Mode of delivery		
Vaginal route	89	98.9
Caesarean section	1	1.1
Total	**90**	**100**
Baby's HIV serostatus		
HIV positive	1	1.1
HIV negative	89	98.9
Total	**90**	**100**

IV- DISCUSSION

Our results have shown that HIV/AIDS remains mainly a disease of the middle aged, sexually active population reflected in the mean age of 31 years and data showing that 70% patients were married and 82% unemployed. Expectedly, almost half of participants are from the centre region where the study was carried out. With regards to HIV status, 54% of partners were HIV seronegative, 34% seropositive and 11% declined to do the screening test giving a voluntary post-counseling acceptance rate of 88.9%, a figure relatively higher than the 78% rate reported in the general population [8].

According to our results, potent triple antiretroviral therapy administered for at least 8 weeks from 28 weeks gestation leads to a significantly low maternal viral load at delivery ($P<0.05$) and consequently to a very low paediatric infection rate (1.1%) without the need for scheduled Caesarean section compared to existing values using other treatment options [1,3,6]. All the

patients who received treatment for at least 8 weeks had a significant reduction in the viral load with absolute immunological improvement (Table III). One patient with an initial viral load of 139,928 copies /ml and a CD4 count level of 296 cells/ mm3 diagnosed HIV-infected at 34 weeks gestation was treated for only 2.5 weeks prior to delivery. She was the only patient whose baby was tested HIV positive giving a paediatric infection rate of 1.11%. However, antiretroviral therapy has been associated with adverse effects on lipid metabolism with possible cardiovascular disease, liver, renal and haematological toxicity [9,10,14]. Fortunately, short courses of potent triple antiretroviral therapy in pregnancy to prevent MTCT suggest that there may be slight significant adverse effects in the short term. Fasting blood sugar, SGOT, haemoglobin concentration values and renal functions before and after antiretroviral treatments were not significantly impaired ($P > 0.05$). The only liver enzymes which was significantly increased was SGPT ($P < 0.05$) possibly indicating viral hepatitis or chemical hepatitis from drug toxicities [9,12,14]. In addition, the significant increase in post treatment alkaline phosphatase values ($P<0.05$) could be more of trophoblastic than of hepatic origin [15].

Although the benefits of triple antiretroviral therapy for both mothers and their babies are apparent and cannot be overemphasized, all antiretroviral drugs should be prescribed with caution and closely be monitored with relevant clinical and laboratory indices, especially in pregnancy.

V- CONCLUSION AND RECOMMENDATIONS

Our results suggest that short courses highly active triple antiretroviral therapy (at least 8 weeks) from 28 weeks gestation to prevent HIV MTCT is efficacious compared to other treatment options and generally safe with minimal adverse effects. It is associated with such a significantly low maternal viral load that scheduled Caesarean section becomes unnecessary. Routine antenatal counseling and HIV screening, the use of triple antiretroviral therapy in HIV infected expectant mothers and the strict application of the preventive obstetric measures in labour as well as artificial feeding of the newborns appear the ideal intervention strategy for preventing paediatric HIV infection in Cameroon. Government subvention for triple antiretroviral therapy in HIV infected pregnant women would significantly reduce pediatric HIV infection in Cameroon ■

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