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TRIMESTRAL EVALUATION OF THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON THE VIRAL LOAD, LIVER AND KIDNEY FUNCTION TESTS OF HIV PREGNANT WOMEN IN THE EAST REGION OF CAMEROON

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ABSTRACT
Highly active antiretroviral is administered to all HIV positive pregnant women in Cameroon since 2012 for viral suppression, health improvement and prevention of HIV transmission to the babies. We evaluated the effect of this therapy on the viral load, liver and kidney function tests of HIV positive pregnant women in the East region of Cameroon.A prospective cohort study that lasted a year involving consented naïve to treatment HIV-infected pregnant women from three catchment health facilities in the East region. Real-time PCR viral load and spectrophotometric measures of ASAT, ALAT and blood creatinine were realized every two months. Data analysis was done using Graph Prism. Level of statistical significance was set $p< 0.05$.Fifty-three (53) women made up the cohort aged 15 - 40 (mean 27.28 ± 5.84) years. Baseline means of their log_{10} viral load, serum aspartate aminotransferase, serum alanine aminotransferase and serum creatinine levels were respectively 4.84, 22.81, 9.77 and 0.78. Six months on ART, the viral load was significantly undetectable ($p < 0.0001$) and ALAT significantly elevated to 16.46 IU/mL ($p = 0.0022$). However, ASAT and Creatinine levels were elevated to a statistical non-significant levels of 27.36 IU/mL ($p=0.6432$) and 0.83 mg/dL ($p= 0.2936$) respectively. Option B+ offers antiretroviral drugs indiscriminately to all pregnant HIV+ women that can effectively suppress their viral load but precautions to avoid liver and kidney adverse effects on the long run are needed.

KEYWORDS: Pregnant, Viral load, Option B+, HAART, Transaminases, Creatinine.

INTRODUCTION
Global morbidity and mortality of women of child-bearing age and children below 15 years of age has tremendously been impacted by the human immune deficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).[1][2] Several efforts have been undertaken globally by Governments, NGOs and other sectors in a bit to curb this tendency and meet the UNAIDS objectives 90, 90, 90 by 2020. Howbeit, in 2018, 4.49% (1.7 million) of the estimated 37.9 million people living with HIV globally, were children between the ages 0-14 years.[3] Over 95% of paediatric HIV infections result from mother-to-child transmission (MTCT) which can occur during pregnancy, labour, delivery or during the postpartum from breastfeeding.[4] The rate of MTCT of HIV varies between 20% to 45%, with 15% to 30% transmission risk in utero or at delivery, and 5% to 20% risk through breastfeeding. The overall transmission risk is approaching 30% to 60% in Low- and Middle - Income Countries (LMIC).[5][6] The risk of MTCT can be reduced to lesser than 2% by interventions that include antiretroviral (ARV) prophylaxis or treatment given to women during pregnancy and labour and to the infant in the first weeks of life. Also, measures like enhanced delivery techniques and complete avoidance of breastfeeding are being employed.[5]

Cameroon, one of the 22 PMTCT priority countries adopted in 2012, the WHO option B+ strategy to prevent mother-to-child transmission of HIV. Here, all HIV+ pregnant women and lactating mothers are placed on ART irrespective of their clinical stage and their new-borns on NVP prophylaxis as from birth. This treatment

modality reduces maternal mortality and morbidity for HIV infected women and is known to be the most effective method of preventing MTCT of HIV. It secures the health of the infected woman and improves the chances of survival of her child, therefore, the child's survival strongly depends on the mother's survival[7][8] The objectives of this strategy are to have her viral load suppressed to undetectable levels, maintain her health and prevent the transmission of HIV to her baby. According to UNAIDS objectives 90, 90, 90, at least 90% of all HIV+ pregnant and lactating women placed on antiretroviral should have their viral load suppressed. This study is therefore aimed at evaluating the effect of antiretroviral on the viral load, liver and kidney functions of HIV+ pregnant women in the East Region of Cameroon.

MATERIALS AND METHODS

2.1 Study site and Population

This study was carried out at the Bertoua (Mokolo 1 Integrated Health Centre and Bertoua Regional Hospital) and Garoua Boulai (Gado Badzere Integrated Health Centre) Health Districts, in the East Region of Cameroon. The population involved naive to highly active antiretroviral therapy (HAART) HIV infected pregnant women who accepted to be initiated on HAART, attending antenatal care (ANC) visits and were to deliver at study sites.

2.2 Participant recruitment and Sampling

In a prospective analytical multi-centric cohort study involving all voluntary ART-naïve HIV-infected pregnant women from February 2018 until February 2019 who accepted to be placed on ART, respected their ANC appointments and delivered at their respective catchment sites. Sampling was by the convenience of occurrence to minimize issues of stigmatization and discrimination. Participants were enrolled after submitting signed informed consent forms. They were assisted to fill structured questionnaires to obtain socio-demographic and clinical data, placed on ART and then follow-up until 6 weeks postpartum (See appendices 1 and 2). The participants were excluded if they were known HIV infected pregnant women on HAART, refused to sign the informed consent form, having known comorbidities or were lost to follow-up. Delivery was the study endpoint.

2.3 Laboratory analysis

Venous blood was collected into two tubes, EDTA and dry, at a two-monthly interval for viral load (by real-time PCR using GENERIC HIV CHARGE VIRALE, BIOCENTRIC, Bandol, France) and for spectrophotometric analysis of ASAT, ALAT and creatinine (using mindray BA-88A, Mindray Medical India Pvt. Ltd. Gurugram, India) respectively at the Bertoua regional hospital laboratory. The upper limits (UL) used for transaminase and creatinine analysis in the female population was set at ASAT UL: <31 IU/L, ALAT UL: <32 IU/L and creatinine UL: <1.1 mg/dL for both this study and by the laboratory. Undetectable viral load was set at < 390 copies/ml (<2.6 $\log_{10}$ copies/ml). While suppressed viral load was set at < 1000 copies/ml.

2.4 Statistical analysis

Data obtained from the questionnaires were entered and managed in MS Excel spreadsheets. And then, imported to Graph Prism (Graph pad 6.0, San Diego, USA) before analysis. The mean (± standard deviation) for continuous characteristics (such as age) and the frequency of categorical characteristics (such as marital status) were described for the study participants. The Fisher exact and Chi-square tests were used to evaluate associations and statistical significance of the distribution of the outcome among the different variables. Differences were considered significant when $p< 0.05$.

RESULTS

3.1 Socio-demographic of participants

Study participant characteristics are detailed in Table 1. It is worth mentioning that seventy women were enrolled in the study; however, 17 were lost to follow – up making an effective cohort of 53 women. Their age ranged between 15 – 40 years with a mean age of 27.28 ± 5.84 years. Most of whom had at least a secondary education and were married. Closed to 60% of the study participants sorted antenatal care at the 3rd trimester of their pregnancy and they were diagnosed and placed on ART late.

Table 1: Sociodemographic characteristics of study participants.

Characteristics		Observation (n)	Percentage (%)
Age		27.28 ± 5.84	
Religion	**Christian**	42	79.25
	Muslim	11	20.75
Level of education	**< Secondary**	17	32.08
	≥ Secondary	36	67.92
Marital status	**Single**	16	30.19
	Married	37	69.81
Profession	**Housewife**	22	41.51
	Others	31	58.49
Trimester at HIV diagnosis	**1st**	2	3.77
	2nd	21	39.62
	3rd	30	56.60

3.2 Trimestral evaluation and evolution of participants' viral load, transaminase and creatinine levels

Patients were stratified based on the severity to the infection (viral load [VL]) and how functional their liver and kidney were as shown in Tables 2, 3 and 4. For viral load evaluation, they were stratified into undetectable, suppressed (VL < 1000 copies/ml),]1000 – 50 000] copies/ml, and > 50 000 copies/ml. In addition, for transaminase and creatinine levels they were stratified into normal (ASAT < 31 IU/L, ALAT < 32 IU/L and Creatinine < 1.1mg/dL) and abnormal (ASAT > 31 IU/L, ALAT > 32 IU/L and Creatinine > 1.1mg/dL).

Baseline data showed that 16.87% (10) of these participants had an undetectable viral load, 83.13% (43), 98.11% (52) and 98.11% (52) had normal values for ASAT, ALAT and Creatinine respectively as shown in Tables 2, 3 and 4 below. After six months on ART, 100% had a statistically significant undetectable viral load (p< 0.0001) while 81.82% had a normal ASAT, 100% had a normal ALAT and 100% had a normal creatinine with no statistically significant difference between normal and abnormal cases (p= 0.73, p= 0.6122 and p= 0.228 respectively). Here, we noticed that the number of cases with suppressed viral load was increasing with time with the highest after 4 months on ART, whereas normal transaminase and creatinine cases were decreasing with time on ART and noticeable after 2 months on ART.

Table 2: Classification of Participants according to viral load count at the various follow-up periods.

Viral Load (copies/mL)	T0: N (%)	T1: N (%)	T2: N (%)	T3: N (%)	p-value (χ2)
Undetectable	10 (18.87)	12 (32.43)	18 (75)	11 (100)	**<0.0001 (53.38)**
≤ 1000	1 (1.89)	1 (2.70)	1 (4.17)	0 (0)	
[1000 - 50,000]	16 (30.18)	18 (48.65)	5 (20.83)	0 (0)	
> 50,000	26 (49.06)	6 (16.22)	0 (0)	0 (0)	

Table 3: Classification of Participants according to Liver Transaminase measurements at the various follow-up periods.

Liver transaminase activity (IU/L)		T0: N (%)	T1: N (%)	T2: N (%)	T3: N (%)	p-value (χ2)
ASAT (IU/L)	**Normal (<31 IU/L)**	43 (81.13)	27 (72.97)	20 (83.33)	9 (81.82)	0.73 (1.29)
	Abnormal (>31 IU/L)	10 (18.87)	10 (27.03)	4 (16.67)	2 (18.18)	
ALAT (IU/L)	**Normal (<32 IU/L)**	52 (98.11)	37 (100)	23 (95.83)	11 (100)	0.6122 (1.81)
	Abnormal (>32 IU/L)	1 (1.89)	0 (0)	1 (4.17)	0 (0)	

Table 4: Classification of Participants according to Creatinine measurements at the various follow-up periods.

Creatinine (mg/dL)	T0: N (%)	T1: N (%)	T2: N (%)	T3: N (%)	p-value (χ2)
Normal (<1.1 mg/dl)	52 (98.11)	34 (91.89)	24 (100)	11 (100)	0.228(4.33)
Abnormal (>1.1 mg/dl)	1 (1.89)	3 (8.11)	0 (0)	0 (0)	

Analytically, prior to treatment initiation means of their $\log_{10}$ viral load, serum aspartate aminotransferase, serum alanine aminotransferase and serum creatinine levels were respectively 4.84 (CI: 3.90 - 5.78), 22.81 (CI: 4.88 - 40.74), 9.77 (CI: 3.02 - 16.52) and 0.78 (CI: 0.63 – 0.93). However, after receiving ART for six months, the viral load was significantly suppressed to an undetectable levels (p < 0.0001) and ALAT significantly elevated to 16.46 IU/L (C I: 15.5 - 39.22, p = 0.0022) as detailed in Tables 5, 6 and 7. ASAT and Creatinine levels were elevated to a statistical non-significant levels of 27.36 IU/L (CI: 9.79 - 23.13, p=0.6432) and 0.83 mg/dL (CI: 0.73 – 0.93, p= 0.2936) respectively (table 5; figs 1 and 2).

Table 5: Comparison of participants' log10 VL, ASAT, ALAT and Creatinine means over time.

Parameter	T0: Mean (SD)	T1: Mean (SD)	T2: Mean (SD)	T3: Mean (SD)	p-value
	N=53	N= 37	N= 24	N= 11	ANOVA
Log_{10} VL (copies/mL)	4.84 (1.17)	3.98 (0.94)	3.38 (0.31)	*Und (0)	**< 0.0001**
ASAT (IU/L)	22.81 (17.93)	24.49 (10.06)	26.54 (11.04)	27.36 (11.87)	0.6432
ALAT (IU/L)	09.77 (6.75)	12.76 (6.08)	14.71 (7.01)	16.46 (6.67)	**0.0022**
Creatinine (mg/dL)	0.78 (0.15)	0.84 (0.17)	0.8 (0.14)	0.83 (0.10)	0.2936

: undetectable was considered as 0

Table 6: Comparison between participants' different log_{10} VL means.

	Comparison	Mean Diff,	p-value
Log_{10} VL (copies/ml)	T0 vs. T1	0.86	< **0.0001**
	T0 vs. T2	1.46	< **0.0001**
	T0 vs. T3	4.84	< **0.0001**
	T1 vs. T2	0.6	**0.0155**
	T1 vs. T3	3.98	< **0.0001**
	T2 vs. T3	3.38	< **0.0001**

Table 7: Comparison between participants' different ALAT means.

	Comparison	Mean Diff,	p-value
ALAT (IU/L)	T0 vs. T1	-2.99	0.1385
	T0 vs. T2	-4.94	**0.0163**
	T0 vs. T3	-6.69	**0.0163**
	T1 vs. T2	-1.95	0.4554
	T1 vs. T3	-3.7	0.2839
	T2 vs. T3	-1.75	0.4681

There was a statistically significant difference in the evolution of viral load and the number of participants with detectable, suppressed, and undetectable viral load ($p < 0.0001$). Contrarily, no statistically significant differences were obtained for transaminase and creatinine evolutions and between their respective normal and abnormal cases ($p = 0.73$, $p = 0.6122$, and $p = 0.228$).

It was also revealed that participants' log_{10} viral load was decreasing as time went on from 4.84 ± 0.94 at initiation (T0), to 3.98 ± 0.85 after eight weeks on treatment (T1), then to 3.38 ± 0.32 after sixteen weeks on treatment (T2) and finally to undetectable viral load after twenty – four weeks on treatment (T3). Also, remarkably, one participant was found with a suppressed viral load and eight weeks later achieved an undetectable viral load. However, their transaminase and creatinine levels were rather increasing over time as shown in Tables 2 – 4 and Figs 1 – 2.

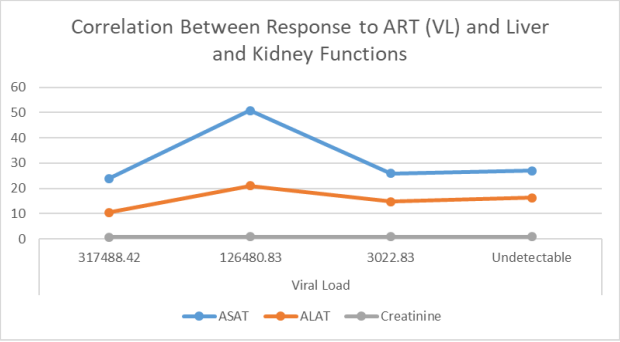

Figure 1: A relationship between VL and Liver and Kidney Functions over time.

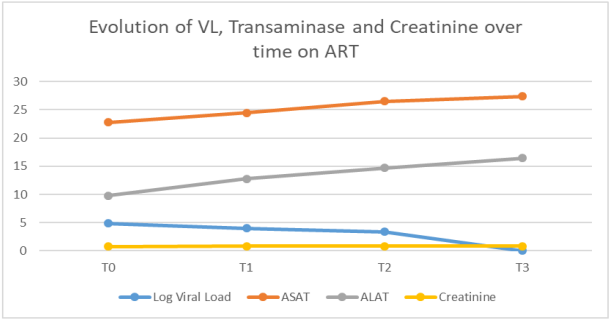

Figure 2: Evolution of participants' VL, transaminase and creatinine over time on ART.

DISCUSSION

The cohort constituted 53 HIV positive pregnant women aged between 15 – 40 years with a mean age of 27.28 ± 5.84 years. Most of whom had at least a secondary education and were married representing approximately 70% of our study population. Close to 60% of these women were involved in an income-generating activity or profession apart from being a housewife. The observed age range correlates with the increased prevalence of HIV globally, as it is a sexually active age group with most women having a greater desire to bearing children.

Ottop *et al*, in 2020 said 'loss to follow-up' was associated with the Muslim religion, primary education and being a housewife.[9] Looking at the socio-demographic data of our study participants, we can say their profile justified their retention in PMTCT care.

Although our participants adhered to their treatment until study endpoint, most were screened HIV positive at their third-trimester antenatal visit and so they were placed on ART late. Hence a shorter time on ART before delivery. Clayden made a similar observation in 2013 with 74% of

their participants initiating ART in the third trimester.[10] Being screened HIV positive at the third trimester does not necessarily mean their first antenatal visit was done in the third trimester.

18.87% of our study participants, before treatment, had undetectable viral load; at study endpoint, they all had a significantly undetectable viral load. Similarly, Gill *et al* in 2016 had 15.4% of their participants with an undetectable viral load.[11] In a previous study in Cameroon in 2011 by Njom - Nlend *et al*, 13% of their participants were diagnosed with HIV with an undetectable viral load.[12] Being diagnosed with an undetectable viral load will mean one of two things, that diagnosis was done just about the time of infection and/or the individual's immune system was not yet compromised. However, more research needs to be carried to confirm this. Conversely, more than 80% of our study population had normal liver and kidney functions at baseline and our study's endpoint, though with no significant difference between normal and abnormal cases.

In this study, we quarterly follow-up viral load, transaminase and creatinine levels in HAART-naïve HIV positive pregnant women until delivery in the EAST Region, Cameroon. An understanding of changes in maternal VL, liver transaminases and creatinine following ART initiation is particularly important, as there is a global increase in the number of pregnant women being placed on ART.[13]

The mean VL, ASAT, ALAT and Creatinine levels at baseline were 4.84-log10 copies/mL, 22.81 IU/L, 9.77 IU/L and 0.78 mg/dL respectively. Our baseline VL was higher than that obtained by Myer *et al*, 2017, who registered a mean VL at initiation on ART of 3.9 log 10 copies/mL.[14] This difference can be explained by the fact that some of the women who Myer *et al* enrolled in their study were reinitiating ART during pregnancy, hence a lower viral load than our participants. The high viral load confirms our participants were indeed primo-infected with HIV as it is with the normal course of HIV infection without treatment. Overall, we had a significant decrease ($p<0.0001$) in the mean value of HIV load with time, similar to what Chendi *et al* (2019) had in a study carried out in Yaounde, Cameroon.[15]

Tesfa *et al* in 2019 recorded a baseline ASAT of 28.00 UI/L and creatinine of 0.641 mg/dL similar to what we observed but a with higher baseline ALAT of 23.97 UI/L than what we obtained.[16] Though there was a higher ALAT level in Tesfa *et al* study than ours, it is worth noting that all these biochemical parameters were normal. This implies that before ART, most newly diagnosed HIV individuals are relatively healthy with a well-functioning liver and kidney. Early detection of a primo infection to HIV may mean a high viral load in a relatively healthy body with well-functioning organs. Hence a perfect avenue or scenario for ART initiation, thus our findings strongly support the test and treat strategy being implemented in Cameroon.

We noticed a two-monthly statistically significant decreased in participants' log VL indicative of the effectiveness of the antiretroviral treatment combination used. However, a modest and statistically significant elevation in ALAT activity was observed as from four months on treatment as well as a modest but non-significant elevated ASAT and creatinine levels. Looking at this trend, we would say that viral suppression and liver, as well as kidney toxicity, is time-on-ART dependant. And, the level of significance increases with time-on-ART as confirmed by other studies. Kovari *et al.* in 2016, for example, observed a significantly elevated level of ALAT with most of the drugs used in the treatment of HIV-infected individuals.[17] They observed that chronic liver enzyme elevation was associated with short-and long-term exposure to tenofovir disoproxil fumarate (<2 years RR=1.55, 95% CI, 1.29 – 1.61) and short-term exposure to efavirenz (<2 years RR=1.14, 95% CI, 1.03 – 1.26). Thus, our observation of a modest but not significant elevation of ASAT and creatinine level may be due to the very short evaluation time (duration on ART of six months).

Our study did not seek to find out factors that may influence or predispose our participants to the observed changes in viral load, transaminase and creatinine levels because of financial constraints. Nevertheless, the strength of this study includes its conduct in a real-life resource-limited setting and its design.

CONCLUSIONS

Most pregnant women are diagnosed in the third trimester of pregnancy with high viral load indicative of primo-infection but with a relatively well functioning liver and kidney required for a favourable metabolism of ARV drugs. These findings support the adoption of the 'test and treat' strategy and the Option B+ approach being implemented in our country. Option B+ provides antiretroviral drugs indiscriminately to all pregnant HIV+ women that can effectively suppress their viral load but with adverse effects on their liver and kidney functions with time.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

OFM, JCNA, MRE and NNM conceived the research question and designed the study. OFM collected data and conducted laboratory assays. JCNA and MRE helped design the study question, assisted with data collection, analyzed data and assisted with data interpretation. All authors wrote and/or reviewed the manuscript.

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