World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Original Article

Changes in hematological profile of HIV infected pregnant women after receiving highly active antiretroviral therapy at Debreberhan referral hospital and Debreberhan health center, Debreberhan, Ethiopia

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Received: 06-06-2017 / Revised Accepted: 18-07-2017 / Published: 01-08-2017

ABSTRACT

Background: Hematological complications have been documented to be the second most common cause of morbidity and mortality in HIV positive persons. In addition, treatment of HIV/AIDS showed side effects on hematological parameters. This study assessed hematological profile of HIV infected pregnant women after initiation of highly active antiretroviral treatment including the new Tenofovir drug.
Method: Retrospective cohort study was conducted to assess hematological profile of HIV infected pregnant women after initiation of HAART at Anti-Retroviral Therapy (ART) clinic of Debreberhan referral hospital and Debreberhan health center in Ethiopia from January to August 2016. Data was collected from 51 patient cards of pregnant women that are available at the two health facilities between September 2009 and August 2016.The data was entered into Excel spread sheet and it was transported into STATA software for analysis. All data were presented as mean ± Standard error of the mean. Comparisons were made using the Paired T-test. A p-value of <0.05 was considered as indicative of a statistically significant difference.
Result: The result from the present study shows that the HAART initiation in pregnant women with HIV increases the CD4 cell count and decreases means corpuscular hemoglobin concentration whereas other hematological parameters assessed here (WBC, lymphocyte count, total mid cell count… PCT) are not significantly affected at ninety five percent confidence interval. From the total of fifty one patient cards with complete CD4 count, twenty nine patient cards were recorded with TDF/3TC/EFV ART regimen. The remaining twenty two patient cards were documented with AZT/3TC/NVP regimen. Comparing the effect of the two Regimens on CD4 count, TDF/3TC/EFV increases the CD4 count significantly in pregnant women with HIV ($p<0.0001$). The other regimen (AZT/3TC/NVP) also increases the CD4 count from initial value as it is indicated by positive paired mean difference but this increase in CD4 count after AZT/3TC/NVP initiation in pregnant women with HIV is not statistically significant at 95 percent confidence interval.
Conclusion: HAART initiation in pregnant women with HIV increases the CD4 cell count and decreases means corpuscular hemoglobin concentration. TDF/3TC/EFV ART regimen increases the CD4 count in pregnant women with HIV.

Keywords: Hematological parameters, HAART, HIV positive pregnant women, Tenofovir

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How to Cite this Article: Kassahun Dires, Tizazu Zenebe, Nigus Zegeye. Changes in hematological profile of HIV infected pregnant women after receiving highly active antiretroviral therapy at Debreberhan referral hospital and Debreberhan health center, Debreberhan, Ethiopia. World J Pharm Sci 2017; 5(8): 189-194.

INTRODUCTION

HIV killed more than 34 million lives so far. In 2014, 1.2 million people died from HIV-related causes globally. There were approximately 36.9 million people living with HIV at the end of 2014 with 2.0 million people becoming newly infected with HIV in 2014 globally, Sub-Saharan Africa, with 25.8 million people living with HIV in 2014. Also sub-Saharan Africa accounts for almost 70% of the global total of new HIV infections, it is estimated that currently only 51% of people with HIV know their status. In 2014, 14.9 million people received ART globally, of which 13.5 million were receiving ART in low- and middle-income countries. The 14.9 million people on ART represent 40% of people living with HIV globally [1].

In Ethiopia, the 2014 estimated number of people living with HIV was 769, 600 with15, 700 new HIV infections and 35, 600 AIDS-related deaths [2]. HIV is characterized by progressive damage to the body's immune system which results in the development of a number of opportunistic infections and other complications [3]. The most important biomarkers of disease stage and progression in patients with an HIV infection are the CD4 count and HIV RNA concentration [4]. However, there are other factors that can influence or predict the prognosis. Hematological abnormalities, such as anemia, neutropenia, and thrombocytopenia, are commonly observed in patients infected with HIV [5]. For this reason the total lymphocyte count, white blood cell count, and hematocrit or hemoglobin concentration have been proposed as alternative markers of the disease, especially for developing countries where financial resources are limited [6]. ART is treatment for AIDS that helps the body's immune system recover from the damage caused by infection with HIV. Although ART cannot cure AIDS, persons on ART will begin to feel better, eat more, and put on weight. Their bodies will recover the ability to fight infections. [7]. The introduction of highly active antiretroviral therapy (HAART) has led to significant reduction in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality. Adverse drug reactions (ADRs) to antiretroviral treatment (ART) are, however, major obstacles in its success. The science of antiviral research was well advanced when HIV/AIDS appeared as a major new virus disease in the early 1980s. The first effective antiviral compound (AZT, zidovudine) was already among the library of compounds screened [8]. HAART drugs aim at reducing HIV- related morbidity and mortality, reducing the viral load (to undetectable levels) for as long as possible in order to halt disease progression and prevent or reduce resistant variants. They also achieve immune reconstitution that is quantitative (CD4 count in normal range) and qualitative (fewer infections and illnesses [8].

Anti-retroviral drugs can have serious side effects such as diarrhea, nausea or abnormal distribution of body fats. Abnormal distribution of body fat is common for protease inhibitors. Even though lamivudine (3TC) is the safest drug, hepatotoxicity and sever rash is more likely to happen with nevirapine (NVP). Efavirenz (EFV) is known for its unwanted CNS effects like insomnia [9]. Currently, stavudine is placed as last option because of peripheral neuropathy and sever lactic acidosis. It has been reported that Tenofovir (TDF) is relatively safe when it is compared with other NRTIS like Zidovudine and stavudine but sometimes kidney failure may occur with TDF. Some common side effects on hematological parameters have been reported from the use of Zidovudine (AZT) [9]. These side effects include among others anemia and neutropenia [10]

The Centre for Disease Control (CDC) advocates that before the use of any anti- retroviral therapy, the safety and efficacy of the drug should be tested [11]. All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk . A once-daily fixed-dose combination of TDF + 3TC + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. After failure on a TDF + 3TC (or FTC) -based first-line regimen, AZT + 3TC is used as the NRTI backbone in second-line regimens [1].
There are limited studies conducted on hematological changes in pregnant women after starting HAART regimen in developing countries especially in Ethiopia and there is no published data showing this change in hematological parameters. This study, therefore, provide information about the change of hematological profile in pregnant women after HAART regimens which may contribute in improving the management of patients after initiation of ART. Moreover, this study provides information for clinicians whether HIV positive pregnant women need frequent hematological tests

MATERIALS AND METHODS

Study design and settings: Retrospective cohort study was conducted to assess hematological profile of HIV infected pregnant women after initiation of HAART at ART clinic of Debreberhan referral hospital and Debreberhan health center in

Ethiopia from January to August 2016.The type of ART regimen, hematological data (White blood cells, CD4+ T cells, hemoglobin, and Platelet count) and values for other hematological indices were carefully extracted from 51 patient follow up cards that were available between September 2009 and August 2016 by using a standardized data extraction form. Ethical clearance was obtained from the Ethics Review Committee of the College of Medicine, Debreberhan University. Official letter was given to the heads of the health facilities to obtain permission to collect the data. Personal identifiers of the patients were kept confidential**.**

Data quality Control: The quality of data was controlled at different levels for completeness and consistency; first by data collectors at the end of each day, then by supervisors every day.

Data processing and analysis: The data was entered into Excel spread sheet and it was transported into STATA software for analysis. All data were presented as mean ± Standard error of the mean. Comparisons were made using the Paired T-test. A p-value of < 0.05 was considered as indicative of a statistically significant difference**.**

RESULT

This study showed that the HAART initiation in pregnant women with HIV increases the CD4 cell count and decreases means corpuscular hemoglobin concentration whereas other hematological parameters assessed; such that, total WBC, lymphocyte count, total mid cell count, PCT and RBCs are not significantly affected at ninety five percent confidence interval. Among a total of 51 pregnant women, twenty nine patients received TDF/3TC/EFV ART regimen and the remaining twenty two patients received AZT/3TC/NVP (table 1, 2).

Table 1: shows the number of patient cards taken for analysis for each hematological parameter.

Hematological parameter	The number of complete patient cards collected and analyzed	
	number	**%**
CD4 count	**51**	**100**
WBC count	**22**	**43**
Lymphocyte count	**21**	**41**
Total mid cell count	**20**	**39**
Granulocyte count	**14**	**27**
RBC count	**20**	**39**
Total haemoglobin	**27**	**53**
Hematocrit	**21**	**41**
Mean cell volume	**21**	**41**
Mean cell hemoglobin	**20**	**39**
Mean cell hemoglobin concentration	**20**	**39**
Red cell distribution width coefficient of variation	**20**	**39**
Total platelet count	**27**	**53**
Mean platelet volume	**20**	**39**
PCT in percent	**19**	**36**

Table 2: shows the number of study participants per treatment regimen

ART regimen	**Number of patient cards per regimen**	
	number	**%**
TDF/3TC/EFV	**29**	**56.68**
AZT/3TC/NVP	**22**	**43.32**
total	**51**	**100**

Comparing the effect of the two Regimens on CD4 count, TDF/3TC/EFV increases significantly the CD4 count in pregnant women with HIV ($p<0.0001$). The other regimen (AZT/3TC/NVP) also increases the CD4 count from initial value as it is indicated by positive paired mean difference but this increase in CD4 count after AZT/3TC/NVP initiation in pregnant women with HIV is not statistically significant at 95 percent confidence interval ($p>0.05$, table 3). Describing the effect on other hematological parameters, HAART initiation in pregnant women with HIV increases the value of lymphocyte count, total mid cell count, red blood cell count, total hemoglobin, hematocrit, mean cell volume, total platelet and PCT in percent as the paired mean difference is positive but the

increments are not significant at ninety five percent confidence interval. On the contrary, the initial value of white blood cell count, granulocyte count, mean cell hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width and mean platelet volume decreases after antiretroviral treatment in pregnant women with HIV because the paired mean difference is negative but still the decrease is not significant at 95 % confidence interval (p>0.05)(table 4).

Table 3: CD4 T-cell changes in pregnant women with HIV per treatment regimen

ART regimen	CD4 before	CD4 after	Paired mean difference	P-value
TDF/3TC/NVP	333±27.09	517±47.33	184±38.10	**P<0.0001**
AZT/3TC/NVP	335±56.80	374±40.47	39±37.24	**P>0.05**

Table 4: Hematological changes in pregnant women with HIV after HAART initiation.

Hematological parameter	Before HAART (baseline)	After HAART	N	Paired mean difference	P-value
CD4 count	334±29.54	435±30.44	51	101±24.85	**P<0.0001**
WBC count	5.78±0.78	5.47±0.48	21	-0.31±0.82	**P>0.05**
Lymphocyte count	1.68±0.11	1.77±0.10	20	0.09±0.12	**P>0.05**
Total mid cell count	0.43±0.02	0.48±0.04	19	0.05±0.04	**P>0.05**
Granulocyte count	2.45±0.29	2.27±0.26	13	-0.18±0.28	**P>0.05**
RBC count	4.34±0.14	4.46±0.17	19	0.12±0.15	**P>0.05**
Total hemoglobin	14.65±0.52	14.68±0.42	26	0.03±0.49	**P>0.05**
Hematocrit	41.45±0.94	42.35±1.09	20	0.90±1.22	**P>0.05**
MCV	95.47±2.18	96.05±1.99	20	0.58±1.39	**P>0.05**
MCH	34.20±0.91	33.41±0.79	19	-0.79±0.27	**P>0.05**
MCHC	35.68±0.35	34.64±0.31	19	-1.04±0.39	**P<0.05**
RDWCV	13.68±0.26	13.17±0.25	19	-0.51±0.31	**P>0.05**
Total platelet	2.34±15.68	2.54±19.34	19	0.20±24.07	**p>0.05**
Mean platelet volume	10.03±0.50	9.95±0.41	19	-0.08±0.61	**P>0.05**
PCT in %	0.22±0.01	0.24±0.01	18	0.02±0.01	**P>0.05**

Note: all values are expressed as Mean ± standard error of the mean
- P< 0.0001- extremely significant
- P<0.05- significant
- P> 0.05 –not significant
- N: degree of freedom

DISCUSSION

Hematological complications have been documented to be the second most common cause of morbidity and mortality in HIV positive persons [12]. In the present study, CD4 T-cell count was increased after initiation of HAART. For those pregnant women who received TDF/3TC/NVP, the numbers of increased CD4 T-cells were 184±38.10 cells and for those who received AZT/3TC/NVP were 39±37.24 cells. The average mean base line value of CD4 cell count in pregnant women before HAART was 334±29.54 and this value was increased by 101±0.9 after treatment by the two regimens. This finding is comparable with other reports done somewhere else. A study conducted in India on AIDS patients showed that Mean baseline CD4+ T cell count was 112+60 cell/ µl. After treatment, a CD4 cell count increased by > 50 cells/ µl in 84.6 % cases [13]. Another study done in Netherland showed that in all children and adults with relatively high CD4+ T cell counts at start of therapy (>200 cells/ µl), total CD4+ T cell numbers were normalized within 1 year of therapy[14].

In our finding, RBC count, hematocrit and hemoglobin level did not change from the baseline data (P>0.05). An observational cohort study done in Tanzania in 2013 described that pregnant woman after receiving zidovudine containing regimen

showed that RBC count decreased within the first four weeks HAART intake and then increased [15]. That final increment in RBC count after long term HAART intake in pregnant women is not consistent with the current study. Another study showed that Red Blood Cell count (RBC) and Hematocrit (HCT) were significantly reduced compared to control subjects [16] to mean that this report is not consistent with the current study.

However, another follow-up study carried out on some hematological and hem rheological changes in HIV-infected pregnant women on highly active antiretroviral therapy in University of Benin Teaching Hospital, Nigeria, from April 2013 to February, 2014 showed that in the first trimester there were no significant changes in Hb [17]. Another study also was done in Burkina Faso, Kenya and South Africa, 2013 by Cherish et al to assess the effect of triple zidovudine containing regimens. ART eligible pregnant women were followed from 28 weeks of pregnancy (n = 1070). At enrolment (corresponded to a median of 32 weeks gestation), the median hemoglobin was 10.3 g/dl. Severe anemia occurred subsequently in 194 (18.1%) of women. After 1–2 months of ARV's, severe anemia was significantly reduced in all groups, though remained highest in the low CD4 cohort and this finding is in agreement with our finding as 43 % of the total sample patient cards were recorded with zidovudine containing regimen And there was an improvement in hemoglobin level from initial value of 14.65±0.52 to 14.68±0.42 after HAART in pregnant women which decreases the probability of occurrence for anemia.

The current study shows that HAART initiation in pregnant women has no significant effect on total platelet and white blood cell count as p-value for both hematological parameters is greater than 0.5 when it is compared with the initial value. This is comparable with a follow-up study carried out on some hematological and hem rheological changes in HIV-infected pregnant women on highly active antiretroviral therapy in University of Benin Teaching Hospital, Nigeria, from April 2013 to February, 2014 showed that in the first trimester there were no significant changes in WBC and WBV (P > 0.05) between test and control subjects [17]. A Study conducted in Markurdi, Benue state of Nigeria indicated that ART brings statistically significant increment in WBC from 4070± 250 cells/ µl at baseline to 4760± 170 cells/ µl after antiretroviral drugs treatment [3]. The result of a study done in Italy indicated that HAART induced a significant increase in the PLT count within the third month which was sustained up to the sixth month of therapy [18]. This shows that the present finding concerning the effect on platelet count and white blood cell count in pregnant women after HAART is against with reports described above.

From the current study, it can be seen that, the mean of mean cell volume in pregnant women after HAART was insignificantly increased (p> 0.05) from 95.47± 2.18 to 96.05 ±1.99 whereas the mean for red cell distribution width was declined from 13.68± 0.26 to 13.17 ±0.25 and this indicates that the effect of HAART on MCV in pregnant women is similar with the above report but the effect on RDW is not in agreement with such report.

The current study indicates that the mean values for MCH and MCHC in pregnant women after receiving HAART were insignificantly declined from 34.20 ± 0.91 to 33.41 ±0.79 and from 35.68 ±0.35 to 34.64 ± 0.31, respectively. This shows that the effect of HAART on these two hematological indices is not consistent with above described cross-sectional study. The present finding also indicates that the mean value of mean platelet volume in pregnant women after HAART was decreased by 0.08 ±0.38 from the initial value which is not supported by the above reports.

CONCLUSION

HAART initiation in pregnant women with HIV increases the CD4 cell count and decreases means corpuscular hemoglobin concentration. TDF/3TC/EFV ART regimen increases significantly the CD4 count in pregnant women with HIV. Unless there is specific clinical condition where TDF/3TC/EFV ART regimen is contraindicated, health care professionals can prescribe this regimen as first line for pregnant women with HIV. Hematological tests for pregnant women with HIV should be performed regularly to follow the effectiveness of HAART.

ACKNOWLEDGEMENT

We would like to express our heartfelt gratitude to those staff working in Debreberhan hospital patient cards for their unreserved help in identifying the required ART patient cards and allowing their office for us during pre-test and actual data collection. We would like also to express our gratitude to Debreberhan Health center (kebele-04) ART patient card handlers for their effort to provide all the necessary documents that help to support this work. Our appreciation also extends to Dr. Asmare Tiruneh, Debreberhan university research and community service director, for providing the Collaboration letter and facilitating conditions while carrying out this study

Competing interests: The authors declare that they have no competing interests.

Ethics approval and consent to participate: Ethical clearance was obtained from the Ethics Review Committee of College of Medicine, Debreberhan University. Official letter was given to the heads of the health facilities to obtain permission to collect the data. Personal identifiers of the patients were kept confidential.

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