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ANAEMIA DUE TO DIFFERENT ANTI-RETROVIRAL REGIMENS IN HIV POSITIVE PATIENTS

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ABSTRACT

Objective: To study the pattern of Anaemia due to different anti-retroviral regimens in HIV/AIDS patients. **Material & Methods**: A prospective observational study was conducted over a period of fifteen months at ART Centre, GSVM Medical College Kanpur. All HIV positive patients attending O.P.D. who encountered ADRs were enrolled in our study irrespective to their age and sex. Data was collected using ADR reporting form issued by Indian Pharmacopoeia Commission. Causality assessment was done by using Naranjo's Probability Scale. Modified Hartwig severity scale was used to evaluate severity, WHO criteria for seriousness and guidelines of council for international organizations of medical sciences to decide the predictability of ADRs. **Results**: A total no of 250 patients encountered various types of ADRs during our study period i.e. January 2015 to March 2016. Total number of ADRs recorded was 452. Out of total ADRs recorded 131 ADRs were anaemia. Maximum burden of anaemia was found in the patients who were on zidovudine based regimen. CD4 count <250 cells/mm3 was observed as a risk factor for development of anaemia. On severity scale most of the cases of anaemia were found to be of mild type. **Conclusion**: Almost every anti-retroviral drug is associated with anaemia but incidence is maximum with zidovudine containing regimens. So clinician should prescribe tenofovir based first line anti-retroviral regimen whenever possible as tenofovir has less adverse drug reactions especially anaemia in comparision to zidovudine and recently WHO also recommended that tenofovir based regimen should be preferred as first line regimen.

KEYWORDS: HIV, Anti-Retroviral Therapy, Adverse Drug Reaction, Anaemia.

INTRODUCTION

Combination antiretroviral (ARV) therapy is the current standard of care for treating patients with HIV/ AIDS. Anti-retroviral therapy has led to substantial reduction in morbidity and mortality in HIV positive patients. The free ART initiative was launched by the Government of India on 1 April, 2004 with a view to improve access to ART for the estimated 2.5 million people living with HIV/AIDS (PLHA) in India. Currently, the National AIDS Control Organization (NACO) recommends the following drugs and drug combinations for first-line regimens.[1]

- Zidovudine (300 mg) + Lamivudine (150 mg)
- Tenofovir (300mg) + Lamivudine (150 mg)
- Zidovudine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg
- Efavirenz (600 mg)
- Nevirapine (200 mg)

These drugs are chosen on the basis of their demonstrated efficacy in suppressing HIV replication, improving survival of PLHA, low cost and wide availability[2] However, concerns have emerged about the safety and tolerability of these regimens. Each anti-retroviral medication is associated with its own specific adverse effects or may cause problems only in particular circumstances. Haematological toxicity is associated with most of the anti-retroviral drugs; but incidence and severity of haematological toxicity varies with different classes of anti-retroviral drugs and with different agents with in the class also. Anaemia is most common haematological toxicity associated with anti-retroviral drugs.[3] Anaemia is responsible not only for troublesome symptoms of fatigue but may have a direct, adverse effect on mortality in HIV infection. Anaemia in HIV-infected patients, if persistent, is associated with substantially decreased survival. So keeping in mind the above outcomes of anaemia our study was conducted to analyse the various risk factors for the development of

anaemia in HIV positive patients and also to assess the risk of anaemia in HIV positive patients on zidovudine based anti-retroviral regimens in comparison with tenofovir based anti-retroviral regimen. As best of our knowledge there are very few studies which compare the risk of anaemia between zidovudine based and tenofovir based regimens. So our study is likely to help the clinicians to foresee the various risk factors for development of anaemia in patients on anti-retroviral drugs and improve the prescription habits of clinicians.

MATERIAL AND METHODS

A prospective observational study was conducted over a period of 15 months from January 2015 to march 2016 on HIV positive patients who attended the NACO sponsored ART centre, GSVM Medical College Kanpur.

Inclusion criteria

1. Both newly and previously registered HIV positive patients who were on anti-retroviral therapy and experienced ADRs.
2. Patients of both gender.
3. Patients who gave written informed consent.

Exclusion criteria

1. Patients unable to respond to verbal questions.
2. Pregnant/ lactating females.
3. Patients with concomitant disorders such as diabetes mellitus and hypertension.

Before enrolling the patients into the study, written informed consent was obtained. Before starting the anti-retroviral therapy baseline laboratory investigations such as haemoglobin estimation, total leukocyte count, differential leukocyte count, serum creatinine, blood urea, serum bilirubin, SGOT, SGPT, blood sugar, CD4 count etc. were done. ADR monitoring was done in a systematic manner adopting both spontaneous and intensive monitoring approaches. Adverse drug reaction reporting form provided by Indian Pharmacopoeia Commission (IPC) Ghaziabad was used for data collection keeping all the norms of confidentiality.

Treatment was initiated as per national guideline in India, according to which fixed dose combination of two NRTIs (zidovudine/tenofovir + lamivudine) and one NNRTI (nevirepine/efavirenz) is recommended.[1]

Haemoglobin estimation was done at the start of antiretroviral therapy, at day 15 and monthly during the first 6 months, thereafter haemoglobin estimation was done every two monthly. Enrolled HIV positive patients were intensively monitored for zidovudine and tenofovir induced anaemia.

Fall in haemoglobin levels <8 g per cent in a patient on zidovudine therapy and subsequent increase in haemoglobin levels on stopping therapy was considered as zidovudine induced anaemia.

Each reported case of zidovudine and tenofovir induced anemia was assessed for its causality by using Naranjo's probability scale.[4] Preventability was assessed using Schumock and Thornton preventability criteria[5] and severity was assessed using the modified Hartwig and Siegel scale.[6] Predictability assessment was done on the basis of modified guidelines developed by the Council for International Organizations of Medical Sciences.[7]

Statistical analysis: For the analysis of data statistically whether the observations are statistically significant or not various statistical parameters like mean, standard deviation were used. For assessing the various risk factors for the development of ADRs mean value of the risk factors were compared between the two groups by using t- test. To see the association between the two variables chi-square test was also used. Calculation of mean and standard deviation was done by using Microsoft excel 2010. For applying t- test and chi-square test we used graph-pad software. In testing the statistical significance between the two means, the level of significance α=0.05 was used.

RESULTS

The present study was conducted at ART centre, P.G. department of internal medicine and department of Pharmacology & Therapeutics, G.S.V.M Medical College, Kanpur.

A total no of 250 patients encountered various types of ADRs during our study period i.e. January 2015 to March 2016. Total number of ADRs recorded was 452. Out of total ADRs recorded 131 ADRs were anaemia.

Total number of patients who were on zidovudine based first line regimen and encountered at least one ADR was 192. Out of these 192; 126 developed anaemia following zidovudine based first line anti-retroviral regimens. So the relative incidence of anaemia due to zidovudine based first line anti- retroviral regimens was found to be 65%.

Total number of patients who were on zidovudine based second line regimen and encountered at least one ADR was 5. Out of these5; 2 developed anaemia following zidovudine based second line anti-retroviral regimens. So the relative incidence of anaemia due to zidovudine based second line anti-retroviral regimens was found to be 40%.

Total number of patients who were on tenofovir based first line regimen and encountered at least one ADR was 53. Out of these 53; 3 developed anaemia following tenofovir based first line anti-retroviral regimens. So the relative incidence of anaemia due to tenofovir based first line anti- retroviral regimens was found to be 5.6%.

Frequency of anaemia due to various anti-retroviral drug regimens: In our study maximum cases of anaemia

was shown due to regimen ZLN followed by ZLE, TLE and ZLAT/r regimen.

In our study no case of anaemia was reported in patients who were on regimen TLN.

Table: 1- Frequency of anaemia due to various anti-retroviral drug regimens

S. No.	Regimen	Anaemia No.	%
1	ZLN	102	77.8%
2	ZLE	24	18.32%
3	TLE	3	2.3%
4	ZLAT/r	2	1.52%
5	TLN	0	0%
	TOTAL	131	100%

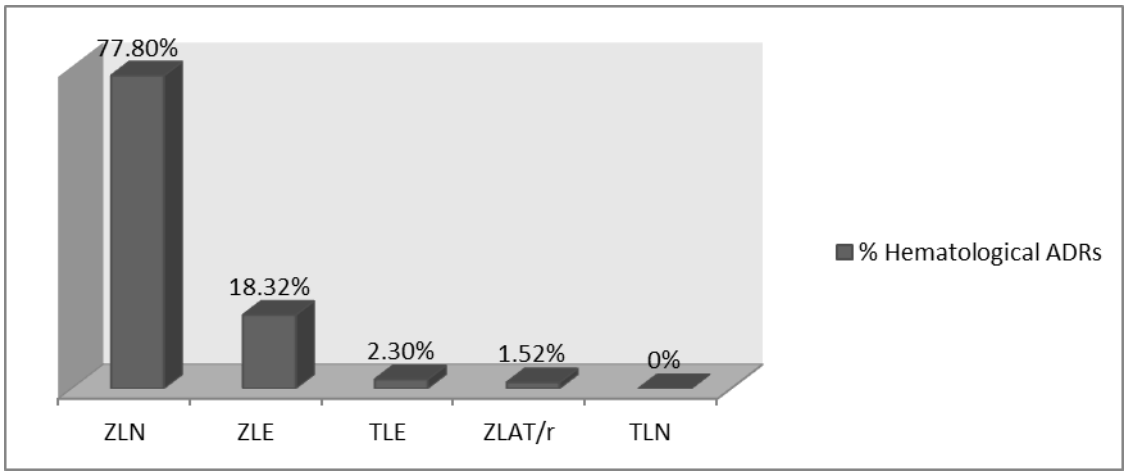

Figure:- Frequency of anaemia due to various anti-retroviral drug regimens

Analysis of various risk factors for development of anaemia pertaining to HAART

We analysed the various demographic parameters as a risk factors for developing anaemia by using appropriate statistical tests. The detail of analysis is shown in the table below.

Table: 2- Various risk factors for developing anaemia pertaining to HAART

S. No.	CHARACTRESTICS	ANAEMIA				Test	α=0.05
		YES (n=131)		NO (n=119)			
		MEAN	SD	MEAN	SD	Result	P
1	**Gender**						
	Male	51		59		χ^2=2.86	0.09
	Female	80		60			
2	**Age(yr.)**	34.33	9.01	37.34	9.72	t=2.53	0.01*
	<20	13.75 (n=4)	3.77	16 (n=4)	4.08	t=0.81	0.44
	21-40	31.54 (n=99)	5.26	33.49 (n=71)	4.93	t=2.45	0.01*
	41-60	46.55 (n=27)	4.65	46.77 (n=42)	4.48	t=0.042	0.97
	>60	n = 1		63.5 (n=2)	2.12		
3	**weight (k.g.)**	50.01	7.96	49.17	9.35	t=0.75	0.44
	<35	29 (n=3)	2.64	32.55 (n=9)	3.50	t=0.47	0.14
	36-55	47.46 (n=100)	4.66	46.87 (n=82)	5.24	t=0.78	0.42
	56-75	61.28 (n=28)	4.35	61.03 (n=26)	4.75	t=0.039	0.25
	>75	0		75.5 (n=2)	0.70		
4	**CD4 Count (cells/mm3)**	259.26	55.61	283.36	89.21	t=2.53	0.01*
	<250	216.82 (n=77)	17.14	223.90 (n=63)	18.66	t=2.31	0.02*
	>250	318.98	29.92	328.57 (n=56)	59.43	t=1.05	0.29

		(n=54)					
5	**Regimen**	No. of	patients	No. of	patients		
	Zidovudine based	126		68		□□□□□ □□□	0.00001**
	Tenofovir based	3		48			
	ZLAT/r (Second line)	2		3			

Age- χ^2=7.64p<0.05* Weight- χ^2=6.29p>0.05

From the above table it is evident that there was no significant difference in the two subgroups of study population (i.e.one is who developed anaemia and another one is who did not develop anaemia) with respect to gender and weight. However significant difference was seen in age, CD4 count and the regimen.

Mean age (33.04 years) of population who developed anaemia was significantly lesser than the mean age (35.61 years) of population who did not developed anaemia. Patients in age group between 21-40 years were encountered maximum burden of anaemia which was found statistically significant. (p<0.05, 95% CI).

In the patients who developed anaemia mean CD4 count 259.26 cells/mm^{3}was significantly lesser than the mean CD4 count (283.36 cells/mm^3) in the patients who did not develop anaemia.(p<0.05, 95% CI). CD4 count <250 cells/mm^3 was observed as a risk factor for development of anaemia which was statistically significant (p<0.05, 95% CI).

Maximum burden of anaemia was found in the patients who were on zidovudine based regimen which was statistically very significant (p<<<0.05, 95%CI).

So to sum up age between 21-40 years, CD4 count <250 cells/mm^3 and zidovudine based anti-retroviral regimen were found the risk factors for developing haematological ADRs in our study.

Causality assessment: All reported cases of anaemia were assessed for causality by using Naranjo's probability scale. On this scale all cases of anaemia were found probable in nature.

Severity assessment: All reported cases of anaemia were assessed for severity by using Modified Hartwig severity levels. Out of total 131 cases of anaemia 116 were of mild type and 15 were of moderate type. No case of severe anaemia was found in our study.

Predictability determination: All reported cases of anaemia were predictable according to CIOMS criteria for determining predictability.

Preventability assessment: By using modified Schumock Thornton preventability criteria all cases of anaemia were found of probably preventable type in our study.

DISCUSSION

Anaemia remains the early primary toxicity associated with different anti-retroviral regimens which develops between 6 weeks to 6 months after starting the anti-retroviral therapy.[8]

In our study incidence of anaemia due to zidovudine and tenofovir based firstline anti-retroviral regimens was found 65% and 5.6% respectively. It is higher than some previously conducted studies[9-12] and lower than the study conducted by Mohsen Meidani et al.[13] in which incidence of anaemia due to zidovudine was found 71%. These differences in the incidence of anaemia can be attributed due to difference in cut off values of haemoglobin taken to define anaemia in different studies.

In our study low CD4 count, age group between 21 to 40 years and zidovudine based anti-retroviral regimens were found the risk factors for development of anaemia. However female gender was not found to be the risk factor for anaemia in our study. Low CD4 count and zidovudine were found risk factors in other studies also.[14-16] Female gender was found to be the risk factor for anaemia in some studies.[13,17-18] These variations in risk factors for development of anaemia in our study from other study may be due to more patients in the age group 21-40 and of male gender are coming to our ART centre where study is conducted. This can be because of high number of HIV positive male patients in 21-40 age group in our region. This can be due to the fact that this age group falls in reproductive age and incidence of HIV/AIDS is naturally more in this age group.

Zidovudine based anti-retroviral regimens were found the risk factor in comparison to tenofovir based anti-retroviral regimens for development of anaemia in our study. One plausible explanation for this may be that tenofovir cause inhibition of mitochondrial gamma polymerase enzyme to the significantly lesser extent in comparison to zidovudine.

In our study most of the cases of anaemia were of mild type followed by moderate type. No severe case of anaemia was found in our study. It can be because anaemia due to anti-retroviral drugs is a reversible and dose limiting adverse drug reaction. If the compliance of patient is good enough anaemia can be recovered easily by decreasing the dose or discontinuing the culprit anti-retroviral drug. However the above finding lies in line with study conducted by Ramezani A et al[19] and differ from study conducted by Chakravarty *et al.*[20]

In our study all cases of anaemia were probable type on causality assessment; all were predictable and probably preventable. This finding is in line with study conducted by Rajesh et al.[21]

CONCLUSION

Anaemia due to anti-retroviral therapy is of great concern these days because it has bad impact on the survival of HIV positive patients. Almost every anti-retroviral drug is associated with anaemia but incidence is maximum with zidovudine containing regimens. So clinician should prescribe tenofovir based first line anti-retroviral regimen whenever possible as tenofovir has less adverse drug reactions especially anaemia in comparision to zidovudine and recently WHO also recommended that tenofovir based regimen should be preferred as first line regimen. While prescribing zidovudine based anti-retroviral regimen; haemoglobin level should be strictly monitored especially in patients on high risk for developing anaemia i.e. low CD4 count and age group 21-40 years.

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