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Therapeutic Monitoring of Antiretroviral Drugs in Immunologically Stable HIV Patients on Art Treatment

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ABSTRACT

In HIV, highly active anti-retroviral therapy helps patients to regain the immune CD4+ cell count. Among all antiretroviral therapy (ART) regimens tenofovir based regimen (TLE; Tenofovir (TDF) + Lamivudine (3TC) + Efavirenz (EFV)) has become the most preferred first line regimen. Present study aimed to identify the therapeutic levels of drugs in tenofovir based regimen in immunologically stable HIV patients. A total of 35 dried blood samples were obtained from HIV patients on TLE treatment visiting ART centre, Mahatma Gandhi Memorial (MGM) Hospital, Warangal, Telangana, during September 2017 to March 2018. Patients with good adherence, without history of smoking & alcoholism and with CD4+ cell count > 350 cells/mm^3 were included. Estimation of drugs was done using pre validated liquid chromatographic method. In total of 35 patients, females were accounted for 62.86%. Patients of this study showed high percentage of illiterates (48.57%) and daily labors (34.29%). As EFV is a narrow therapeutic index drug it showed significant difference in its plasma therapeutic levels (0.005**) whereas TDF & 3TC were not. Total of 8.57% and 91.43% patients were showed EFV plasma levels below and above therapeutic levels respectively. Though the study patients observed with good immunological status, high percentage of patients identified with toxic levels of EFV concentrations. But none of the patients showed any symptoms of toxicity, they are at risk to develop clinical toxicity in future. Present study results suggesting dose adjustments and monitoring of drug levels in these patients to avoid early treatment failures and toxicity.

Keywords: HIV, CD4+ cell count, Tenofovir regimen, Therapeutic level, Monitoring.

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1. INTRODUCTION

Global statistics of UNAIDS 2017 revealed that there were 36.9 million people are living with HIV (PLHIV) and 21.7 million people were accessing antiretroviral therapy (ART).[1] In India there were 21.40 lakhs people were living with HIV.[2] Presently 528 ART centers in India providing health services to PLHIV.[3] The principal impact of HIV infection on the immune system is destruction of the CD4+ T lymphocytes[4] and it is only the parameter used to monitor the immune status of the HIV infection initiated with ART[5] in resource limited settings. Highly active antiretroviral therapy (HAART) is a triple drug therapy consist two nucleoside or nucleotide reverse transcriptase inhibitor backbones with a non-nucleoside reverse transcriptase inhibitor or protease inhibitor[6] recovers the CD4+ T lymphocytes suppressions in the HIV infection.[7] Among all ART regimens, fixed dose combination pill consists of Tenofovir disoproxil fumarate (TDF), Lamivudine (3TC) and Efavirenz (EFV) has become the preferred first line regimen to initiate the ART in PLHIV.[8] Objective of the present study was originate in view to know the levels of a narrow therapeutic index drug (EFV)[9] along with other two drugs in a fixed dose combination in HIV patients with immunologically stable (i.e. CD4+ cell count was > 350 cells/mm^3) to avoid treatment failure as well as toxicity in patients taking this regimen.

2. METHODOLOGY

Present study was under taken at ART centre, Mahatma Gandhi Memorial (MGM) Hospital, Warangal, Telangana, India, duration of the study was 6 months (i.e. September 2017 to March 2018). A total of forty (n=40) PLHIV on TLE treatment for greater than 3 months with no social history of alcohol or smoking consumption, with > 98% medication adherence and CD4+ count > 350 cells/mm^3 were enrolled in the study and five patients were exempted from the study because of not given consent. Institution review board reviewed and approved the protocol. Thirty five (n=35)

dried blood samples from patients with given consent were obtained at the time of their regular review visit after 8 to 14 hours of post dosing.[9] Three antiretroviral drugs of (TDF, 3TC and EFV) TLE regimen were estimated using pre validated liquid chromatographic method.[6] Results were represented in the form of mean±SD.

3. RESULTS AND DISCUSSION

3.1. Study patient's characteristics

Table 1 shows the characteristics of total 35 study patient's data. Out of 35 patients, 37.14% (n=13) were males and 62.86% (n=22) were females. Mean age of overall patients was observed as 41±10.04 (26 – 65) years. Gender distribution of these patients according to age was shown in Figure 1 and most of them were observed in the age group of 30 – 50 years, where it was 15 – 40 years in a surveillance study conducted by UNAIDS in sub-Saharan Africa.[10] Body mass index (BMI kg/m^2) of the patients showed 94.29% were underweight and only 5.71% patients were observed with normal BMI. In present study the most predominant route of HIV infection transmission was noticed as heterosexual route which was similar to the reports of Shen *et al.,* (2016);[11] Lakhashe *et al.,* (2008);[12] Kumarasamy *et al.,* (2005);[13] Godbole *et al.,* (2014).[14] The highest percentage of patients of this study was illiterates (48.57%) and daily labors (34.29%) these results were in parallel to the earlier studies Obiako *et al.,* 2012[15] & Sood *et al.,* 2017.[16]

Table 1: Characteristics of study patients.

Parameter	Number of patients	Percentage (%)
Gender		
Male	13	37.14
Female	22	62.86
Age in years	**Mean±SD**	
Males	45±9.26	0.19 (ns)
Females	38.64±9.93	
Body Weight in Kgs	**Mean±SD**	
≤ 40	09	25.71
40 – 60	22	62.86
≥ 60	04	11.43
BMI (kg/m^2)		
Underweight (< 18.5)	33	94.29
Normal weight (18.5-24.9)	02	5.71
Over weight and obese	-	-
Occupation	**Number of patients**	**Percentage (%)**
Daily labor	12	34.29
Private employee	06	17.14
Agriculture	06	17.14
Home maker	03	8.57
Without occupation	08	22.86
Mode of transmission		
Hetero sexual	29	82.86
Migrant	02	5.71
Mother to child	04	11.43
Educational status		
Illiterates	17	48.57
Primary	06	17.14
Secondary	08	22.86
College &above	04	11.43

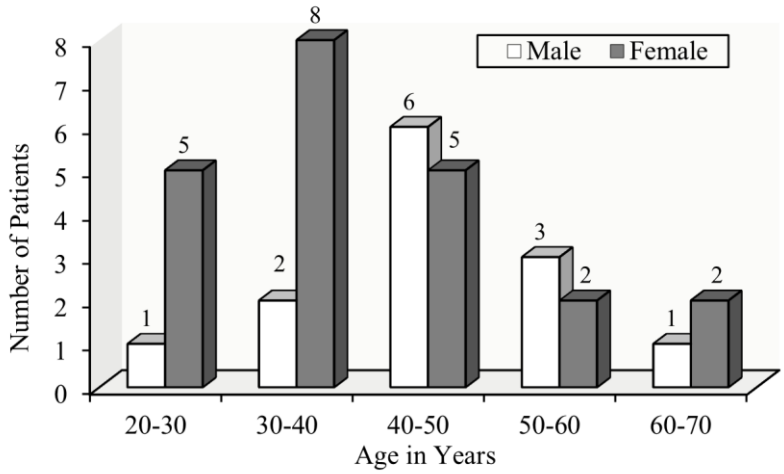

Figure 1: Gender distribution of study patients according to age.

3.2. Basic clinical data and plasma drug levels

Basic clinical data of the study patients were tabulated in Table 2. These patients mean duration of the disease in months was found to be 63.63±42.05 (ranged 7 – 140 months) (males: 59.23±39.92; females: 66.23±43.96). The mean duration of treatment (TLE) received by the time of sample collection was 38.06±24.02 (6 to 88) months (males: 42.45±25.85 and females: 30.62±19.22). The overall mean value of recent $CD4^+$ count of was observed as 515.91±130.97 cells/mm^3, with 358 to 843 cells/mm^3 range.

Table 2: Basic clinical data of the study patients.

Parameter	Values Mean±SD	
	Male	Female
Duration of the disease in months	59.23±39.92	66.23±43.96
Duration of treatment on TLE in months	42.45±25.85	30.62±19.22
Recent $CD4^+$ count in cells/mm^3	501.39±153.77	524.5±118.54

Efavirenz is a narrow therapeutic indexed drug in TLE regimen and its therapeutic level is 1 – 4 mg/L.[9,17,18] As depicted in Table 3 in present study estimated plasma levels of EFV, TDF and 3TC were showed only 8.57% of patients with EFV concentrations within therapeutic level and 91.43% of patients with EFV concentrations above therapeutic level with significant difference (0.005**) in between two therapeutic level groups. On the other hand the overall plasma concentrations of the TDF (p=0.68) and 3TC (p=0.06) were within the limits i.e. C_{min}/C_{max} for TDF and 3TC were 0.06/0.33 mg/L[19,20] and 0.04/2.0 mg/L[21,22] respectively with no significant difference between two groups.

Table 3: Plasma levels of three drugs at different therapeutic levels of EFV.

Patients (n=35)	Values Mean±SD mg/L					
	EFV conc. (mg/L)	P value	TDF conc. (mg/L)	P value	3TC conc. (mg/L)	P value
EFV Within TL (n=03; 8.57%)	3.25±0.37	0.005**	0.16±0.1	0.68 (ns)	0.09±0.04	0.06 (ns)
EFV above TL (n=32; 91.43%)	12.63±11.57		0.14±0.09		0.33±0.02	

From the earlier study of Manosuthi *et al.,* (2009)[23] it was observed that body weight > 60 Kgs will result in low therapeutic levels of plasma EFV. But in present study only four patients body weight was > 60 Kgs with mean plasma EFV level of 9.03±2.70 mg/L i.e. above therapeutic level. As shown in Figure 2 patients body weight has no significant (p=0.34) affect on plasma EFV levels and these results supporting the results of Burger *et al.,* (2005)[17] and Luetkemeyer *et al.,* (2013)[18] where there results proved body weight has no affect on plasma EFV levels. Demographic data of the patients showed 94.29% of the patients were under weight; as reported by Poeta *et al.,* (2011)[24] i.e., BMI is associated significantly and inversely to the EFV concentrations, BMI < 18.5 kg/m^2 (underweight) might be the reason for higher therapeutic levels of EFV in this study patients too.

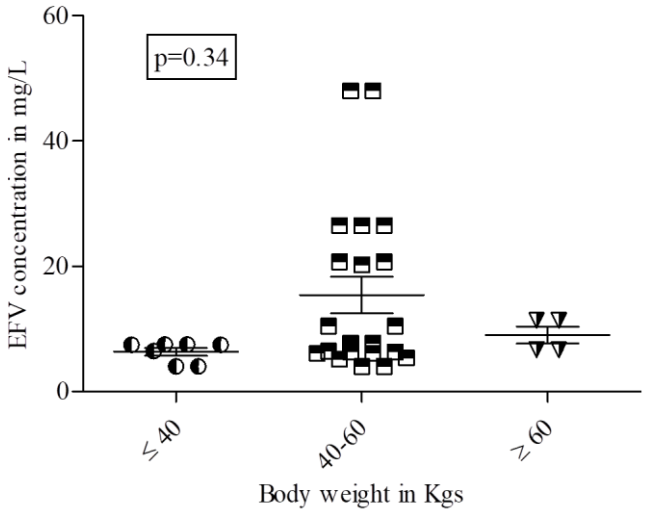

Figure 2: Effect of Bodyweight on plasma EFV concentration.

Table 4 shows the patient's history of past ART regimen and its effect on plasma EFV levels. A total of 46.88% patients underwent regimen change before to TLE regimen and ZLN+TLN was the regimen received by most of the patients. There was a significant (p=0.02*) difference of plasma EFV levels were observed in between past HAART history to no history groups.

Table 4: Effect of medication switches on EFV concentrations

Medication Switch	EFV mg/L (Mean±SD)
ZLN (n=02)	6.71±0.14
SLN+TLN (n=03)	13.99±10.84
ZLN+TLN (n=06)	4.43±0.64
SLE+SLN+TLN (n=02)	7.59±0.07
SLN+TLN+ZLN (n=02)	7.58±0.15
Past HAART history (n=15; 46.88%)	p value 0.02*
No history (n=17; 53.13%)	

Alike, correlation between medication switch to plasma EFV levels, there was a significant effect (p=0.021*) of medication switch on CD4+ cell count was noticed (Figure 3). Increased rate of CD4+ cell count might be as result of multiple HAART regimen exposures over a period of time this strengthen the results of Trotta *et al.,* (2010)[7] and Bisson *et al.,* (2006)[25] that multiple drug regimen exposure increase the CD4+ cell count.

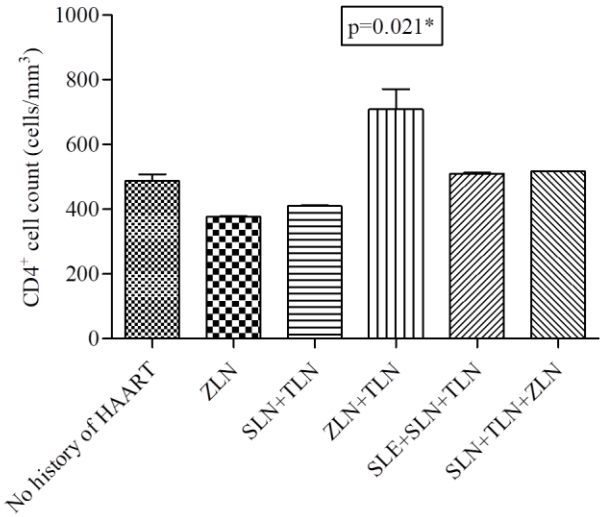

Figure 3: Effect of No past history and history of HAART regimen exposure on $CD4^+$ cell count

4. INTERPRETATION AND CONCLUSION

Though the patients of this study observed with good immunological status (i.e. > 350 cells/mm^3), 91.43% patients identified with toxic levels of EFV concentrations (above therapeutic level). None of the patient showed any symptoms of toxicity they might be in subclinical toxicity stage at the time of study but they are at risk to develop clinical toxicity in future. These patients need dose adjustment to lower dose with frequent monitoring of clinical and immunological status to avoid toxicity related complications in future. Significant difference (p value – 0.02*) of EFV concentration between groups of past and no past HAART history suggesting the monitoring of narrow therapeutic index drug in patients undertake medical switches is necessary to avoid unnecessary regimen switches where limited number of HAART options are presented.

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