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A Study Of Fever Profile In HIV Infected Hospitalized Patients And Its Correlation With ART& CD4 Count.

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Abstract:*Feverin HIV positive patientsis often accompanied by significant morbidity, prolonged hospitalization and extensive evaluation.Whetheretiologic spectrum of fever has changed as a consequence of HAART still remains unknown.Hence we conducted study to identify etiological profile of fever in HIV patients and its correlation with ART & CD4 count.Thisprospective observational study was carried out in 200 adult hospitalised HIV positive patients at tertiary care Hospital in Mumbai.The age of the patients studied ranged between 19 and 59 years with a mean age of 37.7(±8.3) years with 59% were males and 41% were females. Four symptoms namely dyspnea, cough, loss of appetite, weight loss were the common symptoms at presentation (65.5%, 64.5%, 63%, 63%respectively).79.5% of total patients had an opportunistic infection as a cause of fever. Tuberculosis was the most common opportunistic infection. The most common cause of fever in HIV positive patients leading to hospitalization is an opportunistic infection and tuberculosis is the most common opportunistic infection causing fever. There is no correlation between duration of fever in HIV and duration of ART however duration of fever increases as clinical stage increases and CD4 count decreases.*

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I. Introduction

Fever is a non-specific body response to extrinsic and intrinsic factors thatresult in increase of body temperature set-point, with physiological mechanisms.Fever, either continuous or recurrent, is a common finding in patients infected withHIV (human immunodeficiency virus) and is often accompanied by significant morbidity, prolonged hospitalization and extensive evaluation.[1]

The clinical profile ofHIV disease in India includes a wide range of conditions like tuberculosis, cryptococcal meningitis and cytomegalovirus retinitis etc. CD4 counts less than 200 cells/µl, patients are at high risk for developingopportunistic infections (OIs) like tuberculosis (TB), Pneumocystis carinii pneumonia(PCP), toxoplasmosis, and cryptococcal meningitis. Tuberculosis is the most common opportunistic infection in Indian patients with HIV.[2]

Before the existence of highly active antiretroviral therapy (HAART) patientswith HIV infectionexperienced fever with relative frequency. In most cases, feverwas caused by opportunistic infections, mainly tuberculosis, infection with Mycobacterium avium complex & others.[3-7]

Besides infections, IRIS (ImmuneReconstitution Inflammatory Syndrome) is an important cause of fever in HIVpositive patients. The widespread use of HAART over the past few years has led to amarked decrease in the incidence of opportunistic infections in these patients, butwhether fever has also become less frequent or whether its etiologic spectrum haschanged as a consequence of HAART still remains unknown.[8-11]

Thus our study was aims to identify etiological profile of fever in HIVinfected hospitalized patients andits correlation with ART & CD4 count.This will help us know the causes of fever in HIVpatients with different CD4 counts and significance of ART in reducing morbidity,occurrence of fever.

II. Materials And Methods

This prospective observational study was carried out during the period of July 2013 to December 2014 at Topiwala National Medical College & BYL Nair Hospital, Mumbai. Ethical committee of the T. N. Medical College, Mumbai had approved the study. HIV positive patients admitted in BYL Nair Hospital with temperature>38.3°C and age >18 years of either sex as an inclusion criteria were enrolled for the study. In the study group total 200 patients were enrolled. No one refused to participate in the study, hence the total sample

size came to 200 patients. All the patients included in the study were informed about the purpose of the study. Informed consent of each participant was taken.

Inclusion criteria;
1. Age: 18 years & older.
2. Sex: Male & Female.
3. HIV positive hospitalized patient
4. Temperature >38.3°C.

Exclusion criteria:
1. Age<18 years.
2. Co-existing immunosuppressive states-auto-immune conditions, hematological malignancies, chronic steroid use in a case of severe asthma
3. Long standing Diabetes Mellitus.

Detailed clinical history including past history, treatments &clinicalexamination done in each patient. Routine investigation like Hb, CBC, LFT, RFT, RBS, ESR, CD4 counts done. Chest X-ray, USG, CT scan, MRI done as per individual patient requirement.
This is routine standard of care which is followed.

Statistical analysis:

Analysis will be done by using software SPSS 16th version. Correlation and significance will be obtained by applying CHI- SQUARE test.

III. Results

In our study majority of the patients, 80 (40%) were in age the group 31-40years followed by 64 (32%) in age group 21-30 years. Minimum number of patients2 (1%) was in the age group < 20 years.In our study, out of 200 patients 118 (59%) were males and 82 (41%) werefemales.

In our study, out of 200 cases 136 (68%) patients had heterosexual mode ofHIV transmission and 9 (4.5%) patients had history of intravenous drug abuse. In 55(27.5%) casesmode of HIV transmission was not known.

Table 1: Presenting Symptoms

Presenting symptom	Number	%
Loss of appetite	126	63.0
Weight Loss	126	63.0
Diarrhoea	27	13.5
Cough	129	64.5
Chest Pain	36	18.0
Dyspnoea	131	65.5
Haemoptysis	15	7.5
Vomiting	97	48.5
Abdominal Pain	54	27.0
Headache	52	26.0
FND	5	2.5
Convulsions	10	5.0
Altered Sensorium	24	12.0

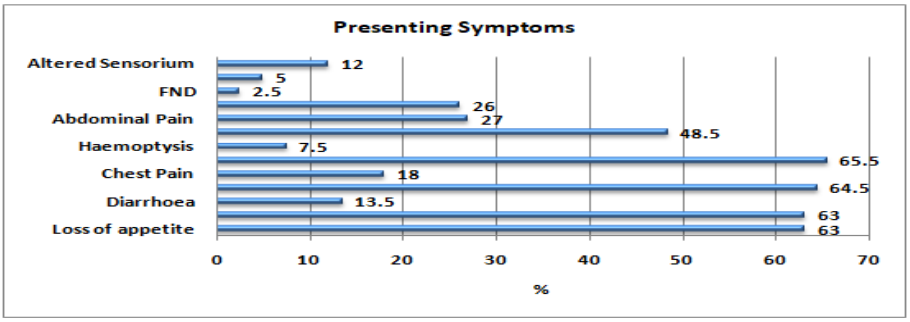

Figure 1

In our study four symptoms namely dyspnoea, cough, loss of appetite, weightloss were the common symptoms at presentation (65.5%, 64.5%, 63%, 63%respectively). Other symptoms were vomiting (48.5%), abdominal

pain (27%),headache (26%), chest pain (18%), diarrhoea (13.5%) haemoptysis (7.5%), alteredsensorium (12%), convulsion (5%) and FND (2.5%).

Table 2. Etiology of Fever

Aetiology	Number	%
Tuberculosis	148	74.0
Malaria	19	9.5
Dengue	10	5.0
Enteric fever	7	3.5
Cryptococcal meningitis	5	2.5
CNS toxoplasmosis	4	2.0
Leptospirosis	4	2.0
CMV proctitis	1	0.5
Drug reaction	1	0.5
Herpes zoster	1	0.5
Total	200	100

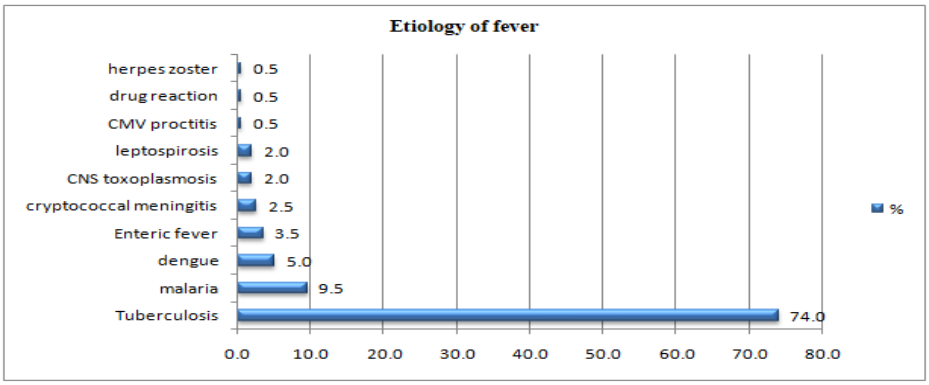

Figure 2

In our study, out of 200 patients 148 (74%) patients had tuberculosis as causeof fever which was also the most common cause.Rest causes of fever (%) weremalaria (9.5) dengue (5), enteric fever (3.5), cryptococcal meningitis (2.5), CNStoxoplasmosis (2), leptospirosis (2), CMV proctitis (0.5), drug reaction (0.5) herpeszoster (0.5).

Table 3: Distribution of patients according to CD4 count.

CD4 Count	Number	%
< 200	64	32.0
200-350	48	24.0
> 350	88	44.0

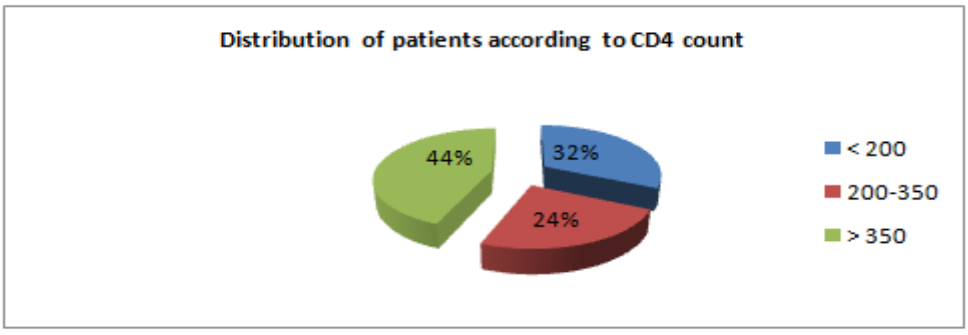

Figure3

In our study majority of patients (68%) had CD4 count > 200/µl, 32% patientshad CD4 count<200/µl.

Table 4. Distribution of patients according to clinical stage

Clinical Stage	Number	%
1	13	6.5
2	5	2.5
3	68	34.0
4	114	57.0

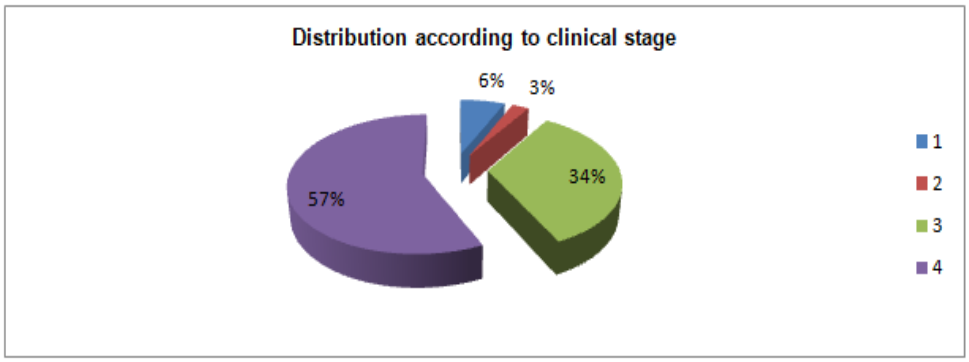

Figure 4

In our study maximum number of patients (57%) were in clinical stage 4 followed by stage 3 (34%) and least (2.5%) in stage 2.

Table 5Distribution of OI according to CD4 count.

	Diagnosis					
CD4 Count	CMV proctitis	CNS toxoplasmosis	Herpes zoster	Tuberculosis	Cryptococcal meningitis	Total
< 200	1	4	1	53	5	64
200-350	0	0	0	40	0	40
> 350	0	0	0	55	0	55
Total	1	4	1	148	5	159

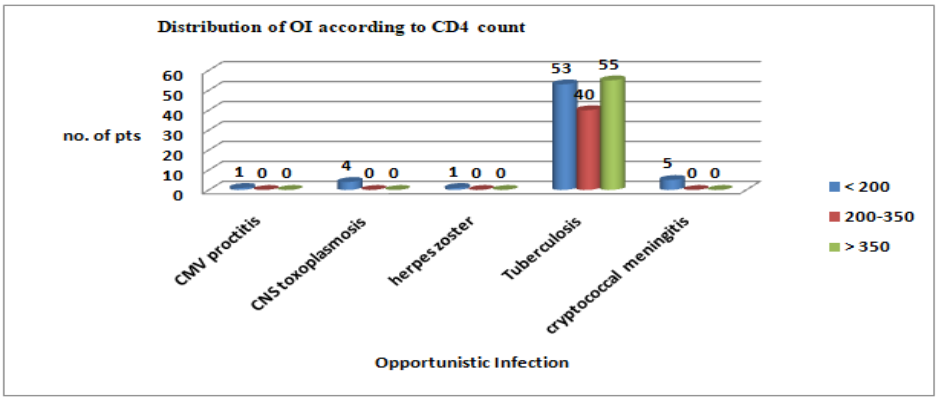

Figure 5

In our study out of 200 patients 159 had OI (opportunistic infection). Patientsdiagnosed as having CMV proctitis, CNS Toxoplasmosis, herpes zoster andcryptococcal meningitis had CD4 count <200/µl. Out of 148 patients havingtuberculosis, 53 had CD4 count < 200/ µl, 40 had CD4 count between 200 - 350/ µl& 55 had CD4 count > 350/ µl.

Table 6. Association between ART & OI

Opportunistic Infection	ART		Total
	Yes	no	
CMV proctitis	0	1	1
CNS toxoplasmosis	0	4	4
Tuberculosis	50	98	148
Cryptococcal meningitis	1	4	5
Herpes zoster	0	1	1
Total	51	108	159

chi-square value	Df	p-value	Result
3.36	4	0.49	not significant

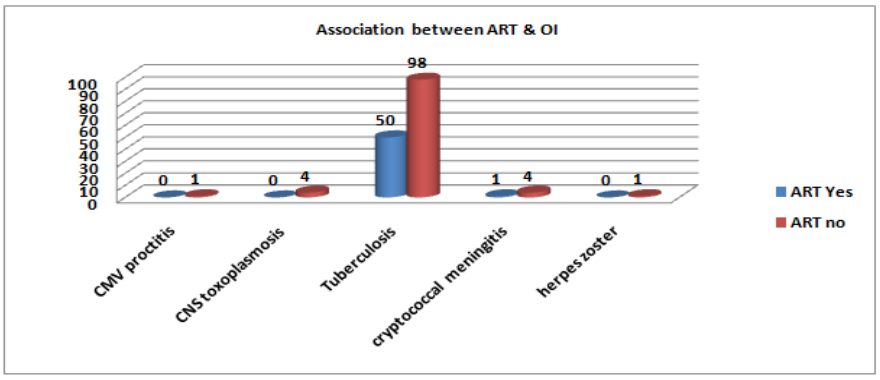

Figure 6

Out of 148 patients who had tuberculosis 98 (66.2%) were not on ART &50(33.7%) were on ART. Out of 5 patients of cryptococcal meningitis 4 were not onART& 1was on ART. All the patients having CMV proctitis, CNS toxoplasmosis andherpes zoster, were not on ART.

Table 7 Association between CD4 count & in-hospital mortality

CD4 count/µl	Outcome		Total
	died	discharged	
<200	25	39	64
200-350	4	44	48
>350	2	86	88
Total	31	169	200

chi-square value	Df	p-value	Result
40.77	2	<0.01	Significant

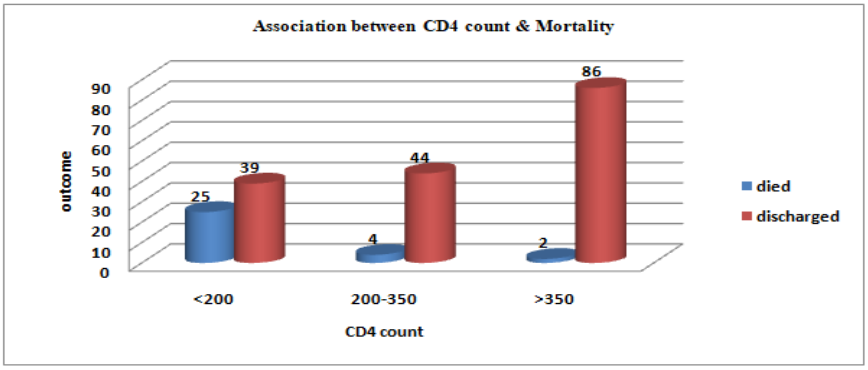

Figure 7

In our study out of 200 patients 31 (15.5%) died and 169 (74.5%) weredischarged. Out of 31 death 25 (80.6%) had CD4 count < 200/µl, 6 (19.4%) had CD4count >200/µl. In-hospital mortality is more in patients with lower CD4 count and thisassociation is statistically significant.

Table 8. Association between ART & in-hospital mortality

Death / Discharged	ART		
	Yes	No	Total
Died	1	30	31
Discharged	81	88	169
Total	82	118	200

chi-square value	df	p-value	Result
19.83	1	<0.01	Significant

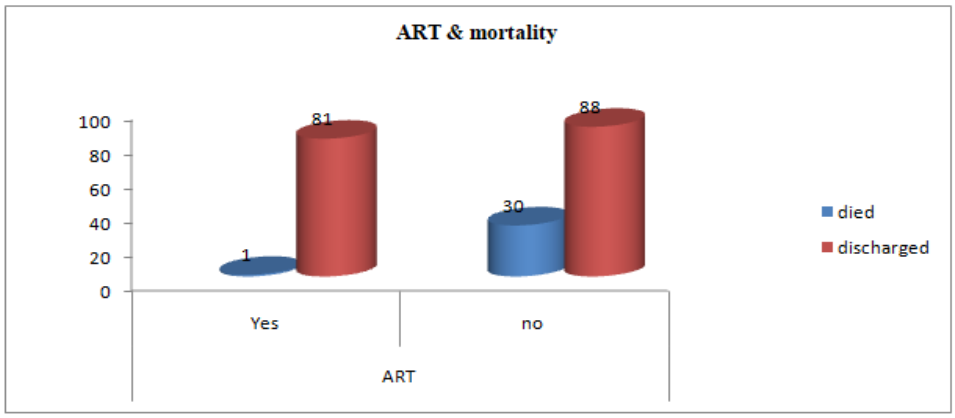

Figure 8

In our study 82(41%) patients were on ART & 118(59%) were not on ART. Out of 31 patients died, 30 (96.8%) were not on ART & 1(3.2%) was on ART.Patients who were not on ART, in-hospital mortality is more and it is statisticallysignificant.

Table 9: Correlation between Fever duration & CD4 Count, Clinical stage, ART duration.

Pearson Correlation	CD4	Clinical Stage	ART Duration
Duration of Fever	-0.43	0.59	-0.09
p-value	<0.01	<0.01	0.21

Coefficients[a]

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	2.45	8.71		0.28	0.78
CD4	-0.03	0.01	-0.23	-2.43	0.02
Clinical Stage	9.32	1.76	0.51	5.30	0.00
ART Duration	0.06	0.10	0.06	0.62	0.54

a. Dependent Variable: Duration of Fever

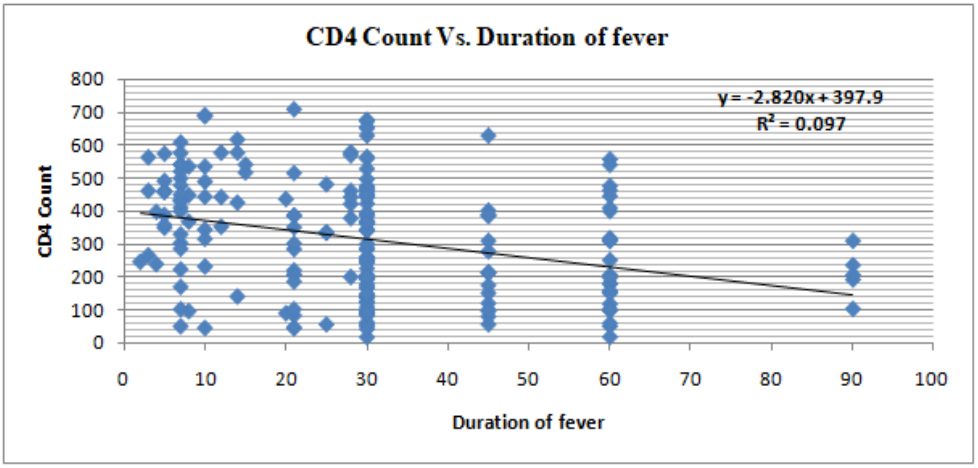

Figure 9

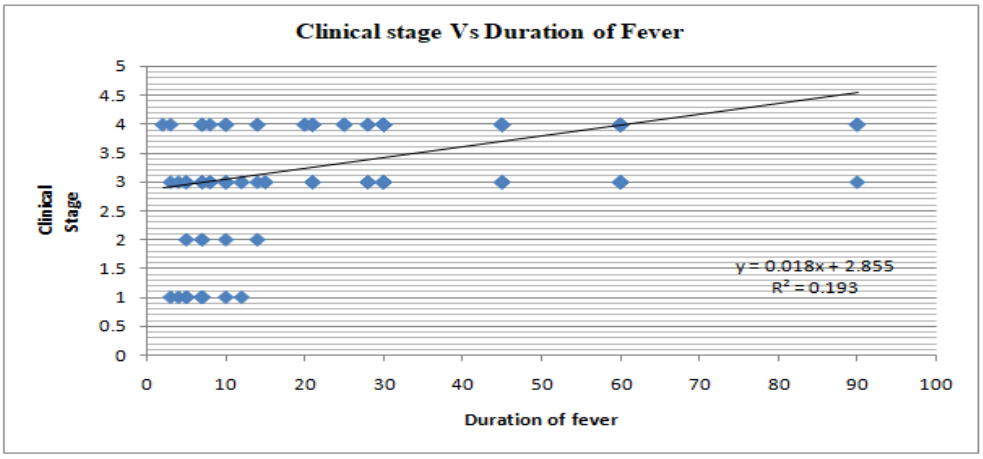

Figure 10

In our study we studied correlation between fever duration & CD4 count,clinical stage and ART duration. We found a significant correlation between durationof fever and CD4 count, clinical stage. As CD4 count decreases duration of feverincreases (inverse correlation) and as clinical stageincreases duration of feverincreases(direct correlation).

IV. Discussion

Fever is a frequent symptom in people infected with HIV. Infection is acommon cause of fever, especially in the symptomatic stages of HIV disease.Previous detailed studies of fever in HIV-infected persons have focused on fever ofunknown origin or on outpatients. In our study we analysed causes of fever in HIVinfected persons admitted for fever to the hospital, and its correlation with CD4 count&ART.Early etiological diagnosis and treatment of infections in symptomaticpatients will help to improve quality of life of HIV patients.

Age, Sex distribution and Mode of HIV transmission;in our study majority of the patients, 80 (40%) were in the age group 31-40years followed by 64 (32%) in age group 21-30 years & least number of patients 2(1%) were in the age group < 20 years. Mean age of the patients was 37.7 ± 8.3years. These findings are in concordance with another study in North India done by Neha et al [12] where majority of the patients were in the age group 21–40 years(79%).

In our study, out of 200 patients 118 (59%) were males and 82 (41%) werefemales. This is similar to nation-level statistics in which, of the 57781 cases ofHIV/AIDS reported to the National AIDS Control Organization (NACO), 89% of thecases were in the age group 15–44 years and 74% were males. This section of the population is more affected because they are sexually more active.[13]In the present study, out of 200 cases 136 (68%) patients had heterosexualmode of HIV transmission and 9 (4.5%) patients had history of intravenous drugabuse. In 55 (27.5%) cases mode of HIV transmission was not known. Mostcommon mode of HIV transmission was heterosexual mode. These findings are in concordance with another study done by Anant et al[14], where the most commonmode of HIV transmission was heterosexual (78.2%). Injectable drug users (IDU)constituted only a minority of the study group as has been observed in other parts ofIndia except for the north-eastern states where IDU is widely prevalent as observed in the study done by Sarkar et al.[15]

Four symptoms namely dyspnea, cough, loss of appetite, weight loss werethe common symptoms at presentation (65.5%, 64.5%, 63%, 63% respectively).Other symptoms were vomiting (48.5%), abdominal pain (27%), headache (26%),chest pain (18%), diarrhoea (13.5%) hemoptysis (7.5%), altered sensorium (12%),convulsion (5%) and FND (2.5%). Higher incidence of tuberculosis in the presentstudy (74%) could be the reason for high proportion of cough, dyspnea and weightloss as presenting symptoms and was comparable to study done by Zaheer et al and Kothari et al.[16,17] In a study done by Sharma et al,[18] most common symptom was fever (70.4%)followed by weight loss(65.2%), cough (42.2%), dyspnea (25.2%), abdominal pain(23.7%), vomiting (16.3%), altered sensorium(3.7%), convulsion(3%).

Etiology of fever: In our study, out of 200 patients 148 (74%) patients had tuberculosis as causeof fever which was the most common cause. Rest causes of fever were malaria(9.5%) dengue (5%), enteric fever (3.5%), cryptococcal meningitis (2.5%), CNStoxoplasmosis (2%), leptospirosis (2%), CMV proctitis (0.5%), drug reaction[secondary to Nevirapine] (0.5%), herpes zoster (0.5%). Out of 200 patients, 159(79.5%) patient had an opportunistic infection as a cause of fever.In a study by Sharma et al[19] tuberculosis (TB) was the commonest OI (71%)followed by candidiasis (39.3%), Pneumocystis jiroveci pneumonia (PCP) (7.4%),cryptococcal meningitis and cerebral toxoplasmosis (3.7% each).

Studies by Lozano et al, Neha et al, Chacko et al & Sircar et al also found tuberculosis as most common opportunistic infection.[5,20,21,22].Some of the opportunistic conditions like Pneumocystis pneumoniaconspicuous by their absence. Some reasons for this could be the predominance ofpulmonary TB, and under-diagnosis of incident cases due to diagnosing difficulty andunavailability of broncho-alveolar lavage as well as decreased incidence secondaryto cotrimoxazole prophylaxis.

We classified these patients according to WHO clinical staging. We observedthat maximum number (57%) of cases was in clinical stage 4 followed by stage 3(34%) and least (2.5%) in stage 2. Thereason behind this as, the study wascarried out on hospitalized patients and patients with milder symptoms were beingtreated on out-patient basis.

In the current study we studied the pattern of opportunistic infection at variousCD4 count. Patients having CMV proctitis, CNS Toxoplasmosis, herpes zoster andcryptococcal meningitis had CD4 count < 200/µl. Out of 148 patients havingtuberculosis, 53 had CD4 count < 200/ µl, 40 had CD4 count between 200 - 350/ µl& 55 had CD4 count > 350/ µl. Unlike other opportunistic infections which have aselective range of CD4 in which the disease occurs, TB occurs throughout the course of HIV. These findings are supported by Swaminathan et al[23]and Ong et al.[24]

Impact of ART on fever: Out of 148 patients who had tuberculosis 98 (66.2%) were not on ART &50(33.7%) were on ART. Out of 5 patients of cryptococcal meningitis 4 were not onART& 1was on ART. All the patients having CMV proctitis, CNS toxoplasmosis andherpes zoster were not on ART. In our study we observed that patients who had OImost of them were ART naïve as most of the patients with HIV presented andadmitted to the hospital with an opportunistic infection. This finding is in concordance with study done by Lozano et al.[20]

Association between CD4 count, ART and mortality: In our study out of 200 patients, 31(15.5%) died and 169(74.5%) weredischarged. Out of 31 deaths 25 (80.6%) had CD4 count <200/µl and 6 (19.4%) hadCD4 count >200/µl. We found significant association ($p < 0.01$) between in-hospitalmortality and lower CD4 count. In-hospital mortality in this study is probably reflectiveof the advanced nature of disease at presentation. This is evidenced by the fact that80% of patients died had CD4+ counts less than 200/µL.In a study done by Sharma et al,65 21 (15.6%) out of 135 patients died andamongst them all except one had CD4 count less than 200/µl.Unexpectedly, CD4+ counts had no independent effect on mortality. A similarobservation has been reported in some previous studies done by Casalino et al and Nickas et al.'[25,26.] It appears that the virulence of the pathogen causing the OI, ratherthan the stage of the underlying disease, tends to influence the shortterm outcome.

In our study 82(41%) patients were on ART & 118(59%) were not on ART.Out of 31 patients died, 30 (96.8%) were not on ART & 1(3.2%) was on ART. Feverappears to have a better prognosis inpatients on ART, since only one in-hospitaldeath recorded among these patients in contrast with the non-ART group. Thisassociation was significant ($p < 0.01$) and was supported by study done by Lozano et al[13]

Correlation between Fever duration & CD4 Count, clinical stage, ART duration:In our study we found a significant correlation between durationof fever and CD4 count,clinicalstage.As CD4 count decreases duration of fever increases (inverse correlation r=0.43) and as clinical stage increases duration of fever increases (direct correlation=0.59).However, the correlation between ART duration and duration of fever wasnot significant.

V. Conclusions

The results of this study suggest that most common cause of fever in HIVpositive patients leading to hospitalization is an opportunistic infection andtuberculosis is the most common opportunistic infection causing fever. There is no correlation between duration of fever in HIV and duration ofART.However, fever appears to have a better prognosis in HIV positive patients onART. The duration of fever in HIV has a direct correlation with clinical stage of HIVand inverse correlation with CD4. The duration of fever increases as clinicalstage increases and CD4 count decreases.

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