

Clinical Study of Infective Aetiology of Fever in HIV Positive Patient in Tertiary Care Centre: A Prospective Study.

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ABSTRACT

Background: - HIV-AIDS is a most common global pandemic associate with destruction of human immunity and presents with various symptoms of infection like fever, cough, dyspnoea, lymphadenopathy and skin rash. Prolonged fever is a common presenting symptom in HIV infected individual. This presentation should not be ascribed to HIV infection itself and should be vigorously investigated to find a cause. For that reason, we conducted this study to find out most common infective aetiology in patients of HIV.

Methods: - It is a prospective observational study which was carried out in SMIMER Hospital, Surat, Gujarat, India over a period of 21 months from November 2020 to August 2022. It is a prospective observational study. All the HIV positive patients of age more than 12 years who admitted with fever ($\geq 100^{\circ}\text{F}$) are included in the study and other HIV negative patients with Fever, Patient who were on ART on OPD basis and HIV positive but age less than 12 years were excluded. The included patients underwent detailed history taking, about symptomatology, present or previous opportunistic infections, associated comorbidities and were thoroughly examined (general as well as systemic). In search of cause of fever patient were investigated preliminary with CBC, PBS, CD4 count, ESR, BSL, BUL, LFT, RFT, TT, CXR and urine (R&M). Sputum for AFB was also done in all patients irrespective of symptoms. Blood and urine cultures were also obtained in all cases along with sputum (C&S), included sputum for PJP in indicated patients. At the end of study, the data was analysed to find out most common cause of fever in these patients. Attempt was made to enumerate causes of fever in HIV patients and formulate sequential diagnostic procedures for evaluation of fever in these patients.

Results: -Most common infective aetiology for fever in this study is Mycobacterium Tuberculosis followed by Fungal aetiology, and then Bacterial, Parasitic and Viral Aetiology respectively.

Conclusion: -In any HIV positive patient who admitted with fever and other associated symptoms like cough, dyspnoea and weight loss, one should always look into the possibility of Mycobacterium infection while ruling out other causes of fever.

KEYWORDS: Fever, Tuberculosis, CD4 Count, Mycobacteria, HIV

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I. INTRODUCTION

HIV-AIDS is a global pandemic and most destructive epidemic in the history so far. Majority of patients present to health system with various symptoms, which may be specific or non-specific to underlying disorder.

Prolonged fever is a common presenting symptom in HIV infected individual. This presentation should not be ascribed to HIV infection itself and should be vigorously investigated to find a cause^[01].

More than 35.4 million people have died of AIDS since start of epidemics. Every week around 7000 young women aged 15-24 years become infected with HIV. In sub-Saharan Africa three in four new infections are among girls aged 15 to 19 years and young women aged 15 to 24 years are twice as likely to be living with HIV than men.

Much higher rates are found among people attending STD clinics (3.6%), sex workers (2.2%), injecting drug users (9.9%) and homosexual men (7.2%). Early descriptions of HIV epidemiology created a general perception that HIV infection was largely restricted to sex workers, truckers, and IDUs. The rest of the population was, and in many cases still is, in denial; meanwhile. The infection has spread further into the general population.

Despite the advances in HIV therapy, fever is one of the most frequent symptoms reported by HIV-infected individuals and is seen in nearer 97 percent of patients with symptomatic HIV infection^[02]. Documenting cause of fever in HIV-infected adult patients may help to improve comprehensive health care in centres with limited facilities. Lack of health facilities, lack of initiatives, social stigma, poor reporting system & surveillance are major obstacles in management of patients infected with HIV. So, every effort should be made to prevent the spread, diagnose this condition in its earliest possible stage and make treatment available to all individuals suffering from this disease. Fever is the most common presenting complaint in this illness, efforts should be taken to diagnose the cause of fever because it is usually due to opportunistic infections which are treatable.

With the help of this study, an attempt has been made to reveal the spectrum of causes of fever in these patients and to give formulated sequential diagnostic algorithm to diagnose fever in HIV infected individuals. This study will also mention the obstacles in managing these patients in the form of delay in diagnosis, limitation in health care facility and patient's barriers in percolating the awareness about this disease. This can overall increase our knowledge of the disease, its diagnosis and management in this HIV pandemic.

II. AIM AND OBJECTIVES

- To evaluate the clinical profile of causes of infective etiology of fever in HIV infected patients by sign, symptoms, clinical examination and laboratory investigations.
- To attempt to compare the cause of fever with disease stage.

III. MATERIAL AND METHODS

A Prospective observational study has been conducted at SMIMER hospital, Surat, Gujarat, India which is a tertiary care teaching referral hospital with approx. 850 beds. This hospital has facilities such as portable X-ray, CT scan, MRI imaging, CT scan, haematology, advance biochemistry laboratory, endocrine and microbiology laboratories.

The study was carried out on 95 patients admitted in hospital between November 2020 to August 2022 who are HIV positive and have fever.

Sample Size calculations:

Sample size:

P= 90% (Prevalence of fever in HIV cases)^[03]

Confidence level =95%

Power = 80%

Absolute Precision = E = 9%

$$n = \frac{(Z_{\alpha} + Z_{\beta})^2 P(1-P)}{E^2} \\ = \frac{\{(1.96 * 1.96) + (0.84 * 0.84)\} * \{(90 * 10)\}}{(9 * 9)} \\ = 87.11 = 88$$

So, we have taken 95 cases.

Criteria for Inclusion

- 1) All patients who are seropositive for HIV -1 or HIV- 2, either with ELISA or rapid kit or both.
- 2) Age of patient must be above 12 years.
- 3) They should have documented at least one episode of fever for or over 3 days after admission to hospital.

- 4) Fever should be documented at least on one occasion and must be more than 100-degree F.

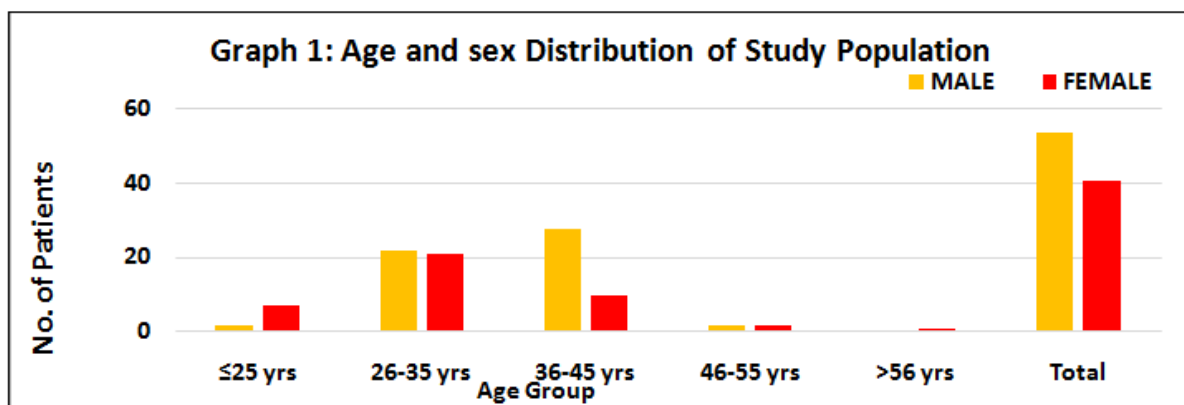
Criteria for Exclusion

- 1) HIV negative patients or those with unknown serological status who admitted with fever.
- 2) HIV positive patients with age less than 12 years.
- 3) The outpatient department patients who are coming in either medicine or ART OPD with h/o fever.
- 4) Failure to document fever after admission or fever less than 100-degree F.

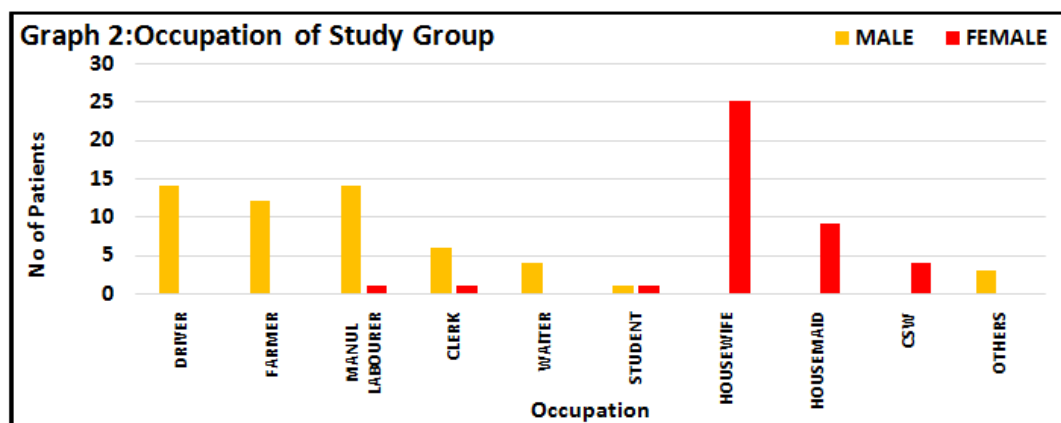
The included patients underwent detailed history taking, about symptomatology, present or previous opportunistic infections, associated comorbidities and were thoroughly examined (general as well as systemic). In search of cause of fever patient were investigated preliminary with CBC, PBS, CD4 count, ESR, BSL, BUL, LFT, RFT, TT, CXR and urine (R&M). Sputum for AFB was also done in all patients irrespective of symptoms. Blood and urine cultures were also obtained in all cases along with sputum (C&S), included sputum for PJP in indicated patients. CD4 count was estimated by flow cytometry in all patients.

If diagnosis was not achieved with these baseline investigations, further investigations carried out to find out cause of fever as per symptomatology and clinical judgment. The investigations were carried out until cause of fever was found out. If all required investigations failed to reveal the cause of fever, then we proceeded with liver biopsy. After diagnosis patients were staged according to WHO classification and CDC staging. Patients were reviewed daily as their investigations progressed and diagnosis was made. At the end of study, the data was analysed to find out most common cause of fever in these patients. Attempt was made to enumerate causes of fever in HIV patients and formulate sequential diagnostic procedures for evaluation of fever in these patients.

IV. Observations And Results



This study was conducted in HIV Positive adult patients who were admitted in medicine wards with history of fever with, at least one episode of documented fever >100-degree F. collected data was analysed and salient features of study data are as follows. In conducted study majority of patients were of age group 26-35 years and sexually active group (26-45 years). The no. of males included 54 and total no. of females were 41.



The most common occupation seen in males included in this study were drivers and manual laborers. Out of 41 females included in the study 25 were housewives, 9 were housemaid, 4 were commercial sex workers and others were potter, salesman and shopkeeper.

TABLE NO: 01 SYMPTOMATOLOGY OF CASES

Sr. No.	Symptom	No. of cases	Percentage
1.	DYSPNOEA	24	25.26%
2.	CHEST PAIN	12	12.63%
3.	COUGH & OR EXPECTORATION	24	25.26%
4.	FATIGUE	50	52.63%
5.	WEIGHT LOSS	35	36.84%
6.	SKIN RASH	02	2.10%
7.	HEADACHE	24	25.26%
8.	CONVULSION	17	17.89%
9.	ALTERED SENSORIUM	22	23.15%
10.	FOCAL NEUROLOGICAL DEFICIT	13	13.68%

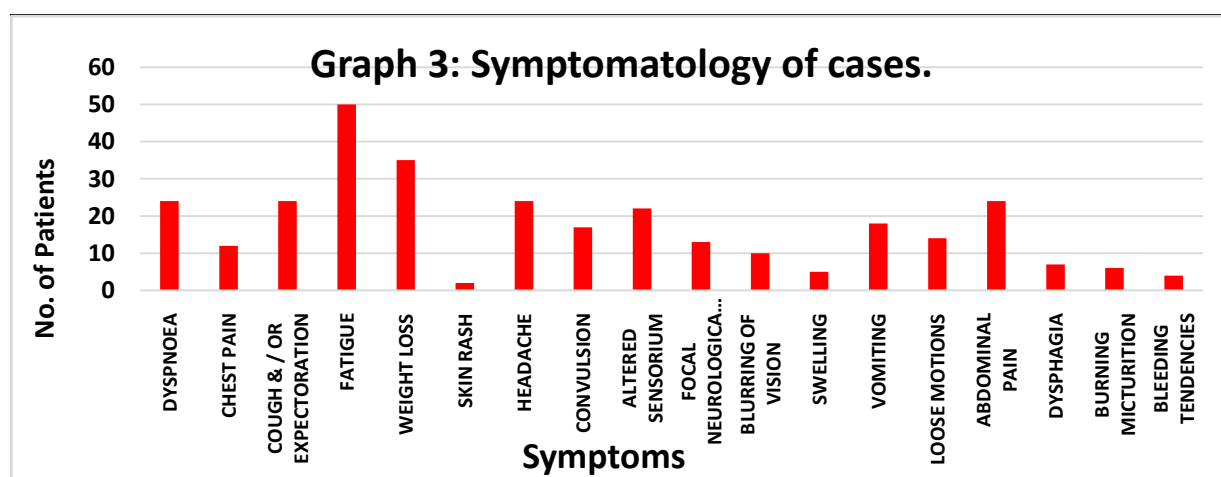


TABLE NO: 02 CAUSES OF FEVER IN THIS STUDY

Causes	No. of Patients	Percentage (%)
MYCOBACTERIA	34	35.78 %
BACTERIAL	18	19.94 %
PARASITIC	15	15.78 %
FUNGAL	19	20 %
VIRAL	09	9.47 %

TABLE NO: 03 SYSTEM WISE PRESENTION OF CASES

TABLE NO: 3.1 NERVOUS SYSTEM		
DISEASE	NO OF CASES	PERCENTAGE
Tubercular meningitis	08	21.05%
Cryptococcal meningitis	13	32.21%
Toxoplasma encephalitis	10	26.31%
Tubercular brain abscess	01	02.63%
HSV encephalitis	01	02.63%
Bacterial meningitis	04	10.53%
PML	01	02.63%
Total	38	100

TABLE NO: 3.2 RESPIRATORY SYSTEM		
DISEASE	NO OF CASES	PERCENTAGE
Sputum (+) Koch's	05	38.46
Bacterial pneumonia	05	38.46
PJP	03	23.07
TOTAL	13	100

TABLE NO: 3.3GASTROINTESTINAL SYSTEM		
DISEASE	TOTAL CASES	PERCENTAGE
Abdominal Koch's	06	24.00

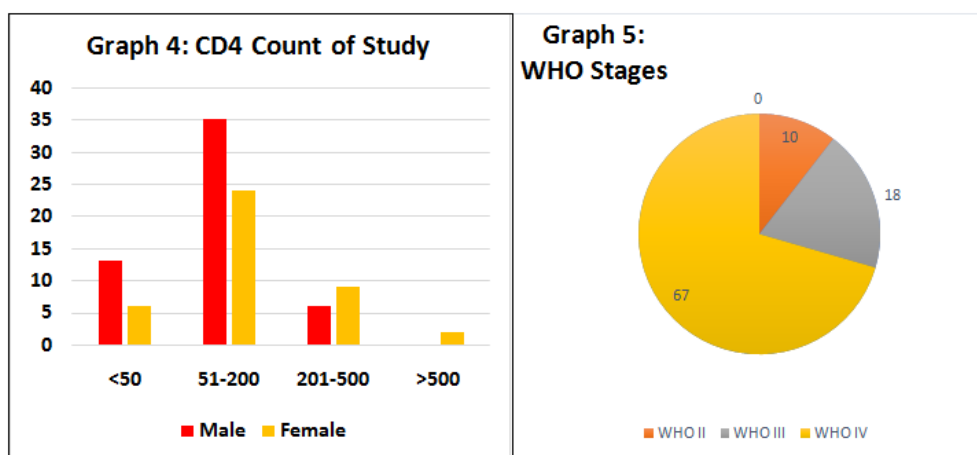
Enteric fever	03	12.00
Urinary tract infection	05	20.00
Cryptosporidium diarrhoea	01	04.00
Amoebic dysentery	01	04.00
Candida esophagitis	03	12.00
CMV esophagitis	02	08.00
Tubercular esophagitis	01	04.00
Idiopathic HIV ulcer	01	04.00
Pyogenic Liver abscess	01	04.00
Hbs Ag (+) hepatitis	01	04.00
TOTAL	25	100

TABLE NO: 3.4 OTHER MENIFESTATIONS

DISEASE	NO OF CASES	PERCENTAGE
Disseminated Tuberculosis	07	36.84
Disseminated Atypical Mycobacterial infection	01	5.26
Lepromatous Leprosy	01	5.26
Tubercular pericardial effusion	01	5.26
Tubercular Lymphadenitis	03	15.78
Herpes Labialis	01	5.26
Malaria	03	15.78
Dengue	02	10.52
Total	19	100

TABLE NO: 4 GENERAL EXAMINATION IN STUDY POPULATION

SIGNS OF GENERAL EXAMINATION	NO.	PERCENTAGE (%)	COMMENT
Pallor	93	97.89%	As patients were seen in advanced stage
Oral candidiasis	24	25.26	
Lymphadenopathy	9	9.4%	Mainly cervical.
Herpes zoster scar	04	4.21%	Mainly thoracic segments
Herpes rash	01	1.05%	Active herpes labilis



SPECIAL INVESTIGATIONS USED IN STUDY

TABLE NO 5.1: EXAMINATION OF CSF IN STUDY POPULATION

Disease entity	Protein Mg/dl	Sugar Mg/dl	Cells	Differential Count	Special Investigations used
Cryptococcal meningitis	16-58	17-70	0-76	Predominantly Lymphocytes	India Ink-09 Ag-03
Toxoplasma encephalitis	20-120	16-92	0-200	Predominantly Lymphocytes	Toxoplasma antibodies
Tubercular meningitis	50-306	15-60	40-162	Predominantly Lymphocytes	ADA 19-23
Bacterial meningitis	80-200	10-15	5000-15000	Predominantly Polymorph	CSF culture
HSV encephalitis	83	49	50	Predominantly Polymorph	HSV Igm+
PML	20	85	1	Lymphocyte	Brain biopsy

TABLE NO. 5.2 SEROLOGICAL INVESTIGATION

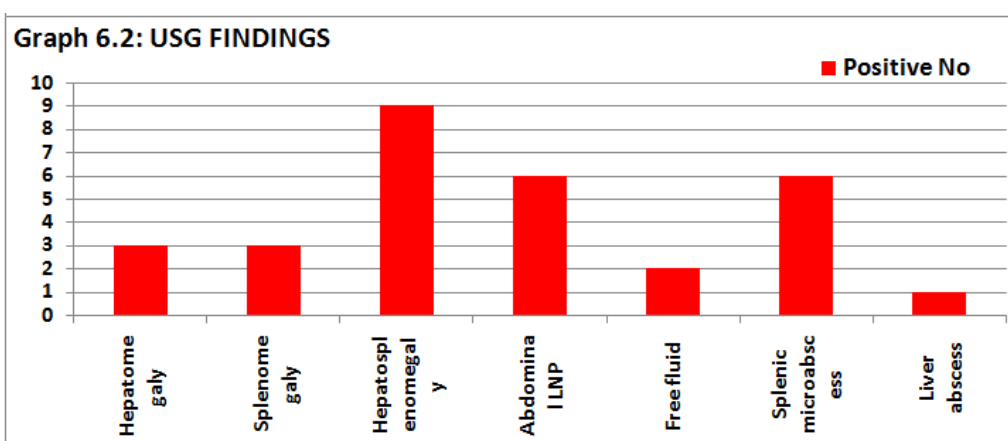
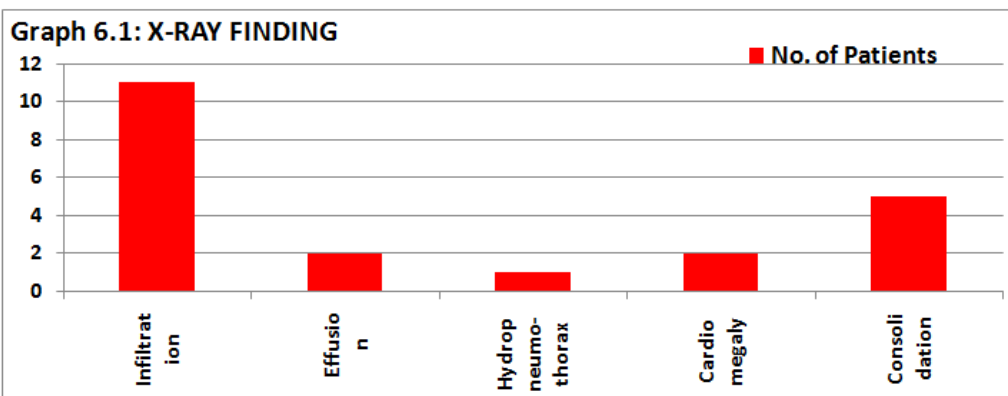
Serological Investigation	Positive
VDRL	00
HBsAg	01
Widal	00
Dengue IgM	02
Toxoplasma antibodies	10
CSF HSV Ig M antibody	01

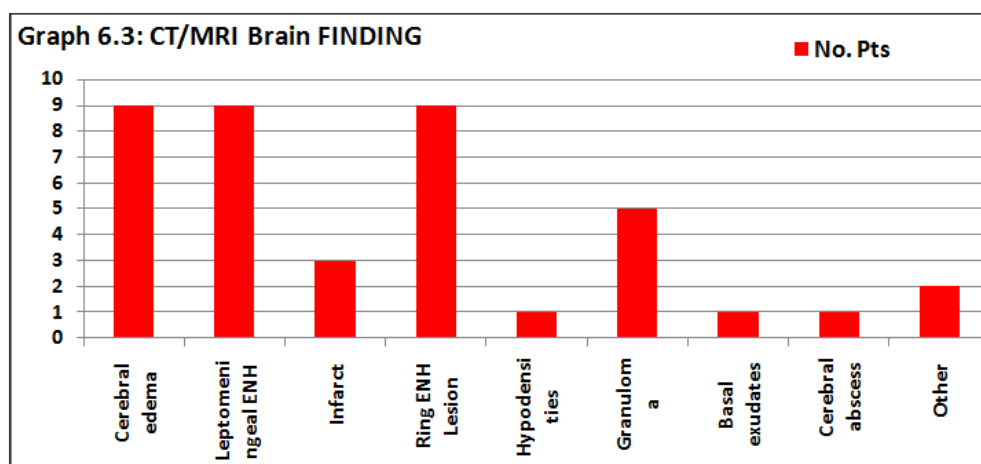
TABLE NO: 5.3MICROBIOLOGICAL INVESTIGATION

Serological Investigation	Done in	Positive	Percentage
Blood culture	95	09	9.47%
Urine culture	95	05	5.26%
Stool culture	00	00	00%
Sputum culture	56	03	5.35%
Sputum AFB	95	06	6.31%

TABLE NO: 5.4 & RADIOLOGICAL INVESTIGATIONS IN THIS STUDY

Radiology	Done in	Positive	Percentage
XRC	95	21	22.10%
USG (A&P)	95	23	24.2%





The histopathological specimen examined in this study included lymph nodes, bone marrow examination, liver biopsies, oesophageal mucosal biopsies taken on OGD Scopey and one brain biopsy in case of PML. It was found that these histopathological specimens studied mainly gave diagnosis of tuberculosis which is comparable to Orenstein study, but we have not got fungal infection in these biopsy specimens (except one cryptococci in lymph node biopsy).

V. Discussion

The epidemic of HIV has become truly global in scope and cuts the conventional boundaries of nationality, sex, age and race. We have studied 95 HIV seropositive in this study and data of these- patients has been elaborated in the section of 'RESULTS'. We have tried to analyse the common cause of fever in this study group as well as the baseline characteristic of the study population and how to derive an algorithm for causes of prolonged fever in HIV infected patients.

Age and Sex Distribution. (Graph 01)

Out of 95 patients, 54 were males and 41 were females. The male-female ratio was 1.31:1. Various studies in INDIA show different sex distribution with Kumar Swamy et al^[04] giving a ratio of 2:1. National Indian ratio given by NACO, India is around 3: 1. Out of 95 patients 43 patients belonged to the age group of 26-35 years which is a sexually active group of the community, similar results were found by Nair et al^[05]. In our study age range was 14 -60 with 2% of population above 56 years. This is mainly true for these above-mentioned studies which were done to determine the clinico-epidemiological profile of HIV infected patients.

Occupation in the Study Group. (Graph 02)

The most common occupation seen in males included in the study were driver 14 and manual laborers 14 followed by farmers 12, clerk 6 and 4 were waiters, 1 was a student, out of 41 females included in study 25 were housewives. The most common Occupation in female study group was housemaid in 9 patients While 4 were commercial sex workers. Others were student, labourer and clerk one each. Manual laborers formed the major group of cases (15.7%). Majority of the laborers were migrants from different parts of the country like Bihar, Uttar Pradesh and South India. This sexually active group has to stay away from their homes and wives for months. Thus, leading to promiscuous behaviour increasing their exposures to commercial sex workers. This also increases their risk of contracting STDs including HIV.

Symptomatology of Cases (Table no 1, Graph 3)

Along with fever which was inclusion criteria of study population, the other common symptoms seen in the study population were fatigue seen in 50 patients followed by weight loss affecting 36.84 % of patients. Since most of the patients had never recorded weight prior to study, few patients with probably significant weight loss may have been missed. As we have discussed further tuberculosis is the commonest cause of fever in our study where weight loss is common. The weight loss can be explained and anticipated as not only because of HIV disease but also due to associated opportunistic infections also contributes to it. The association of weight loss at presentation of TB in HIV infected patients has been reported before.^[06] The second most common symptom found was dyspnoea. Other symptoms were abdominal pain (25.2%), cough (25.26%), headache (25.2%), altered sensorium (23.15%). Focal neurological deficit was found in 13.68% patients and convulsions in 17.9 %. These findings are similar to those observed by Munir et al^[07].

HIV infection per se can cause lymphadenopathy which is often seen after primary infection. The common causes include infections bacterial like tuberculosis, syphilis, fungal including histoplasmosis, parasitic toxoplasmosis, malignancies like NHL and Kaposi's sarcoma. Among neurological complaints headache was common complaint, the finding is similar to Hollander H. et al.^[08]

In abdominal symptomatology, abdominal pain was commonly seen in 24 patients, vomiting in 18, loose stools in 14 patients. 7 of them presented with dysphagia and 6 with burning micturition. Skin rash was seen in 2 patients. Bleeding manifestations were seen in 4 patients.

Causes of Fever (Table 2)

As it is rightly said that fever in HIV is usually due to treatable opportunistic infections^[1] Various other studies also demonstrate infections presenting with fever in HIV as very common^[9] Though limited data is available regarding the causes of fever in HIV infected Indian patients, however we could find a cohort study in which causes of prolonged fever were profiled and developed suitable algorithms to assist in an early diagnosis^[10] The clinical implication of fever in the HIV infected population has not been evaluated yet, patient very commonly present with fever as described by Kent et al^[11].

In our study we found Mycobacterial infections as the most common cause of fever in HIV patients seen in 34 patients, followed by fungal infection in 19 patients and bacterial infections in 18 patients. Parasitic infections found in 15 patients most commonly being toxoplasmosis, in 9 patients showed viral pathology including CMV esophagitis and idiopathic HIV ulcer. In this it has been recommended that mycobacterial infection should be considered as a first- line diagnosis in febrile course of HIV infections. For diagnosis of causes of fever in HIV infected patients the diagnostic approach is followed as per given by Rupali et al^[10].

System Affections (Table 3).

These etiological findings are described in terms of system affection table (03) revealed majority of patients affected with nervous system in total of 38 cases followed by abdominal system affection in 25 cases. We have seen in symptomatology that cough and dyspnoea presented in 48 cases compared to FND and convulsion in 30 cases which could be explained by the fact that as 7 patients had disseminated tuberculosis, 1 had disseminated atypical mycobacterial infection, 3 had TB lymphadenitis. Following causes of fever, we have briefly presented the various system affected with the diagnosis in table no 3.

General Examination (Table no 4)

In our study we have noted almost all patients with pallor 97.89 % followed by oral candida 24 patients. Zoster scars seen in 4 patients; lymphadenopathy found in 9 patients. Nalini et al^[12] also found 10 % patients with oral candida. Detailed general physical examination not only adds valuable information but is also useful to determine stage of disease as primary HIV infection is associated with lymphadenopathy, macular rash. Though only 2 patients actively complained of skin rash, we found erythema multiforme along with zoster rash, other skin findings were xerosis seen in fourteen patients which is higher percentage compared to Dann et al^[13] who found an incidence of 8%.

Base Line CD4 in Study (Graph 4)

Out of 95 patients 20 % of population had CD4 of <50 cells/mic.L and around 62.1 % had between 50-200cells/mic. L. slightly higher than Riera et al^[14]. As we know there is good correlation between CD4 count and immune competence of individual, and so CD4 is used as standard test to assess prognosis for progression to AIDS or death^[13]. It is also useful for etiological diagnosis of diseases in natural history of HIV infection. There is very well documented correlation between CD4 count and stage of disease. It also helps to make therapeutic decisions regarding antiviral treatment^[15] and prophylaxis for OIs. CD8 cell counts have not been measured in all cases as it is known that it does not predict outcome^[16]. Fortunately, we have access to CD4 count at our centre and could determine CD4 in all patients but it has been suggested that clinician who do not have access to CD4 will probably use total lymphocyte count.

Clinical Stage of Study Population (Graph 5)

After discussing CD4 count of study population, let us review the clinical stage of patients. In this study maximum no of patients belonged to stage IV disease which accounted for 70 % of total similar to Genne et al^[17] who found 90% of his study group presented in stage IV disease. It is clear that fair no. of patients presented to medical care very late in their disease stage. Barriers in accessing antiretroviral therapy

- The transportation and supplementary food costs
- Referral hospital's reputation for being unfriendly and confusing
- Fear of stigma
- Difficulties in sustaining long term treatment

Similar study was conducted in Chennai by Kumarswamy et al^[18], analysed that cost of therapy was major barrier for accessing health care and other centred on privacy and stigma issues.

Other thing to note is that none of them were diagnosed in stage I, an indirect clue of either delayed diagnosis, delayed referral and unawareness of HIV statuses a result of which these patients being admitting in our tertiary

disseminated form in 7 patients. Table no 13 gives tuberculosis affection in our study. Other mycobacterial infections were disseminated atypical mycobacteria in one and lepromatous leprosy in one patient. The causes of fever found in the present study has been compared with study done by Rupali et al ^[10]. In our study tuberculosis is the most common aetiology identified as a cause of fever similar to previous study. The extra pulmonary tuberculosis included abdominal, tubercular meningitis, tubercular pericarditis with pericardial effusion, tubercular brain abscess, tubercular oesophageal ulcer and tubercular lymphadenitis. Also, a study done by Ragini et al ^[23] who studied clinico-epidemiological profile of HIV- TB co-infected patients in Vadodara, Gujarat, found 68.3% affected with extra pulmonary sites and 23.19% presented with disseminated form with pulmonary as well as other sites. In our study we found 20 patients with TB and 7 with disseminated TB. Table 5 discusses profile of extra pulmonary tuberculosis in present study. It is quite evident to diagnose common causes of fever the common diagnostic tests are useful and systemic approach and guided investigations can diagnose majority of causes of fever in HIV infected patients.

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ABBREVIATIONS

1.	ADA	Adenine deaminase	33.	MO	Medical officer
2.	AIDS	Acquired immunodeficiency syndrome	34.	MRI	Magnetic resonance imaging
3.	ART	Anti-retroviral therapy	35.	HIV	Human immunodeficiency virus
4.	ATT	Antitubercular therapy	36.	HRCT	High resolution computed tomography
5.	BSL	Blood sugar level	37.	HSV	Herpes simplex virus
6.	BUL	Blood urea level	38.	HTLV	Human T cell lymphotropic virus
7.	CBC	Complete blood count	39.	IDU	IV drug abuse
8.	CD	Cluster of differentiation	40.	LFT	Liver function test
9.	CDCV	Centre for disease control	41.	LNP	Lymphadenopathy
10.	CMI	Cell mediated immunity	42.	LP	Lumbar Puncture
11.	CMV	Cytomegalo virus	43.	MAC	Mycobacterium Avium Complex
12.	CRP	C-reactive protein	44.	MO	Medical Officer
13.	CT	Computed tomography	45.	MRI	Magnetic resonance imaging
14.	CXR	Chest X-Ray	46.	NHL	Non-Hodgkin's Lymphoma
15.	EBV	Ebstein Barr virus	47.	OPD	Outpatient department
16.	EIA	Enzyme immune assay	48.	PBS	Peripheral blood smear
17.	ELISA	Enzyme linked immunosorbent assay	49.	PCR	Polymerase chain reaction
18.	ESR	Erythrocyte sedimentation rate	50.	PJP	Pneumocystic Jiroveci Pneumonia
19.	FNAC	Fine needle aspiration cytology	51.	PLHA	Person Living with HIV AIDS
20.	FND	Focal neurological deficit	52.	PML	Progressive multifocal leukoencephalopathy
21.	FUO	Fever of unknown origin	53.	PNS	Peripheral Nervous system
22.	HAART	Highly active antiretroviral therapy	54.	PUO	Pyrexia of unknown origin
23.	HHV	Human herpes virus	55.	RFT	Renal function test
24.	HIV	Human immunodeficiency virus	56.	STD	Sexually transmitted diseases
25.	HRCT	High resolution computed tomography	57.	TB	Tuberculosis
26.	HSV	Herpes simplex virus	58.	TLC	Total leucocyte count
27.	HTLV	Human T cell lymphotropic virus	59.	TT	Tuberculin test
28.	IDU	IV drug abuse	60.	USG	Ultrasonography
29.	LFT	Liver function test	61.	VDRL	Venereal disease research laboratory
30.	LNP	Lymphadenopathy	62.	VZV	Varicella Zoster Virus
31.	LP	Lumbar Puncture	63.	WB	Western Bolt
32.	MAC	Mycobacterium Avium Complex	64.	WHO	World health organization