

Fever in patients with HIV infection in a teaching hospital in Iran

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ABSTRACT

Background: Fever, is a common sign during the course of HIV infection. The aim of this study was to describe the etiology and clinical characteristics of fever among HIV/AIDS patients in a teaching hospital in Iran.

Patients and methods: In this existing data study, we retrospectively reviewed the charts of admitted HIV/AIDS patients with fever to Imam Khomeini hospital, from October 1995 to March 2005 to assess the causes of their fever.

Results: Totally, 125 admissions were performed for 120 patients. The mean (\pm SD) age was 34.8 ± 14.7 years. The final diagnosis of fever was determined in 65.6% of all admissions. Mostly (34.4%), the cause of fever remained undiagnosed. Pulmonary tuberculosis was the most commonly identified etiology of fever (33.6%), followed by opportunistic infections such as oral candidiasis, *Pneumocystis jirovecii* pneumonia and cerebral toxoplasmosis.

Conclusion: Tuberculosis is the most common infection in Iranian HIV/AIDS patients and appropriate workup should be considered in all feverish HIV/AIDS patients.

Keywords: HIV/AIDS, Fever, Tuberculosis.

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INTRODUCTION

Fever is a nonspecific body response to extrinsic and intrinsic factors that result in increase of body temperature set-point, with physiological mechanisms (1). Fever, either continuous or recurrent, is a common finding in patients infected with HIV (human immunodeficiency virus) and is often accompanied by significant morbidity, prolonged hospitalization, and extensive evaluation (2). Fever usually represents a superimposed opportunistic infection and is almost always a treatable condition (3). Previous studies of fever in HIV-infected persons have focused on fever of

unknown origin (FUO) or outpatient conditions (4,5). Barat and co-workers concluded that bacterial infection, especially pneumonia, is a common cause of fever in HIV-infected patients admitted to Boston city hospital (6). Armstrong and his colleagues found that the most common diagnoses for FUO and HIV in United States were disseminated *Mycobacterium avium* infection, *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection (7). Riera et al remarked that FUO in patients with HIV infection in Balearic Islands is caused primarily by endemic opportunistic infections specially tuberculosis and visceral leishmaniasis, and rarely can be attributable to HIV or neoplastic diseases (8).

Keep in mind prior studies and the fact that there is no thorough evaluation of fever causes in

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Iranian HIV patients in the literature, we surveyed causes of fever in HIV-infected patients admitted to the Infectious Diseases Ward at Imam Khomeini hospital, Tehran, Iran.

PATIENTS and METHODS

For this existing data study, we analyzed the demographic and clinical parameters of patients with fever and HIV/AIDS infection who were admitted to the Infectious Diseases Ward of Imam Khomeini Hospital, Tehran, Iran from October 1995 to March 2005. The following inclusion criteria were applied at baseline: reactive ELISA twice followed by positive western-blot test, an oral temperature of $\geq 100.4^{\circ}\text{F}$ (38°C) on two consecutive days or $\geq 101^{\circ}\text{F}$ (38.3°C) during any single measurement within the first 48 hours of admission.

Study variables included: age, sex, chief complaint, HIV risk factors (history of unsafe sexual contact, injection drug use, being in prison, homelessness, and tattooing), opportunistic diseases, T cell CD4 count, prescribed medication (antiretroviral and prophylactic drugs), type of organisms isolated from blood or urine (sterile parts of body) and final diagnosis.

There were no specific ethic miss points in this study and patients' data remained secret.

RESULTS

The study population included 109 males and 11 females with the mean ($\pm\text{SD}$) age of 34.8 ± 14.7 years and 125 episodes of fever. Totally, 46 patients (38.3%) aged 31-40 years and 19 patients (15.8%) had a history of unsafe sexual contact while 87 patients (72.5%) were injection drug users (IDUs).

Pulmonary complaint was the first cause of admission, found in 29.6% of patients. Complaints of gastrointestinal, nervous and musculoskeletal systems were found in 18.4%, 8.8% and 6.4% of

patients, respectively. CD4 count was charted in only 56 episodes of 125 fever episodes, most of which had CD4 count $>200/\text{mm}^3$ (36 fever episodes or 64.3%).

Antiretroviral drugs had been prescribed in 31 episodes (24.8%), and prophylactic drugs had been administered in 38 episodes (30.5%).

As shown in table 1, the most common opportunistic diseases in fever episodes of patients with HIV/AIDS were oral candidiasis, *Pneumocystis jirovecii* pneumonia and cerebral toxoplasmosis. On the other hand, 37.5% (6 out of 16) of organisms isolated from sterile parts of the body (blood or urine) in feverish patients were *Candida*. Other isolated organisms were as follow: *Escherichia coli*(25%), *Staphylococcus aureus* (18.8%), *Salmonella typhi*(6.3%), *Enterobacter spp.*(6.3%), *Staphylococcus epidermidis* (6.3%).

The final diagnosis of fever was determined in 65.6% of episodes. In other words, 43 episodes (34.4%) of fever were categorized under fever of unknown origin (FUO). Besides, 42 episodes (33.6%) were ultimately diagnosed with pulmonary tuberculosis. Other final diagnoses were as follow: Pneumonia (21.9%), toxoplasmosis encephalitis (15.9%), endocarditis (6.1%), and others (syphilis, extrapulmonary tuberculosis, lymphoma) (4.9%).

Table 1. Frequency of opportunistic infections in febrile HIV/AIDS patients

Opportunistic infections	Number	%
Oral candidiasis	16	35.5
PCP	10	22.5
TE	10	22.5
Oral candidiasis and TE	3	6.6
Osteoarticular TB	3	6.6
TB meningitis	2	4.4
TB peritonitis	1	2.2

PCP: *Pneumocystis jirovecii* pneumonia, TB: Tuberculosis, TE: Toxoplasmosis encephalitis

DISCUSSION

In this study we evaluated the causes of fever in patients with HIV/AIDS who were admitted to Imam Khomeini Hospital between 1995 and 2005.

Our demographic data revealed that majority of HIV-infected patients presenting with fever aged between 31-40 years. A finding that is in agreement with Barat and Armstrong studies (6,7). The high prevalence of HIV in this age group within this setting may in part be attributed to the associated high incidence of risk factors for HIV infection among the same age group (injection drug use and unsafe sexual contact). Among this age group, 90% were men as compared with 72%, 88%, and 72% reported by Barat, Armstrong, and Abellan-Martinez, respectively (6,7,9). Interestingly, only a few patients reported history of unsafe sexual contact as the likely source of primary HIV infection, with majority citing a history of IDU rather than sexual promiscuity. These findings suggested that IDU may be the most common risk factor to HIV in this setting. The later may be due to stringent cultural and religious values in our country where extramarital sex relationship are non-permissive. However, just as differences in cultural values (societal and religious non-permissiveness for extramarital sex) may explain why sexual contact may not be the most reported risk factor to HIV in this setting relative to studies elsewhere (6), we note also that such norms may equally be the cause of a non- or low-reporting state of unsafe sexual contact for fear of societal rebuke. Our findings show a slightly higher (72%) association between fever and IDU when compared with data reported by Barat (64%) (6). We have attributed this discrepancy to the fact that IDU, the most common reported risk factor to HIV among our study population, is also a mean of transmission for several blood borne pathogens whose course is known to be associated with fever such as bacterial endocarditis. In addition, although several findings in this study denote a number of similarities to those documented by previous studies (6,7), a number of discrepancies can be also noted. For instance, we found a comparatively similar report of pulmonary disease as the chief complaint (29.6%) among HIV patients presenting

with fever in our setting as reported by Barat in Boston (6). This is in agreement with another study from Belgium in which 61% of HIV patients presenting with fever had respiratory and gastrointestinal symptoms (10). On the other hand, while oral candidiasis was found as the most common opportunistic infection in this study (35.5%); Barat et al and Armstrong et al found *Pneumocystis jirovecii* pneumonia and diffused *Mycobacterium avium* as the most common opportunistic infections (6,7). We believe that such discrepancies may in part be explained by: 1) variations in HIV disease staging at which the study subjects were recruited in the various studies, 2) the sensitivity of clinical evaluation and diagnostic interventions, and 3) variations in the prevalence of endemic pathogens that are potential causes of opportunistic infections in HIV/AIDS. Our results also show that most patients presenting with fever in this setting have a CD4 cell count more than $200/\text{mm}^3$, which is consistent with the findings of previous related studies (5-10). Such findings cumulatively serve to emphasize the fact that fever may be a common occurrence even among patients with CD4 that are above 200 cell/mm³ (the figure widely employed to determine initiation of HAART). Only 24.8% of our patients had prior use of anti-retroviral drugs (ARVs) compared to 56% in Barat study (6). The low rates of ARV use in this setting may in part be due to the fact that HIV/AIDS is only an emerging health problem here, and the necessary referral systems through which patients can access HAART are not well developed at the time that study was performed. To note also is that these drugs were not available free of charge in this setting at the time this study was conducted. However, majority of our subjects had a CD4 cell count above the minimum CD4 cell widely employed to determine initiation of HAART ($200 \text{ cell}/\text{mm}^3$), hence, it is not surprising that only a few had prior use of HAART.

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The incidence of positively isolating pathogenic organisms from sterile parts of the body by blood and urine culture was lower in our study (12.8%) as compared with others (4,6,8). This could mainly be attributed to prior antibiotic use.

Generally, the most common causes of fever in our study were fever of unknown origin (FUO) and pulmonary tuberculosis as opposed to bacterial infections (especially bacterial pneumonia) in Barat study (6). While we could not speculate at this point on what may be the underlying cause of FUO in this setting, we noted that in a study of 70 HIV patients in the United States with FUO, Amstrong et al found disseminated *Mycobacterium avium* infection, *Pneumocystis jirovecii* pneumonia and cytomegalovirus infection as the most common causes of fever of unknown origin in HIV patients (7). On the Other hand, pulmonary tuberculosis is a common occurrence among HIV patients, and our findings are not far from the picture seen elsewhere. For instance, Riera et al found pulmonary tuberculosis and visceral leishmaniasis as the most common causes of fever (8). While previous studies of persons living with HIV/AIDS (PLWHA) have shown that a CD4 cell count below 200 cells/mm³ is highly associated with pathogens that characteristically represent AIDS-defining diagnoses including *Pneumocystis jirovecii* pneumonia (10,11), disseminated *Mycobacterium avium* and cytomegalovirus infection (13-15); we show here that pulmonary tuberculosis can occur at CD4 cell counts above 200 cells/mm³, implying that TB should be considered as a differential diagnosis in all persons with HIV, presenting with fever in the clinic regardless of degree of immunosuppression. In general, despite the variations in the modes of spread between HIV (blood and body fluid borne) and TB (air borne); the prevalence of active tuberculosis in patients with HIV infection has been noted to become significantly higher in IDUs (which may be due to closer contacts during needle sharing, and the fact that IDU is a risk factor for HIV) and residents in

selective locations where TB is generally a problem (16). HIV has been denoted as one of the greatest risk factors for developing active tuberculosis, with some regions in Sub-Saharan Africa having TB and HIV co-infections correlations as high as 50%. Just as HIV infection increases the risk for development of active TB and TB recurrence (17), tuberculosis may similarly accelerate the progression of HIV infection (17). Keep in mind the high prevalence of tuberculosis in Iran, it is, therefore, not surprising that the majority of our final diagnoses were pulmonary tuberculosis. Hence, we recommend that more emphasis be put on building capacity for the diagnosis and treatment of tuberculosis among PLWHA in this region where HIV/AIDS is only an emerging problem.

This study had some restrictions such as the technical problems in obtaining appropriate specimens and invasive procedures for detecting the causes of fever in patients with HIV/AIDS. Additionally, evaluation for CMV infection was not performed in these patients.

Finally, the following recommendations are proposed:

1. Since majority of cases with HIV/AIDS in our setting cite IDU as the likely primary source of infection, focusing prevention and control measures to IDUs may play a significant role in curtailing HIV prevalence within this setting.

2. FUO and TB form the major causes of fever in PLWHA within this setting. Although tuberculosis is not blood borne, the high risk of acquiring HIV associate with IDU equally makes TB a common finding among IDUs- PLWHA here, since HIV has been noted to be one of the greatest risk factors for developing active TB disease. Building capacity for effective TB diagnosis and treatment may reduce the outcome of patients presenting with fever in this setting. In addition, since the high prevalence of fever of unknown origin (FUO) in this study may be due to the lack of exact evaluation of patients with necessary

invasive methods, the problems in taking appropriate samples and technical problems, ensuring that appropriate tests are done in a timely manner may increase the number of patients with identifiable etiologies. Although FUO is caused by multiple etiologies, with regarding high prevalence of FUO and tuberculosis in this Iranian hospital setting, there is a need to rule out pulmonary tuberculosis in all patients with pyrexia. Last but not least, emergency trial or experimental therapy against tuberculosis in severely ill HIV/AIDS patients presenting in this Iranian setting contribute towards reducing associated mortality and morbidity among PLWHA who presenting with fever within this setting, since the majority diagnosable cause of fever was tuberculosis.

3. Generally, within resource limited or constrained settings, understanding of the most prevalent causes of fever in PLWHA may be one of the strategies to employ in planning and budgeting where resources should be concentrated to reduce morbidity and mortality associated with fever in PLWHA.

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