PROLONGED FEVER ETIOLOGIES IN HIV/AIDS PATIENTS AND THE RELATION WITH TCD4 COUNT (1/2016 - 6/2019)

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Summary

Objectives: Prolonged fever is a challenge for clinician in managing patients with HIV/AIDS. Their TCD4 counts can be helpful in the diagnosis and treatment. Our goal was to determinethe most common etiologies of prolonged fever and their distribution in different TCD4 count levels in HIV/AIDS patients. *Subjects and method:* A cross - sectional descriptive study was conducted on 195 HIV/AIDS patients with fever of unknown origin admitted to our hospital from January 2016 to June 2019. We recorded clinical parameters, immune status and etiologies for each patient. Patient immune status based on TCD4 counts was stratified into three levels: < 50 cells/mm^3; 50 - 100 cells/mm^3 and > 100 cells/mm^3. We determined the prolonged fever etiologies in HIV infected patients and compared the distributionof these etiologies in different TCD4 count levels. *Results:* Among 195 HIV - infected cases with fever of unknown origin, opportunistic infections accounted for 93.3%, non - infectious etiologies took 3.6% and 3.1% were not identified causes. *M. tuberculosis* was the most common opportunistic infection (46.7%), followed by *Talaromycosis* (29.2%) and Pneumocytisjiroveci (20.5%), Bacterial pneumonia (11.3%), sepsis (10.3%), CMV (10.3%), *Toxoplasma* (5.6%), *Cryptococcus* (2.6%) and *MAC* (1.0%). *Tuberculosis* was predominant in all stratified CD4 levels. Most of cases with *Talaromycosis* had CD4 counts below 50cells/mm^3. Besides, CD4 count below 50cells/mm^3 was reported in all cases with either *Cryptococcus* infection or *MAC* infection. Infections with CMV and *toxoplasma* were not seen in patients with CD4 count over 100cells/mm^3. -7 out of 195 cases were non - infectious etiologies including 4 cases (2.1%) with hemophagocytic lymphohistiocytosis (HLH) syndrome and 3 cases (1.5%) with non - Hodgkin lymphoma. -53.8% of cases were infected by one pathogen while 38% of patients were co - infected by two different pathogens. Co - infection of three pathogens was recognized in 8.2% of study patients.There is no difference between the number of concurrent etiologies and TCD4 levels. *Conclusion:* Opportunistic infections, especially *M. tuberculosis* is still the leading cause of prolonged fever in HIV/AIDS patients. *T. marnefei* should be screened in patients with CD4 < 50cells/mm^3. It is important to note that there may be many concurrent etiologies of prolonged fevers in HIV/AIDS patients.

Key words: HIV/AIDS, prolonged fever, TCD4.

INTRODUCTION

Fever is a condition of increased body temperature due to disorders in thermoregulatory center. Fever of unknow origin was defined as body temperature over 38.3^{0}C (101^{0}F) for more than three weeks without clear diagnosis despite three days of investigations in hospital. Fever of unknown origin is divided into four groups, including

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(a) classic FUO by definition of Petersdorf and Beeson in 1961; (b) FUO in hospital; (c) FUO associated with leukopenia and (d) FUO associated with HIV[1]. According to WHO, there were 37,9 million people living with HIV and 1,7 million people newly infected HIV in 2018 all over the world. In Vietnam, there were 208750 people living with HIV and 5768 people newly infected HIV. Therefore, HIV/AIDS is a public health and one of the leading health burdens in Vietnam.

Fever of unknown origin is a common complaint in patients with HIV/AIDS. It appears in 3.4 - 21% of HIV infected patients admitted to hospitals and includes both infectious and non - infectious causes[2].

The prevalence of etiology causing prolonged fever in HIV infected patients depends on their immune deficiency status which is reflected by CD4 cell count. Thus, CD4 cell counts could be useful in predicting common pathogens causing prolonged fever in patients with HIV. Despite advances in diagnostic methods to identify pathogens, making diagnoses of pathogens causing prolonged fever in HIV infected patients remains a challenge.

Therefore, to have more insightful knowledge about the association between pathogens and immune status in patients with HIV/AIDS, we conducted this study with objective of investigating the associations between some common etiologies causing prolonged fever in HIV infected patients and their immune status.

SUBJECTS AND METHODS

Subjects: 195 HIV infected patients presented with prolonged fever and admitted to National Hospital for Tropical Diseases from January 2016 to June 2019 were selected. Criteria for selection included:

- Age ≥ 18 years.

- Being infected HIV, confirmed by three testing methods as approved by Ministry of Health[3].

- Having prolonged fever defined as armpit temperature from 38,3^{0}C lasting at least 3 weeks.

Exclusion criteria included patients whose in-hospital duration was too short to make diagnoses.

Method: We carried out a cross - sectional descriptive study and recruited 195 eligible patients. Collected data included complaints at admission, history of ART treatment and clinical manifestation. Laboratory tests performed in patients included:

- Routine tests: CBC, biochemical blood tests, chest – xray and abdominal ultrasound.

- CD4 cell count.

- Specific tests for identifying etiologies including: Culture for bacteria, fungi and M.*tuberculosis* from blood, other body fluids and skin lesion.

- Other examinations and diagnostic tests to support causative diagnoses: head CT scan, head MRI scan, fundoscopic examination.

- Bone marrow aspiration or biopsy was performed in patients with abnormal CBC.

A case was defined being infected opportunistic infection if there was at least one isolated pathogen. A patient was diagnosed with blood stream infection if there was at least a positive blood culture and systemic inflammatory response syndrome.

A case was defined being suffered a non - infectious condition if there was at least one confirmed non - infectious cause such as hematologic diseases, malignancies, autoimmune diseases…

All patients were evaluated clinical stages and immune stages then identified causes of fever. TCD4 cell count was divided into three levels that were lower 50 cells/mm^3, 50 - 100 cells/mm^3 and over 100 cells/mm^3 to investigate association with causes of prolonged fever.

Data analysis: Data was analyzed with software SPSS 20.0. Comparisons between categorical variables were tested by Chi - square and Fisher's exact test.

Differences were considered as statistical significance when p value < 0.05.

Ethics: This study was approved by Board of Directors of National Hospital for Tropical Diseases. All data documented from medical records was used only for study and patients information was kept confidential.

RESULTS

Table 1. Characteristics of study population

Characteristics	n (%) N = 195	Median - IQR
Male	147 (75.4%)	
Age		36 (32 - 42)
BMI		18.36 (16.65 - 19.50)
Currently on ART	70 (35.9%)	
CD4 count (cells/uL)		19 (8 - 50)
≥ 350	5 (2.6%)	
200 - 349	4 (2.1%)	
101 - 199	13 (6.7%)	
≤ 100	173 (88.6%)	
Clinical stages		
Stage I, II	1 (0.5%)	
Stage III	22 (11.3%)	
Stage IV	172 (88.2%)	

195 eligible patients were included. There were 147 male patients, accounted for 75.4%. The ratio male: female was about 3:1.

Median of age among study patients was 36 years (IQR: 32 - 42). Minimum value of age was 18 years and maximum value of age was 69 years. 52.8% of study patients was in working age which was from 31 - 40 years old.

35.9% of patients was currently on ART.

TCD4 count below 200tb/mm^3 appeared in 97.4% of patients while 88.6% of patients had TCD4 count ≤ 100tb/mm^3 and 74.3% patients had TCD4 dưới 50 tb/mm^3.

Table 2. Prevalence of etiologies by levels of CD4 count

Subgroup by level of CD4 count (cells/uL)	Total (N = 195)	< 50 (n = 145) (1)	50 - 100 (n = 28) (2)	> 100 (n = 22) (3)	P (1,2,3)
Opportunistic infections	182/195 (93.3%)				
Tuberculosis	91/195 (46.7%)	60/145 (41.4%)	17/28 (60.7%)	14/22 (63.6%)	0.040
Talaromycosis	57/195 (29.2%)	48/145 (33.1%)	5/28 (17.9%)	4/22 (18.2%)	0.036
PCP infection	40/195 (20.5%)	30/145 (20.7%)	6/28 (21.4%)	4/22 (18.2%)	1.000
Bacterial pneumonia	22/195 (11.3%)	18/145 (12.4%)	2/28 (7.1%)	2/22 (9.1%)	0.705
Sepsis	20/195 (10.3%)	19/145 (13.1%)	1/28 (3.6%)	0/22 (0%)	
Diseases related to CMV	20/195 (10.3%)	16/145 (11.0%)	4/28 (14.3%)	0/22 (0%)	
Cryptococcosis	5/195 (2.6%)	5/145 (3.4%)	0/28 (0%)	0/22 (0%)	
MAC infection	2/195 (1.0%)	2/145 (1.4%)	0/28 (0%)	0/22 (0%)	
Toxoplasmosis	11/195 (5.6%)	7/145 (4.8%)	4/28 (14.3%)	0/22 (0%)	
Non-infectious causes	7/195 (3.6%)				
Hemophagocyticlymphohistiocytosis (HLH) syndrome	4/195 (2.1%)	1/145 (0.7%)	1/28 (3.6%)	2/22 (9.1%)	
Non-Hodgkin Lymphoma	3/195 (1.5%)	2/145 (1.4%)	0 (0.0%)	1/22 (4.5%)	
Undefined causes	6/195 (3.1%)				

Chi - square test, Fisher's exact test

Table 3. Prevalence of coinfection by level of TCD4 count.

	Total (N = 195)	< 50 (n = 145) (1)	50 - 100 (n = 28) (2)	> 100 (n = 22) (3)	P (1,2,3)
1 pathogen	105/195 (53.8%)	79/145 (54.5%)	13/28 (46.4%)	13/22 (59.1%)	0.663
2 pathogens	74/195 (38%)	53/145 (36.5%)	13/28 (46.4%)	8/22 (36.4%)	0.647
3 pathogens	16/195 (8.2%)	13/145 (9%)	2/28 (7.2%)	1/22 (4.5%)	0.842

Chi - square test, Fisher's exact test

Opportunistic infections accounted for 93.3% of 195 HIV - infected cases with fever of unknown origin. *Tuberculosis* was the most common opportunistic infection (46.7%), followed by *Talaromycosis* (29.2%) and *PCP* infection (20.5%). Less common pathogens for opportunistic infections included bacterial pneumonia (11.3%), sepsis (10.3%), CMV (10.3%), *Toxoplasma* (5.6%), *Cryptococcus* (2.6%) and *MAC* (1.0%).

Tuberculosis was predominant in all subgroups by stratified CD4 levels. Most of cases with *Talaromycosis* had CD4 counts below 50cells/mm^3. Besides, CD4 count below 50cells/mm^3 was reported in all cases with either *Cryptococcus* infection or *MAC* infection. Infections with *CMV* and *toxoplasma* were not seen in patients with CD4 count over 100cells/mm^3.

We reported 7 out of 195 FUO cases (3.6%) without opportunistic infections. They included 4 cases (2.1%) with hemophagocytic lymphohistiocytosis (HLH) syndrome and 3 cases (1.5%) with non - Hodgkin lymphoma.

53.8% of cases were infected by one pathogen while 38% of patients were co - infected by two different pathogens. Co - infection of three pathogens was recognized in 8.2% of study patients.

There was no significant difference between the number of pathogens in co - infections and TCD4 levels.

DISCUSSION

Among 195 HIV infected patients with prolonged fever, the male took the rate three fold higher than the female (75.4% versus 24.6%). This result was similar to the study of DanaiKitkungvan in Thailand where the percentage of male and female were 61% and 39%, respectively[4]. In Vietnam, the study by Nguyen Tien Lam showed that the men took 76.8% and the women took 23.2%[5].

Prolonged fever is a common symptom in HIV - infected people, especially in those with advanced disease. In this study, the median number of TCD4 cells was 19tb/mm^3 (IQR 8 - 50), the TCD4 lowest number was 1tb/mm^3 and the highest one was 713tb/mm^3. Up to 74.3% of patients had TCD4 count below 50tb/mm^3 and the majority of patients were in clinical stage IV (88.2%).

The study by RomaneeChaiwarith in Thailand on HIV infected patients with prolonged fever also showed that the average TCD4 count was 56cells/mm^3, the median was 30cells/mm^3, the highest number was 500cells/mm^3, the lowest is 0 cells/mm^3[2]. Thus, HIV infected patients with prolonged fever usually had serious immunodeficiency status.

The fever was primarily related with opportunistic infections and sometimes with malignancies. OIs depend on the immunodeficiency status of HIV infected people, local circulating diseases, the primary and secondary prophylaxis.

Our study identified that the infectious etiologies accounted for the highest proportion (93.3%). 7/195 cases of non - infectious etiology accounted for 3.6% including hemophagocyticlymphohistiocytosisof 4/195 patients (2.1%) and non - Hodgkin lymphoma 3/195 patients (1.5%). There are 3.1% of cases unable to identify the etiology. Our research results are similar to those of Arnaund Hot in the US (2007) on HIV infected patients with prolonged fever, indicating the OIs of 90.6%[6]. One research in Thailand showed that of 90 HIV infected patients studied, 71 patients identified the cause of prolonged fever, 70/71 patients (98.6%) were caused by infectious etiology and 01/71 patients with non - infectious etiology (1.4%)[2].

Among the infectious etiologies of prolonge fever in HIV infected patients, *tuberculosis* accounted for the highest proportion of 46.7%, followed by *T. marnefei* fungus of 29.2% and PCP of 20.5%; less common causes were bacterial pneumonia (11.3%), CMV (10.3%), toxoplasmosis (5.6%) and Cryptococcus (2.6%).

The prevalence of *tuberculosis* is similar to some studies in regional countries as well as in the world[4,7].This result can be explained by the fact that HIV is the virus that injured the body's immune system through TCD4, TCD8, macrophages, thus making TB bacteria survive, reactivate latent *tuberculosis* and spread of *tuberculosis* bacteria are higher than other organisms[8].

Among 91 patients with *tuberculosis*, 60 patients had TCD4 below 50cells/mm^3 accounted for the highest proportion (41.4%), followed by TCD4 from 50 - 100cells/mm^3 and TCD4 over 100cells/mm^3. The difference in the incidence of *tuberculosis* was statistically significant between the two groups of TCD4 < 50 and the TCD4 group from 50 - 100tb/mm^3 with $p < 0.05$. In

DanaiKitkungvan's study, HIV infected patients with prolonged fever had the median TCD4 counts of 178/mm^3 (89 - 581/mm^3)[4]. The prevalence of *T. marnefei* fungal infection in our study was similar to the PM prevalence of 24.1% in a study in Northern Thailand[2]. Talaromyces fungus grow in tropical regions, especially in Southeast Asia where the climate is hot and humid. In addition to humans, bamboo rats are natural hosts for Talaromyces, which are also found in this area[9].

Among 57 patients with *T. marnefei* infection, 48 patients with TCD4 < 50tb/mm^3 accounted for the highest proportion. The difference in the incidence of *T. marnefei* was statistically significant between the two groups of TCD4 < 50 and the TCD4 group from 50 - 100 with $p < 0.05$. This result is similar to the studies of DanaiKitkungvan[4].

In our study, PCP - associated pneumonia was the third most common cause, taking 20.5%. In DanaiKitkungvan study PCP was also the third common cause of prolonged fever in HIV infected patients with 13%[4]. Our research showed that PCP is a common cause of prolonged fever and is a common cause of pneumonia in HIV - infected patients. Therefore, when inHIV infected patients with prolonged fever who have respiratory diseases, the two most common causes are *tuberculosis* and PCP. Among 40 patients diagnosed with PCP, the proportion of patients with CD4 count < 50cells/mm^3 accounted for the highest proportion (75.0%), CD4 group from 51 - 100cells/mm^3 and CD4 > 100cells/mm^3 took, 15 % and 10%, respectively. In DanaiKitkungvan's study, the TCD4 median was 187 cells/mm^3 (14 - 251cells/mm^3)[4].

In previous studies CMV is an uncommon infectious cause of prolonged fever in HIV infected patients. CMV is an OI with the rate varies by gender, age, socioeconomic status and geographic location. Worldwide, the lowest rate of CMV is in Western Europe and the United States, the highest in South America, Africa and Asia, often among non - white ethnic minorities and in low income countries[10].

No patients with Cryptococcus, CMV, toxoplasmosis, MAC had TCD4 > 100/mm^3. All 05 patients infected with Cryptococcus belonged to TCD4 group < 50cells/mm^3. Thus, CMV infection and Cryptococcus infection are opportunistic conditions occurring during the period of severe immunodeficiency, common in patients with a TCD4 count < 100/mm^3, especially in patients with TCD4 < 50/mm^3.

In non - infectious etiology, non - Hogkin lymphoma is a commonly mentioned cause in the studies. In this study, the proportion of non - Hodgkin lymphoma patients was 1.5%, similar to the and Danai Kitkungvan (4%)[4].

In addition, our study also noted that HLH was a non - infectious cause of prolonged fever in HIV patients. In non - infectious etiology Non - Hodgkin lymphoma are found at all TCD4 count levels.

In severe immunodeficiency HIV patients with very low TCD4, prolonged fever may be caused by two or more concomitant aetiologies.

Of the 195 patients studied, there were 105 patients with 1 etiology accounting for the highest proportion (53.8%), followed by 74 patients with 2 etiology (38.0%), 16 patients with 03 or more causes (8.2%). There is no difference between the number of concurrent etiologies and TCD4 levels

In the study of Danai Kitkungvan in Thailand, 73.6% of patients had 1 infectious etiology, 26% of patients had 2 or more co - infected pathogen[4]; Research by Romanee Chaiwarith (2005) on 71 patients with prolonged fever, 58/71 patients had 1 etiology, 13/71 patients had 2 or more concurrent etiologies[2]. In all of the above studies, the results were similar to our study.

CONCLUSION

In a study of 195 cases of prolonged fever in HIV/AIDS patients, we had some conclusions as follows:

Opportunistic infections, especially M. *tuberculosis* is still the leading cause of prolonged fever in HIV/AIDS patients. *T. marnefei* should be screened in patients with CD4 < 50cells/mm^3. It is important to note that there may be many concurrent etiologies of prolonged fevers in HIV/AIDS patients.

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