

## CLINICAL STUDY

## Factors associated with fatigue in acquired immunodeficiency syndrome patients with antiretroviral drug adverse reactions: a retrospective study

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### Abstract

**OBJECTIVE:** To retrospectively study the prevalence of fatigue and factors associated with fatigue among acquired immunodeficiency syndrome (AIDS) patients with antiretroviral drug adverse reactions.

**METHODS:** Data were collected from case report

forms (CRFs) for a project funded by the 11th National 5-year Special Science and Technology Program on Major Infectious Diseases. Fatigue was defined by patient self-report. The outcomes were the prevalence of fatigue and the potential risk factors of fatigue. Univariate and multivariate logistic regression analyses were conducted to identify the factors associated with fatigue.

**RESULTS:** Among the 228 subjects, the prevalence of fatigue was 86.8%. In univariate analysis, the significant differences in demographic characteristics between patients with and without fatigue were: gender [ $OR=2.29$ ; 95%  $CI$  (1.05-4.98)], education level [ $OR=0.40$ ; 95%  $CI$  (0.18-0.85)], anemia [ $OR=3.80$ ; 95%  $CI$  (1.27-11.31)], time of HIV diagnosis [ $OR=0.29$ ; 95%  $CI$  (0.13-0.65)], and route of infection [ $OR=0.14$ ; 95%  $CI$  (0.06-0.32)]. Abnormal taste and rapid pulse were more commonly seen in patients with fatigue ( $P<0.05$ ), while abdominal distension and lumbar soreness were encountered less often in patients with fatigue ( $P<0.05$ ). Multivariate analysis showed that the four main factors associated with fatigue were anemia [ $OR=3.50$ ; 95%  $CI$  (1.01-12.15)], route of infection [ $OR=3.40$ ; 95%  $CI$  (1.21-9.58);  $P=0.02<0.05$ ], lumbar soreness [ $OR=0.06$ ; 95%  $CI$  (0.02-0.18);  $P=0.000<0.05$ ], and rapid pulse [ $OR=10.58$ ; 95%  $CI$  (2.16-51.75);  $P=0.004<0.05$ ].

**CONCLUSION:** This study demonstrated that fatigue is common (86.8% prevalence) in AIDS patients with antiretroviral drug adverse reactions, and that anemia, route of infection (i.e., non-commercial blood donation) and rapid pulse were risk factors, while lumbar soreness was a protective factor related to fatigue. More attention should be

paid to fatigue and more efforts should be made to find ways to prevent, control and eliminate this symptom in AIDS patients with antiretroviral drug adverse reactions.

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**Key words:** Retrospective studies; Acquired immunodeficiency syndrome; HIV; Anemia; Fatigue

## INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), has become a major public health problem in China<sup>1</sup> since 1985, the year that the first Chinese HIV/AIDS case was reported by the Peking Union Medical College Hospital in Beijing.<sup>2</sup>

Fatigue is the status of subjective tiredness, and affects nearly 10% of the general population worldwide.<sup>3</sup> It is also a common symptom among the HIV/AIDS patients.<sup>4</sup> Researchers have paid close attention to this troublesome symptom.<sup>5</sup> According to the literature, fatigue may result in patients' poor adherence to medications, poor effects from medical treatment and care, increased drug resistance, lowered quality of life, and increased morbidity and mortality.<sup>6-8</sup> In addition, relieving fatigue can improve the quality of life of and reduce mental depression in patients.<sup>9</sup>

In this retrospective study, the prevalence and risk factors of self-reported fatigue were analyzed among AIDS patients with antiretroviral drug adverse reactions.

## MATERIALS AND METHODS

### *Study design and data collection*

A retrospective study was conducted at the First Hospital Affiliated to Henan College of Traditional Chinese Medicine, Zhengzhou, China. The data were collected from case report forms (CRFs) that had been completed in 2010 for a project of the 11th National 5-year Special Science and Technology Program on Major Infectious Diseases.

The case inclusion criteria were that the baseline data were recorded and available, and the intact informed consent forms were signed. Patients with abnormal values or missing data for renal function, liver function, or CD4<sup>+</sup> T-cell counts were excluded.

The data included three sections: general information, clinical signs and symptoms, and laboratory findings. General information included age, gender, marital status, level of education, occupation, route of HIV infection, time of commencement of antiretroviral treatment, personal history of disease, and obstetrical history. The signs and symptoms collected from the original

case reports were fatigue, shortness of breath, a feeling of tightness in the chest, dizziness, poor appetite, abdominal distension, lumbar soreness, abnormal urination and defecation, sleeplessness, abnormal taste, distending pain in the hypochondrium, headache, waist-leg weakness, abnormal sweating, pulse condition, and tongue image. The laboratory findings included CD4<sup>+</sup> T-cell counts and hemoglobin counts.

### *Definitions*

All signs and symptoms were described according to *Zhong Yi Lin Chuang Zhen Liao Shu Yu* (2007)<sup>10</sup> and Terms in *Traditional Chinese Medicine and Pharmacy* (2005).<sup>11</sup>

Fatigue was self-reported by patients, and was divided into three degrees: mild (lower energy and somewhat lowered physical activity), moderate (mental weariness and much lower physical activity), and severe (extreme tiredness, daily activities can hardly be completed).

### *Outcomes*

The outcomes were the prevalence and the potential factors associated with self-reported fatigue.

### *Statistical methods*

The SPSS 19.0 software package (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. We described the patients' characteristics as means  $\pm$  standard deviation (*SD*) and frequencies (%). Categorical variables were compared using the *Chi*-square test or Fisher's exact test. Continuous variables were compared using the students' *t*-test or Mann-Whitney test. Analysis of the clinical and demographic factors associated with self-reported fatigue was performed for all patients to avoid bias associated with the likelihood of performing a test. Factors considered relevant and associated with fatigue in univariate analysis at  $P < 0.10$  were included in the multivariate model, and  $P < 0.05$  was considered statistically significant.

## RESULTS

### *General demographic characteristics*

Of the 228 cases analyzed in this study, 40.4% were male and 59.6% female. The mean age was 46.0 (*SD*, 8.1). A total of 193 patients (84.6%) were infected with HIV from commercial blood donations. All patients received antiretroviral drugs free from the local government. A total of 151 patients (66.2%) were illiterate or graduated from primary school or junior middle school, and 77 patients (33.8%) graduated from senior middle school. A total of 173 patients (75.9%) were married, and 55 patients (24.1%) were either divorced, widowed, or single. The median CD4<sup>+</sup> T-cell count was 147.5 cells/mm<sup>3</sup> (range: 3-729 cells/mm<sup>3</sup>). Among the 228 patients, 198 patients (86.8%) complained of fatigue (79 mild cases, 87 moderate cases, and 32 severe cases). The statistically significant differ-

ences in general demographic characteristics between those with and without fatigue were: gender [ $OR=2.29$ ; 95%  $CI$  (1.05-4.98)], education level [ $OR=0.39$ ; 95%  $CI$  (0.18-0.85)], anemia [ $OR=3.80$ ; 95%  $CI$  (1.27-11.31)], time of HIV diagnosis [ $OR=0.29$ ; 95%  $CI$  (0.13-0.65)] and route of infection [ $OR=0.14$ ; 95%  $CI$  (0.06-0.32)] (Table 1).

### Comparison of symptoms between patients with and without fatigue

In the 228 patients, the signs and symptoms with incidences exceeding 10% were as follows: shortness of breath, a feeling of tightness in the chest, dizziness, poor appetite, abdominal distension, lumbar soreness, sleeplessness, abnormal taste, pain in the hypochondrium, headache, waist-leg weakness, abnormal sweating, light red tongue, deep pulse, rapid pulse and thready pulse. The proportions of some signs and symptoms differed between patients with and without fatigue. Abnormal taste and rapid pulse were more commonly seen in those with fatigue ( $P<0.05$ ), but abdominal dis-

tension and lumbar soreness were encountered less in those with fatigue ( $P<0.05$ ) (Table 2).

### Logistic regression analysis of risk factors associated with fatigue

We conducted logistic regression analysis to determine risk factors associated with fatigue. The dependent variable was fatigue (yes vs no), and the independent variables were gender, education level, anemia, HIV confirmed time, route of infection, lumbar soreness, abdominal distension, rapid pulse, abnormal taste, thready pulse and light red tongue. Education level was defined as either junior middle school or below versus senior middle school or above; time of HIV diagnosis was defined as either before or after 2004; and, the route of infection was defined as either commercial blood donation or other. The four factors associated with fatigue were anemia [ $OR=3.50$ ; 95%  $CI$  (1.01-12.15);  $P=0.05<0.05$ ], route of infection [ $OR=3.40$ ; 95%  $CI$  (1.21-9.58);  $P=0.02<0.05$ ], lumbar soreness [ $OR=0.06$ ; 95%  $CI$  (0.02-0.18);  $P=0.00<0.05$ ],

Table 1 Demographic characteristics of the patients [n (%)]

Variable	Studied case (n=228)	Without fatigue (n=30)	With fatigue (n=198)	OR (95% CI)	P value
Age (years)					
≤44	106 (46.5)	16 (53.3)	90 (45.5)	1.37 (0.64-2.96)	0.439
≥45	122 (53.5)	14 (46.7)	108 (54.5)		
Gender					
Male	89 (39.0)	17 (56.7)	72 (36.4)	2.29 (1.05-4.98)	0.034
Female	139 (61.0)	13 (43.3)	126 (63.6)		
Marital state					
Married	173 (75.9)	23 (76.7)	150 (75.8)	1.05 (0.52-2.60)	0.914
Divorced, widowed or single	55 (24.1)	7 (23.3)	48 (24.2)		
Education level					
Junior middle school or below	151 (66.2)	14 (46.7)	137 (69.2)	0.39 (0.18-0.85)	0.015
Senior middle school or above	77 (33.8)	16 (53.3)	61 (30.8)		
CD4T (cell /mm <sup>3</sup> )					
≤199	153 (67.1)	19 (63.3)	134 (67.7)	0.82 (0.37-1.84)	0.637
≥200	75 (32.9)	11 (66.6)	64 (32.3)		
Anemia <sup>a</sup>					
No	151 (66.2)	26 (86.7)	125 (63.1)	3.80 (1.27-11.31)	0.012
Yes	77 (33.8)	4 (13.3)	73 (36.9)		
Time of HIV diagnosis					
Before the year 2004	168 (73.7)	15 (50.0)	153 (77.3)	0.29 (0.13-0.65)	0.002
After the year 2004	60 (26.3)	15 (50.0)	45 (22.7)		
Route of infection					
Commercial blood donation	193 (84.6)	16 (53.3)	177 (89.4)	0.14 (0.06-0.32)	0.000
Others	35 (15.4)	14 (46.7)	21 (10.6)		

Note: <sup>a</sup>Hemoglobin level below 12 g/dL (male) or below 11 g/dL (female).

and rapid pulse [ $OR=10.58$ ; 95%  $CI$  (2.16-51.75);  $P=0.004<0.05$ ]. Anemia, route of infection and rapid pulse were risk factors, while lumbar soreness was a protective factor (Table 3).

## DISCUSSION

Morbidity and mortality of HIV-infected patients have been greatly lowered by highly active anti-retroviral therapy (HAART), but the prevalence of HIV-related and non-HIV-related diseases and symptoms have increased in HIV-infected patients.<sup>12</sup> Recently, symptoms are more apt to be due to adverse effects of antiretroviral drugs, rather than symptoms induced by co-morbid diseases and poorly understood complications due to the long-standing HIV disease.

Fatigue is a common subjectively experienced symptom of HIV/AIDS patients. Epidemiology research of fatigue among HIV/AIDS patients has reported that HIV-related fatigue is reported in 33%-88% of the pa-

tients.<sup>13</sup> However, research on HIV-related fatigue is seldom published in China.

We found that among 228 AIDS patients with antiretroviral drug adverse reactions, 198 cases reported fatigue, with an prevalence of 86.8%. In addition, our retrospective study showed that the prevalence of fatigue was higher among HIV/AIDS patients with antiretroviral drug adverse reactions than among the general population.

The factors that influence the occurrence of fatigue among HIV/AIDS patients are complicated and still unclear. For example, some researchers report that age, gender, AIDS stage, CD4<sup>+</sup> T-cell count, HAART, psychological functions, and patients in different geographic regions are important factors,<sup>14,15</sup> but others have reported different results.<sup>16,17</sup>

It is well known that patients with antiretroviral drug adverse reactions may have many symptoms along with fatigue, such as fever, gastrointestinal symptoms, breathing difficulties, limb numbness, and insomnia.

Table 2 Comparison of signs and symptoms between patients with and without fatigue [n (%)]

Symptom and sign	Studied case (n=228)	Without fatigue (n=30)	With fatigue (n=198)	$\chi^2$	P value
Shortness of breath	99 (43.4)	10 (33.3)	89 (44.49)	1.431	0.232
A feeling of tightness in the chest	153 (67.1)	17 (56.7)	136 (59.6)	1.705	0.192
Dizziness	197 (86.1)	27 (90.0)	170 (74.6)	0.380	0.537
Poor appetite	34 (14.9)	5 (16.7)	29 (14.6)	0.084	0.772
Abdominal distension	116 (50.9)	24 (80.0)	92 (46.5)	11.723	0.001
Lumbar soreness	75 (32.9)	25 (83.3)	50 (25.3)	39.814	0.000
Sleeplessness	96 (42.1)	9 (30.0)	87 (43.9)	2.077	0.150
Abnormal taste	162 (71.1)	16 (53.3)	146 (73.7)	5.273	0.022
Pain in hypochondrium	90 (39.5)	10 (33.3)	80 (40.4)	0.545	0.460
Headache	109 (47.8)	18 (60.0)	91 (46.0)	2.058	0.151
Waist-leg weakness	106 (46.5)	17 (56.7)	89 (44.9)	1.438	0.230
Abdominal sweating	100 (43.9)	15 (50.0)	85 (42.9)	0.529	0.467
Light red tongue	87 (38.2)	7 (23.3)	80 (40.4)	3.217	0.073
Deep pulse	77 (33.8)	12 (40.0)	65 (32.8)	0.599	0.439
Rapid pulse	54 (23.7)	2 (6.7)	52 (26.3)	2.347	0.020
Thready pulse	55 (24.1)	3 (10.0)	52 (26.3)	1.936	0.066

Table 3 Logistic regression analysis of factors associated with fatigue

	B	SE	$\chi^2$	P value	OR (95% CI)
Anemia	1.253	0.635	3.897	0.048	3.50 (1.01-12.15)
Route of infection	1.225	0.528	5.385	0.020	3.40 (1.21-9.58)
Lumbar soreness	-2.816	0.559	25.403	0.000	0.06 (0.02-0.18)
Rapid pulse	2.359	0.810	8.474	0.004	10.57 (2.16-51.75)
Constant	1.868	0.625	8.947	0.003	-

We found that some of the symptoms were different between patients with and without fatigue. Abnormal taste and rapid pulse were more commonly seen in those with fatigue ( $P < 0.05$ ). By multivariate logistic regression analysis, rapid pulse [ $OR = 10.58$ ; 95%  $CI$  (2.16-51.75);  $P = 0.004 < 0.05$ ] was more likely to occur in patients with fatigue, but lumbar soreness [ $OR = 0.06$ ; 95%  $CI$  (0.02-0.18);  $P = 0.00 < 0.05$ ] more often appeared in those without fatigue.

There are conflicting reports in the literature regarding the relationship between  $CD4^+$  T-cell count and fatigue, because some studies have confirmed the relation<sup>18</sup> but the others have denied it.<sup>19</sup> In our study, using univariate analysis we found no statistically significant difference in  $CD4^+$  T-cell counts between the two groups.

The occurrence of anemia increases with HIV stage.<sup>20</sup> Anemia is a common and prognostic marker of disease progression, and anemia is independent of  $CD4^+$  T-cell counts and viral load.<sup>21</sup> HAART is associated with a significant improvement in hemoglobin levels.<sup>22</sup> In our study, the prevalence of anemia was 33.8%, and there was a significant difference between those with fatigue (36.9%) and those without fatigue (13.3%). More importantly, anemia was a risk factor [ $OR = 3.50$ ; 95%  $CI$  (1.01-12.15)] related to fatigue among the AIDS patients with antiretroviral during adverse reactions.

It has not been reported whether the route of infection is one cause of fatigue. However, we found that the route of infection was a risk factor [ $OR = 3.40$ ; 95%  $CI$  (1.21-9.58)] of fatigue among AIDS patients with antiretroviral drug adverse reactions. This needs further study.

The present study showed that fatigue among AIDS patients with antiretroviral drug adverse reactions was common, and the prevalence was 86.8%. This study also demonstrated that anemia, route of infection (i.e., non-commercial blood donation) and rapid pulse were risk factors, while lumbar soreness was a protective factor of fatigue among AIDS patients with antiretroviral drug adverse reactions.

Furthermore, it should be noted that at present there is no specific treatment for fatigue among AIDS patients. Traditional Chinese Medicine, one of the important parts of complementary and alternative medicine, has shown efficacy for treatment of many diseases, and has been used for treatment of AIDS and its complications in the last three decades.<sup>23,24</sup> This may be an opportunity for Chinese medicine practitioners to find treatment methods to conquer fatigue.

In conclusion, fatigue is a common symptom; however, more attention should be paid to fatigue in HIV/AIDS patients, and more efforts should be made for better control and treatment of fatigue in AIDS patients, to improve patients' quality of life.

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