Journal of Microbiology, Immunology and Infection (2019) 52, 700—709

Available online at www.sciencedirect.com

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journal homepage: www.e-jmii.com

Original Article

Clinical features of acute human immunodeficiency virus infection in Taiwan: A multicenter study

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https://doi.org/10.1016/j.jmii.2018.01.005

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Received 19 September 2017; received in revised form 27 December 2017; accepted 8 January 2018
Available online 2 March 2018

KEYWORDS
Acute HIV infection;
Aseptic meningitis;
Combination antiretroviral therapy;
Fiebig stage;
Infectious mononucleosis

Abstract *Background/purpose:* Acute HIV infection is characterized by a high concentration of HIV RNA in the plasma and rapid depletion of the CD4 cell count. This multicenter, retrospective observational study aimed to characterize the manifestations of acuteHIV infection in Taiwan.
Methods: Between 1 January 2012 and 31 December 2016, all patients aged 20 years or greater who presented with acute HIV infection were included. Demographic and clinical characteristics of the patients at diagnosis were collected. Baseline laboratory assessment included hemogram, CD4 count, plasma HIV RNA load (PVL), serologic markers of syphilis and hepatitis A, B, and C viruses, and serum biochemistry.
Results: The proportion of acute HIV infection was 6.9% among the patients with newly diagnosed HIV infection during the study period. The most common presenting symptoms of acute HIV infection were fever, fatigue, and myalgia. The median PVL at diagnosis was 5.9 $\log_{10}$ copies/ml, and median CD4 count was 307 cells/mm^3. A total of 68 patients (27%) had baseline CD4 count less than 200 cells/mm^3. Multiple logistic regression analysis, showed that the baseline CD4 count (OR, 4.02; $p = 0.013$) and aspartate aminotransaminase levels (OR, 3.49; $p = 0.002$) were associated with high PVL (>5 $\log_{10}$ copies/ml); and high baseline PVL (OR, 2.64; $p = 0.002$) was associated with symptomatic acute HIV infection.
Conclusions: Manifestations of acute HIV infection are nonspecific and of wide spectrum ranging from fever to severe illness. A higher proportion of patients with initial CD4 counts of 200 cells/mm^3 or less during acute HIV infection warrants early, timely diagnosis and treatment to prevent rapid disease progression.

Introduction

The clinical spectrum of human immunodeficiency virus (HIV) infection includes acute infection, asymptomatic infection, early symptomatic infection, and advanced immunodeficiency with opportunistic complications.[1] Acute HIV infection is characterized by high concentration of HIV RNA in the plasma and rapid depletion of the CD4 cell count. Acute HIV infection has attracted tremendous attention because events during acute HIV infection may modulate the long-term course of HIV infection. Several studies have demonstrated that symptomatic acute HIV infection is associated with more rapid disease progression.[2–4] Investigations of individuals with acute HIV infection provides the best opportunity for understanding HIV transmission in humans.[5] Furthermore, patients with acute HIV infection are maximally contagious, thus contributing significantly to the epidemic spread of HIV.[6–8] Early treatment during this stage could dramatically reduce epidemic spread and the size of HIV reservoir.[9–11]

The prevalence rates of acute HIV infection varies among different studies, which may be related to the populations studied, testing performed and criteria used for acute HIV infection. Pincus et al. found that approximately 1% of patients presenting with flu-like illness at an urban urgent care in Boston were finally diagnosed with acute HIV infection.[12] Bebell et al. found that, 1% of patients with acute febrile illness, suspicious of malaria in rural Uganda, were diagnosed with acute HIV infection.[13] In a retrospective study from Rosenberg et al., 1.2% of patients with infectious mononucleosis had acute HIV infection.[14]

The clinical manifestations of patients with acute HIV infection are nonspecific and variable. The onset of the symptoms may range from 1 to 6 weeks after exposure to the virus but peak at 3 weeks. Approximately 50–90% of the patients with acute HIV infection develop symptoms,[15] including fever, myalgia, headache, diarrhea, arthralgia, cough, nausea, fatigue, vomiting, night sweats, skin rash, oral ulcer and lymphadenopathy.[16,17] The exanthem is characterized by a transient maculopapular rash that predominates on the thorax and face but may also include the palms and soles and is usually associated with fever, headache, arthralgia, and night sweats.[18] Oral ulcers generally appear as small single or multiple painful lesions on an erythematous base on the lips, buccal mucosa, hard plate, and gums. Approximately 10%–30% of patients with acute HIV infection develop lymphadenopathy. Acute HIV infection may include neurological complications. Khan et al. found that 24% of patients with acute HIV infection presented with aseptic meningitis.[19] The clinical manifestations coincide with host cellular immune responses and correlate with the degree of cytokine storm.[20]

Most cohort studies regarding patients with acute HIV infection were performed in Europe and North America;[21–23]

therefore, those findings may not be extrapolated across all Asia—Pacific regions because of different host responses, social, and viral characteristics. This multicenter, retrospective observational study aimed to characterize the presentations of patients with acute HIV infection in Taiwan.

Methods

Study population and setting

This retrospective observational study was conducted at nine designated hospitals for HIV care in Taiwan (four in northern Taiwan, three in central Taiwan and two in southern Taiwan), as part of the HIV cohort study in Taiwan. The study design and details of the cohort study were described previously.[24,25] Patients ≥20 years old, who satisfied the inclusion criteria of documented acute HIV infection between 1 June 2012 and 31 December 2016, were included. A case record form was used to collect information on the demographic and clinical characteristics of the patients at diagnosis, which included age, sex, and route of HIV transmission. A detailed history of symptoms and physical examination were obtained at presentation. The trends of proportion of acute HIV infection among the patients with newly diagnosed HIV infection were assessed during the study period. The study was approved by the Research Ethics Committee or Institutional Review Board of each participating hospital and informed consent was waived.

Laboratory investigations

The Taiwan Centers for Disease Control (CDC) and National Health Insurance have provided HIV-positive patients with free-of-charge medical services, including combination antiretroviral therapy (cART), management of opportunistic illnesses, and laboratory testing, including monitoring of CD4 cell count and plasma HIV RNA load (PVL). Baseline assessment prior to cART initiation included hemogram, CD4 count, PVL, serologic markers of syphilis and hepatitis A, B, and C viruses, and serum biochemistry, including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and renal function.

Definitions

Acute HIV infection was defined as presentations of patients with negative or indeterminate Western blot in the presence of a positive p24 antigen and detectable HIV RNA; or documented seroconversion with an antigen/antibody Combo test with or without symptoms within 90 days.

The stages of acute HIV infection were classified according to the stages clarified by Fiebig et al.[26] The initial stage, eclipse stage, in which the virus replicates in the local tissues but remains undetectable by standard laboratory methods. Stage I denotes detection of viral RNA in the blood. Detection of the p24 antigen in the serum defines stage II. Stage III occurs when the enzyme-linked immunosorbent assay (ELISA) becomes positive as a result of development of antibodies to HIV. The Western blot is negative during this stage. Stage IV occurs when the ELISA is positive, but Western blot is indeterminate. In stage V, the Western blot is positive but the antibody to the p31 antigen remains negative. Stage VI is chronic infection and includes a positive Western blot with the antibody to p31.

High PVL was defined as an HIV RNA load >5 $\log_{10}$ copies/ml and low CD4 count as a CD4 count of 200 cells/mm^3 or less. Symptomatic infection was defined as acute HIV infection with any symptoms recorded during the study.

Statistical analysis

Categorical variables were analyzed using X^2 tests and continuous variables were compared using the Student's *t* test. A *P*-value of <0.05 was considered statistically significant. Factors associated with high PVL (>5 $\log_{10}$ copies/ml) and symptomatic acute HIV infection were identified using the univariate logistic regression model. Statistically significant variables in univariate analyses were selected for subsequent multivariable analyses. Ninety-five percent confidence intervals (CIs) of odds ratios (ORs) were computed to estimate the effects of each variable. All statistical analyses were performed with the SPSS software version (SPSS Inc., Chicago, IL, USA).

Results

Among 3626 antiretroviral-naïve patients, who were newly diagnosed with HIV infection at the participating hospitals during the study period, 252 patients (6.9%) satisfied the diagnostic criteria of acute HIV infection and were included in our study. The increasing trends of the proportion of patients with acute HIV infection since 2013 are shown in Fig. 1.

The baseline demographics and clinical characteristics of patients with acute HIV infection are shown in Table 1. The great majority (98.8%) of patients were male, with a median age of 26 years. Men who had sex with men (MSM), heterosexuals, and injection drug users accounted for 94.0%, 5.6% and 0.4% of the patients, respectively. The median PVL at diagnosis was 5.9 $\log_{10}$ copies/ml

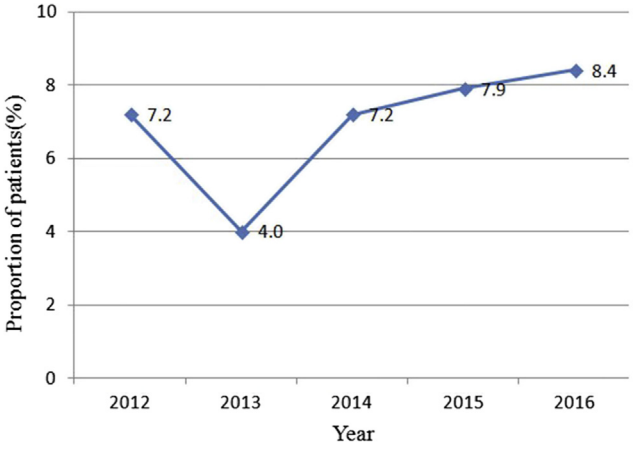

Fig. 1. Trends of proportion of patients with acute HIV infection among the newly diagnosed HIV infection patients from 2012 to 2016.

Table 1 Demographic and clinical characteristics of patients with acute HIV infection stratified by baseline plasma HIV RNA load (PVL).

	All patients (n = 252)	Baseline PVL >5 $\log_{10}$ copies/ml (n = 194)	Baseline PVL ≤5 $\log_{10}$ copies/ml (n = 58)	*p* value
Age, median (IQR), years	26 (23–30)	26 (23–30)	25 (23–29)	0.854
Male, n (%)	249 (98.8)	194 (100)	55 (94.8)	<0.001
Risk group for HIV transmission, n (%)				0.851
Men who have sex with men	237 (94.0)	182 (93.8)	55 (94.8)	0.775
Heterosexuals	14 (5.6)	11 (5.7)	3 (5.2)	0.885
Injecting drug users	1 (0.4)	1 (0.5)	0 (0)	0.584
HBsAg positivity, n (%)	11 (4.4)	7 (3.6)	4 (6.9)	0.245
Anti-HBs positivity, n (%)	135 (53.6)	106 (54.6)	29 (50.0)	0.590
Anti-HCV positivity, n (%)	9 (3.6)	6 (3.1)	3 (5.2)	0.389
Anti-HAV IgG positivity, n (%)	26/190 (13.7)	20/147 (13.6)	6/43 (14.0)	0.953
Baseline CD4, median (IQR), cell/mm^3	307 (197–440)	269 (175–378)	472 (327–623)	<0.001
Baseline PVL, median (IQR), $\log_{10}$ copies/ml	5.9 (5.1–6.6)	6.2 (5.6–6.8)	4.5 (4.1–4.8)	<0.001
Fiebig stage				0.255
Stage I	6 (2.4)	6 (3.1)	0 (0)	0.175
Stage II	5 (2.0)	4 (2.1)	1 (1.7)	0.871
Stage III	39 (15.5)	34 (17.5)	5 (8.6)	0.100
Stage IV	201 (79.8)	149 (76.8)	52 (89.7)	0.033
Stage V	1 (0.4)	1 (0.5)	0 (0)	0.584
CART, n (%)	214 (84.9)	173 (89.2)	41 (70.7)	0.001
NRTI + NNRTI	164 (65.1)	132 (68.0)	32 (55.2)	0.071
NRTI + PI	24 (9.5)	20 (10.3)	4 (6.9)	0.437
NRTI + II	26 (10.3)	21 (10.8)	5 (8.6)	0.628

Abbreviations: CART, combination antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; II, integrase inhibitor; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; nNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PVL, plasma HIV RNA load.

Table 2 Clinical manifestations and physical findings of patients with acute HIV infection stratified by baseline plasma HIV RNA load (PVL).

	All patients (n = 252)	Baseline PVL >5 $\log_{10}$ copies/ml (n = 194)	Baseline PVL ≤5 $\log_{10}$ copies/ml (n = 58)	*p* value
Clinical manifestations, n (%)				
Fever	194 (77.0)	159 (82.0)	35 (60.3)	0.001
Skin rash	78 (31.0)	59 (30.4)	19 (32.8)	0.735
Pharyngitis	126 (50.0)	96 (49.5)	30 (51.7)	0.765
Lymphadenopathy	34 (13.5)	29 (15.0)	5 (8.6)	0.216
Myalgia	77 (30.6)	61 (31.4)	16 (27.6)	0.576
Headache	59 (23.4)	48 (24.7)	11 (19.0)	0.362
Diarrhea	63 (25.0)	48 (24.7)	15 (25.9)	0.863
Arthralgia	9 (3.6)	6 (3.1)	3 (5.2)	0.454
Cough	43 (17.1)	31 (16.0)	12 (20.7)	0.403
Nausea	47 (18.7)	41 (21.1)	6 (10.3)	0.064
Fatigue	89 (35.3)	65 (33.5)	24 (41.4)	0.271
Vomiting	27 (10.7)	23 (11.9)	4 (6.9)	0.284
Weight loss	30 (11.9)	26 (13.4)	4 (6.9)	0.179
Night sweats	1 (0.4)	1 (0.5)	0 (0)	0.584
Genital ulcer	11 (4.4)	9 (4.6)	2 (3.5)	0.697
Oral ulcer	25 (9.9)	20 (10.3)	5 (8.6)	0.706
Aseptic meningitis	15 (6.0)	12 (6.2)	3 (5.2)	0.775
Coinfection, n (%)				
Syphilis	59 (23.4)	44 (22.7)	15 (25.9)	0.616
Gonorrhea	2 (0.8)	1 (0.5)	1 (1.7)	0.363

(*continued on next page*)

Table 2 (*continued*)

Chlamydia	4 (1.6)	3 (1.5)	1 (1.7)	0.924
Condyloma	3 (1.2)	2 (1.0)	1 (1.7)	0.669
Candidiasis	9 (3.6)	9 (4.6)	0 (0)	0.102
Cryptococcosis	1 (0.4)	1 (0.5)	0 (0)	0.592
Pneumocystosis	7 (2.8)	6 (3.1)	1 (1.7)	0.607
Salmonellosis	1 (0.4)	1 (0.5)	0 (0)	0.592

(interquartile range [IQR], 5.1–6.6 $\log_{10}$), and the median CD4 count was 307 cells/mm^3 (IQR, 197–440). Hepatitis B virus surface antigen (HBsAg) and anti-HCV antibody was tested positive in 11 (4.4%) and 9 patients (3.6%) with acute HIV infection, respectively. Positive antibody for hepatitis A (anti-HAV IgG) and B (anti-HBs IgG) was detected in 13.7% and 53.6% of the patients, respectively.

The most common Fiebig stages of the patients with acute HIV infection were stages III and IV, which in combination accounted for 95.3% of all patients. At presentation, patients with high baseline PVL were more likely to have lower median CD4 count (269 vs 472, $p < 0.001$). A total of 214 patients (84.9%) started cART soon after they were diagnosed with acute HIV infection; of those, 164 (65.1%) received nNRTI-based regimens; 26 (10.3%) integrase inhibitor-based regimens and 24 (9.5%) protease inhibitor-based regimens.

Clinical manifestations and physical findings of patients with acute HIV infection are shown in Table 2. The most common symptoms were fever (n = 194; 76.9%), fatigue (n = 89, 35.3%), myalgia (n = 77, 30.6%), diarrhea (n = 63, 25%) and headache (n = 59, 23.4%). Patients with a high PVL (PVL >5 $\log_{10}$ copies/ml) were more likely to have fever (82% vs 60.3%, p = 0.001). The most common physical findings were pharyngitis (n = 126, 50%), skin rash (n = 78, 30.9%), lymphadenopathy (n = 34, 13.5%), oral ulcer (n = 25, 9.9%), and aseptic meningitis (n = 15, 6.0%). Syphilis coinfection at the diagnosis of acute HIV infection was found in 59 patients (23.4%). Other sexually transmitted diseases were chlamydial infection (n = 4, 1.6%), condyloma (n = 3, 1.2%) and gonorrhea (n = 2, 0.8%). Candidiasis (n = 9, 3.6%) was the most common opportunistic infection occurred together with acute HIV infection. Other opportunistic infections included were *Pneumocystis jirovecii* pneumonia (n = 7, 2.8%), cryptococcosis (n = 1, 0.4%), and non-typhoid *Salmonella* bacteremia (n = 1, 0.4%).

Demographic and clinical characteristics of patients with acute HIV infection stratified by baseline CD4 count are shown in Table S1. A total of 68 patients had initial CD4 count less than 200 cells/mm^3 (27.0%). Compared with patients with high baseline CD4 counts (>200 cells/mm^3), patients with low baseline CD4 count (≦200 cells/mm^3) were more likely to have higher baseline PVL (6.4 vs 5.6 $\log_{10}$ copies/ml, $p < 0.001$). Clinical manifestations and physical findings of patients with acute HIV infection stratified by baseline CD4 count are shown in Table S2. Patients with low baseline CD4 count were more likely to present with fatigue (48.5% vs 30.4%, p = 0.008), weight loss (26.5% vs 6.5%, $p < 0.001$), and *P. jirovecii* pneumonia (8.8% vs 0.5%, $p < 0.001$).

Laboratory values of patients with acute HIV infection are shown in Table 3. The median value of AST was 36 U/L (IQR, 24–83), whereas that of ALT was 45 U/L (IQR, 25–85). The values of hemoglobin and platelets were lower in patients with high PVL compared to patients with low PVL (14.1 vs 14.7 g/dL, p = 0.018; and 186 vs 214 × 10^3/mm^3, p = 0.028, respectively). Compared to patients with low baseline PVL, those with high baseline PVL were more likely to have higher aminotransferase levels (AST, 46 vs 28 U/L, $p < 0.001$; ALT, 52 vs 29 U/L, $p < 0.001$). Initial laboratory values of patients with acute HIV infection stratified by initial baseline CD4 count are shown in Table S3. White blood cell count, hemoglobin and platelet levels and

Table 3 Initial laboratory values of patients with acute HIV infection stratified by baseline plasma HIV RNA load (PVL).

	All patients (n = 252)	Baseline PVL >5 $\log_{10}$ copies/ml (n = 194)	Baseline PVL ≤5 $\log_{10}$ copies/ml (n = 58)	*p* value
WBC, cells/mm^3	5545 (3955–7180)	5295 (3805–7130)	6045 (4775–7405)	0.038
Hemoglobin, g/dL	14.2 (13.2–15.0)	14.1 (13.2–14.9)	14.7 (13.8–15.3)	0.018
Platelet × 10^3 cells/mm^3	193 (138–236)	186 (127–233)	214 (166–248)	0.028
Lymphocyte, %	35.0 (26.9–42.9)	33.9 (24.4–42.0)	39.0 (34.0–45.0)	0.016
Total bilirubin, mg/dL	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.8 (0.5–0.9)	0.607
AST, U/L	36 (24–83)	46 (26–94)	28 (22–35)	<0.001
ALT, U/L	45 (25–85)	52 (27–98)	29 (18–51)	<0.001
BUN, mg/dL	10.9 (8.6–14.2)	11.0 (9.0–14.3)	9.4 (8.0–13.7)	0.283
Creatinine, mg/dL	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.936

*All values presented are median (IQR).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; IQR, interquartile range; PVL, plasma HIV RNA load; WBC, white blood cell count.

lymphocyte percentage were lower in patients with low baseline CD4 count than those of patients with high baseline CD4 count. Compared to patients with high baseline CD4 counts, those with low CD4 count were more likely to have higher aminotransferase levels (AST, 54 vs 33 U/L, $p = 0.003$; ALT, 62 vs 38 U/L, $p = 0.032$).

Demographics, clinical characteristics and laboratory values of patients with acute HIV infection stratified by symptom presentation are shown in Tables 4 and 5. Compared with the patients with asymptomatic acute HIV infection, those with symptomatic acute HIV infection were more likely to have higher baseline PVL (5.8 vs 5.2 $\log_{10}$ copies/ml, $p = 0.032$). The values of white blood cell count and hemoglobin were lower in symptomatic patients than those in asymptomatic patients. Compared to asymptomatic patients, those with symptomatic infection were more likely to have higher aminotransferase levels (AST, 43 vs 23 U/L, $p < 0.001$; ALT, 46 vs 25 U/L, $p < 0.001$).

Univariate and multivariate analyses of the factors associated with high PVL for all patients are shown in Table 6. We found that only baseline CD4 count (OR, 4.02; 95% CI, 1.34—12.00) and AST levels (OR, 3.49; 95% CI, 1.60—7.6) were statistically significantly associated with high baseline PVL in multivariate analysis.

Univariate and multivariate analyses of the factors associated with symptomatic acute HIV infection are shown in Table 7. We found that only high baseline PVL (OR, 2.64; 95% CI, 1.17—5.97) was statistically significantly associated with symptomatic infection in multivariate analysis.

Discussion

In this multicenter study conducted at 9 designated hospitals for HIV care in Taiwan, we found that the overall proportion of acute HIV infection in newly diagnosed HIV-positive patients was 6.9%. Patients with high PVL were more likely to have fever, elevated aminotransferases, and lower hemoglobin, white blood cell count, and platelet count. Low baseline CD4 count and higher aminotransferase levels were independently associated with high PVL; and higher baseline PVL was associated with symptomatic acute HIV infection.

The prevalence rate of acute HIV infection ranges from 1 to 8.3% among different populations.[12—14,27—29] Wong et al. found that approximately 3% of patients with newly diagnosed HIV infection presented with acute HIV infection in Singapore.[27] In a cross-sectional, retrospective study by Ammassari et al., 8.3% of newly diagnosed HIV-positive individuals were diagnosed with acute HIV infection in Italy.[28] Similar to those studies, we found that the proportion of patients with acute HIV infection among newly diagnosed HIV-positive patients was 6.9%. The increasing trend of acute HIV infection diagnosis over the 5-year study period may be due to the increasing numbers of screening programs implemented, including anonymous screening provided by the government, hospitals and non-governmental organizations. Increased awareness of regarding the symptoms related to acute HIV infection within the at-risk population and health care providers may have also played a role.

The most common mode of HIV transmission in patients with acute HIV infection was male-to-male sex contact, which ranges from 53% to 95% in the published studies from different regions.[4,27—32] MSM accounted for 94% of the patients diagnosed with acute HIV infection in our study. MSM with a higher incidence of HIV infection tend to have more HIV screening in Taiwan, which may result in a higher percentage of newly diagnosed acute HIV infection.[33] However, early diagnosis of acute HIV infection in women or heterosexual men, who undergo tests less frequently, is

Table 4 Demographic and clinical characteristics of patients with acute HIV infection stratified by the presence of symptoms.

	Symptomatic (n = 223)	Asymptomatic (n = 29)	*p* value
Age, median (IQR), years	26 (23—30)	25 (22—28)	0.352
Male, n (%)	221 (99.1)	28 (96.6)	0.233
Risk group for HIV transmission, n (%)			0.461
Men who have sex with men	211 (94.6)	26 (89.7)	
Heterosexuals	11 (4.9)	3 (10.3)	
Injecting drug users	1 (0.5)	0 (0)	
HBsAg positivity, n (%)	10 (4.5)	1 (3.4)	0.831
Anti-HBs positivity, n (%)	116 (52.0)	19 (65.5)	0.122
Anti-HCV positivity, n (%)	8 (3.6)	1 (3.4)	0.996
Anti-HAV IgG positivity, n (%)	20/166 (12.1)	7/24 (29.2)	0.025
Baseline CD4, median (IQR), cell/mm^3	295 (196—432)	324 (248—438)	0.303
Baseline PVL, median (IQR), $\log_{10}$ copies/ml	5.8 (5.1—6.6)	5.2 (4.9—5.9)	0.032
Fiebig stage			0.216
Stage I	6 (2.7)	0 (0)	0.999
Stage II	5 (2.2)	0 (0)	0.999
Stage III	38 (17.0)	1 (3.5)	0.059
Stage IV	173 (77.6)	28 (96.6)	0.017
Stage V	1 (0.5)	0 (0)	0.999

Abbreviations: CART, combination antiretroviral therapy; HAV, hepatitis A virus; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IQR, interquartile range, PVL, plasma HIV RNA load.

Table 5 Initial laboratory values of patients with acute HIV infection stratified by the presence of symptoms.

	Symptomatic (n = 223)	Asymptomatic (n = 29)	*p* value
WBC, cells/mm^3	5400 (3820–7100)	6320 (5190–7470)	0.026
Hemoglobin, g/dL	14.1 (13.2–14.9)	14.8 (14.4–15.3)	0.007
Platelet $\times$ 10^3 cells/mm^3	190 (135–238)	201 (165–230)	0.431
Lymphocyte, %	34.8 (27.0–43.1)	35.0 (23.3–39.9)	0.707
Total bilirubin, mg/dL	0.7 (0.5–0.9)	0.6 (0.4–1.0)	0.751
AST, U/L	43 (25–89)	23 (21–33)	<0.001
ALT, U/L	46 (26–93)	25 (15–41)	<0.001
BUN, mg/dL	11.0 (8.8–14.5)	10.0 (8.0–12.0)	0.406
Creatinine, mg/dL	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.449

*All values presented are median (IQR).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; IQR, interquartile range; PVL, plasma HIV RNA load; WBC, white blood cell count.

Table 6 Logistic analysis to identify factors associated with high plasma HIV RNA load (PVL).

Variables	Univariate analysis OR (95% CI)	*p*	Multivariable analysis OR (95% CI)	*p*
Demographic characteristics				
Age, per 1-year increase	0.99 (0.95–1.03)	0.670		
Risk group for HIV transmission				
Men who have sex with men	0.90 (0.24–3.35)	0.878		
Heterosexual	1.00 (reference)			
Clinical characteristics				
HBsAg positivity	0.48 (0.13–1.70)	0.254		
Anti-HBs positivity	1.18 (0.64–2.18)	0.591		
Anti-HCV positivity	0.54 (0.13–2.24)	0.396		
Anti-HAV IgG positivity	0.97 (0.36–2.60)	0.953		
Baseline CD4 count $\leq$200 cells/mm^3	5.10 (1.94–13.38)	0.001	4.02 (1.34–12.00)	0.013
Fiebig stage				
Stage I/II/III	2.54 (1.02–6.31)	0.044	0.61 (0.26–1.43)	0.256
Stage IV/V	1.00 (reference)		1.00 (reference)	
Clinical manifestations				
Fever	2.99 (1.57–5.67)	0.001	1.59 (0.70–3.60)	0.266
Skin rash	0.90 (0.48–1.68)	0.735		
Pharyngitis	0.91 (0.51–1.64)	0.765		
Lymphadenopathy	1.86 (0.69–5.06)	0.222		
Myalgia	1.20 (0.63–2.31)	0.576		
Headache	1.40 (0.67–2.92)	0.364		
Diarrhea	0.94 (0.48–1.85)	0.863		
Arthralgia	0.59 (0.14–2.42)	0.459		
Cough	0.73 (0.35–1.53)	0.404		
Nausea	2.32 (0.93–5.78)	0.070	1.74 (0.60–5.01)	0.308
Fatigue	0.71 (0.39–1.30)	0.272		
Vomiting	1.82 (0.60–5.48)	0.290		
Weight loss	2.09 (0.70–6.25)	0.188		
Genital ulcer	1.36 (0.29–6.49)	0.698		
Oral ulcer	1.22 (0.44–3.40)	0.706		
Aseptic meningitis	1.21 (0.33–4.44)	0.775		
Coinfection				
Syphilis	0.84 (0.43–1.65)	0.616		
Condyloma	0.59 (0.05–6.67)	0.673		
Pneumocystosis	1.74 (0.21–14.78)	0.611		
Laboratory investigations				
WBC <4000 cells/mm^3	2.89 (1.23–6.79)	0.014	1.23 (0.38–3.99)	0.733
Hemoglobin, per 1-g/dL decrease	1.27 (1.02–1.57)	0.029	0.91 (0.70–1.18)	0.470
Platelet <150 $\times$ 10^3 cells/mm^3	2.24 (1.06–4.74)	0.036	1.38 (0.53–3.58)	0.514

Table 6 (*continued*)

Total bilirubin >1 mg/dL	1.00 (0.37–2.65)	0.996		
AST >40 U/L	4.03 (1.88–8.66)	<0.001	3.49 (1.60–7.60)	0.002
ALT >40 U/L	2.99 (1.52–5.90)	0.002	1.62 (0.64–4.15)	0.311
BUN, per 1-mg/dL increase	1.03 (0.96–1.11)	0.374		
Creatinine, per 1-mg/dL increase	1.69 (0.40–7.04)	0.473		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HAV, hepatitis A virus; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IQR, interquartile range; PVL, plasma HIV RNA load; WBC, white blood cell count.
Backward stepwise logistic regression model.
Variables with p value <0.1 in the univariate analysis were included in the multivariate analysis.

also an important issue in the era of antiretroviral therapy scale-up.

The most common symptoms in our cohort were fever, fatigue, myalgia, diarrhea, and headache. The most common physical findings were pharyngitis, skin rash, lymphadenopathy, oral ulcer, aseptic meningitis, and genital ulcer. These findings are in line with those from previous published reports. As demonstrated, the clinical manifestations of acute HIV infection were nonspecific and variable. Acute HIV infection may also be complicated with aseptic meningitis. Fifteen patients with acute HIV infection, presented with symptoms and signs consistent with aseptic meningitis. Hanson et al. found that 5.3% of patients with acute HIV infection showed detection of HIV RNA in the cerebrospinal fluid, a clinical finding consistent with aseptic meningitis.[34] Patients with high baseline PVL tended to have more febrile symptoms, and higher baseline PVL was associated with symptomatic infection in multivariate analysis. This finding is not surprising, because patients with high viral load would have higher inflammatory cytokine production, resulting in more febrile symptoms.

Initial laboratory values of patients with acute HIV infection revealed that hemoglobin was lower in patients with high baseline PVL than in patients with low baseline PVL. Compared to the patients with low baseline PVL, patients with high baseline PVL were more likely to have impaired liver function. Once infection occurs, massive viral replication, and usually the inflammatory state correlate with high PVL.[35] This inflammatory cytokine storm may result in hepatocellular injury and bone marrow suppression, thus resulting in more severe acute liver injury and reduced hemoglobin levels.

A total of 68 patients (27.0%) had initial CD4 counts of 200 cells/mm^3 or less was observed while acute HIV

Table 7 Logistic analysis to identify factors associated with symptomatic acute HIV infection.

Variables	Univariate analysis OR (95% CI)	*p*	Multivariable analysis OR (95% CI)	*p*
Demographic characteristics				
Age, per 1-year increase	1.03 (0.97–1.10)	0.314		
Male sex	3.83 (0.34–43.54)	0.279		
Risk group for HIV transmission				
Men who have sex with men	2.14 (0.56–8.16)	0.265		
Heterosexual	1.00 (reference)			
Clinical characteristics				
HBsAg positivity	1.30 (0.16–10.54)	0.807		
Anti-HCV positivity	1.03 (0.12–8.54)	0.979		
Baseline CD4 count ≤200 cell/mm^3	1.76 (0.64–4.84)	0.273		
Baseline PVL >5 log$_{10}$ copies/ml	3.02 (1.35–6.76)	0.007	2.64 (1.17–5.97)	0.02
Fiebig stage				
Stage I/II/III	8.12 (1.08–61.12)	0.042	6.37 (0.84–48.56)	0.074
Stage IV/V	1.00 (reference)			
Laboratory investigations				
WBC <4000 cells/mm^3	9.71 (1.29–73.26)	0.027	3.57 (0.43–29.43)	0.236
Hemoglobin, per 1-g/dL decrease	0.73 (0.52–1.01)	0.059	0.70 (0.46–1.05)	0.087
Platelet <150 × 10^3 cells/mm^3	2.33 (0.77–7.08)	0.135		
Total bilirubin >1 mg/dL	0.72 (0.22–2.32)	0.580		
AST >40 U/L	4.75 (1.56–14.48)	0.006	2.23 (0.48–10.25)	0.303
ALT >40 U/L	2.73 (1.08–6.93)	0.034	1.64 (0.50–5.42)	0.416
BUN, per 1-mg/dL increase	1.08 (0.92–1.28)	0.331		
Creatinine, per 1-mg/dL increase	3.11 (0.27–35.58)	0.361		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; PVL, plasma HIV RNA load; WBC, white blood cell count.

infection diagnosed, which is higher than previously published reports.[27,36] Wong et al. found that approximately 14% of patients with acute HIV infection had initial CD4 counts of 200 cells/mm^3 or lower in Singapore.[27] In a study by Kassutto et al., 3.9% of patients with acute HIV infection in America showed CD4 cell count lower than 200 cells/mm.[36] The explanation for the significant depletion of CD4 count at initial diagnosis that HIV infection is not clear in our study without characterization of the HIV viruses recently circulating among the patients who acquired HIV through sexual transmission, though a more virulent HIV infection has been postulated.[37]

Patients with low baseline CD4 count were more likely to have high PVL. They also tend to have more candidiasis and pneumocystosis. White blood cell count, hemoglobin levels, and the percentage of lymphocytes were lower in patients with low baseline CD4 count than those with high baseline CD4 count. Multivariate analysis, showed that low baseline CD4 count and low baseline AST levels were independently associated with high PVL. Langerhans cells, which are located in the lamina propria adjacent to the genital mucosa, are the first cellular targets of HIV. These cells propagate locally and disseminate into the drainage lymph nodes. Within 30 days after infection, massive viral replication occurs, accompanied by CD4 T cell death.[38] Patients with high PVL present with more severe inflammation, which results in rapid depletion of CD4 cells with subsequent opportunistic infections if patients are not untreated.

Our findings may have clinical implications for the diagnosis of acute HIV infection. Most symptoms and signs of acute HIV infection are nonspecific and timely diagnosis maybe difficult and challenging. Weintrob et al. found that 83% of acute HIV infections were not detected at the first medical encounter.[39] Besides, unfamiliarity with the diagnostic tools that may be used in acute HIV infection makes early diagnosis even more difficult. Provision of information and continued education of primary health care providers regarding HIV care and diagnosis may increase the chances of early diagnosis acute HIV infection.

There are several limitations in our study. First, collection of the information on the presentations of acute HIV infection was not conducted with a checklist, and it is likely that our description of the clinical manifestations may have not been complete because of the retrospective study design. Second, it is likely that only symptomatic patients sought medical attention and HIV testing. We might have over-estimated the rate of patients with symptomatic acute HIV infections. Third, identification of factors associated with high PVL may not have significant clinical implications because currently all patients with HIV infection are treated with effective cART, regardless of the CD4 count and PVL at presentation according to the "treat-all" recommendation of the national HIV treatment guidelines.

In conclusion, our study showed that the proportion of patients with acute HIV infection among newly diagnosed HIV infection was 6.9%. Most symptoms and signs of acute HIV infection were nonspecific and ranged from fever to severe illness such as aseptic meningitis. The finding of a higher proportion of patients with initial CD4 counts of 200 cells/mm^3 or less during acute HIV infection warrants early, timely diagnosis and treatment to prevent rapid disease progression.

Funding

This study was supported by grants from the Centers for Disease Control, Taiwan (MOHW105-CDC-C-114-000104), the Ministry of Science and Technology, Taiwan (MOST106-2314-B-016-026-MY3), Tri-Service General Hospital (TSGH-C104-118 and TSGH-C105-114). The funding sources had no role in study design and conduct; data collection, analysis, or interpretation; or in the writing of the manuscript or the decision to submit it for publication.

Conflicts of interest

C—C. H. has received research support from Janssen, Abbvie, Merck, Bristol-Myers Squibb, and ViiV and speaker honoraria from Bristol-Myers Squibb, ViiV, Abbvie, and Gilead Sciences, and served on advisory boards for Gilead Sciences, Abbvie, ViiV, and Janssen. Other authors, none to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmii.2018.01.005.

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