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ORIGINAL ARTICLE

Etiology of pulmonary complications of human immunodeficiency virus-1-infected patients in Taiwan in the era of combination antiretroviral therapy: A prospective observational study

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KEYWORDS
Bacterial pneumonia;
Cytomegalovirus pneumonitis;
Interstitial pneumonitis;

Objectives: We aimed to investigate the etiology of pulmonary complications of human immunodeficiency virus-(HIV)-1-infected patients in Taiwan in the era of combination antiretroviral therapy (cART).
Methods: From July 2009 to March 2012, a prospective observational study was conducted to identify the etiology of pulmonary complications in HIV-1-infected patients who sought HIV care at a university hospital in Taiwan. A stepwise diagnostic approach was adopted, which included radiography, serology, microbiology, bronchoscopy or video-assisted thoracoscopic surgery, and polymerase chain reaction assays for cytomegalovirus and *Pneumocystis jirovecii*.

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Pneumocystis jirovecii pneumonia;
Pulmonary complication;
Tuberculosis

Results: During the study period, a total of 203 episodes of pulmonary complications that occurred in 190 patients with a mean CD4 count of 123 $\times$ 10^6 cells/L were analyzed. Thirty-eight episodes (18.7%) occurred in patients with a CD4 count >200 $\times$ 10^6 cells/L, 71 (35.0%) between 50 and 200 $\times$ 10^6 cells/L, and 94 (46.3%) <50 $\times$ 10^6 cells/L. *Pneumocystis* pneumonia accounted for more than half of the complications in patients with a CD4 count <200 $\times$ 10^6 cells/L. In patients with a CD4 count >200 $\times$ 10^6 cells/L, the etiology of pulmonary complications was diverse, with bacterial infections (47.4%) being the most common, followed by tuberculosis (15.8%) and lung edema (13.2%). Pneumocystosis and cytomegalovirus pneumonitis were seen mostly or exclusively in patients with a CD4 count <200 $\times$ 10^6 cells/L and were the leading causes of interstitial pneumonitis. On the other hand, empyema, legionellosis, and lung edema were more commonly seen in patients with a CD4 count >200 $\times$ 10^6 cells/L.
Conclusions: The etiology of pulmonary complications in HIV-1-infected patients was diverse and varied with the categories of CD4 counts. Pneumocystosis remained the leading cause of pulmonary complications in patients with lower CD4 counts in Taiwan in the cART era.

Introduction

Pulmonary complications remain the leading cause of morbidity and mortality of human immunodeficiency virus-(HIV)-1-infected patients in the era of combination antiretroviral therapy (cART) while its spectrum is changing.[1,2] For patients who are taking effective cART and antimicrobial prophylaxis, opportunistic infections have declined in frequency, and prolonged survival with cART has allowed other processes to occur, such as bronchogenic carcinoma, chronic obstructive pulmonary disease, and pulmonary hypertension.[3–5] In contrast, for patients who have limited access to HIV care and who are not taking cART or antimicrobial prophylaxis, opportunistic infections and immunosuppression-related neoplasms continue to occur.[1]

CART was first introduced into Taiwan in April 1997. Currently, all HIV-infected patients are provided free access to inpatient or outpatient care including cART at designated hospitals around Taiwan. The survival of HIV-infected patients has significantly improved[6–8] and incidences of several opportunistic infections have declined with introduction of cART.[6,9] However, pulmonary complications that require critical care and result in substantial mortality continue to occur in the cART era.[10] With improved survival, aging, and a high prevalence of smoking, pulmonary complications are likely to play an increasingly important role in morbidity and mortality in HIV-infected patients who receive cART.[4] While several retrospective studies in Taiwan have reported on specific pulmonary complications in HIV-infected patients,[11–13] little is known about the spectrum of pulmonary complications in this population in the cART era. In this prospective observational study, we investigated the etiology of pulmonary complications among HIV-infected patients who sought HIV care at a university hospital in Taiwan.

Methods

Study population and data collection

From July 2009 to March 2012, a prospective observational study was conducted at the National Taiwan University Hospital, the largest referral hospital for HIV care in Taiwan. HIV-infected patients aged ≥20 years who presented with respiratory symptoms and signs and required inpatient care were identified. After obtaining a clinical history and physical examination, a stepwise diagnostic approach was adopted as part of routine clinical care, which included chest radiography, serologies, and acid-fast staining and microbiologic cultures of clinical specimens. For patients with interstitial pneumonitis that was demonstrated by high-resolution computed tomography (HRCT) of the chest, blood specimens and sputum or bronchoalveolar lavage (BAL) specimens were obtained for polymerase chain reaction (PCR) assays for cytomegalovirus (CMV) and *Pneumocystis jirovecii*, respectively. Serologic tests included cryptococcal antigen and aspergillus antigen of the serum specimens,[14] and pneumococcal and legionella antigen of the urine specimens. Chest sonography- or CT-guided aspiration/biopsy would be performed in patients with tumors that were peripherally located and bronchoscopy and/or video-assisted thoracoscopic surgery were performed after consulting with chest medicine specialists and chest surgeons when previous investigations remained nondiagnostic.

A standardized case record form was used to collect the clinical, laboratory, and histopathologic data, including gender; age; HIV-related variables (CD4 count, plasma HIV RNA load, and cART); smoking; baseline pulmonary and systemic diseases; results of cultures, serological tests, PCR assays, and pathology; clinical diagnosis; and outcomes. Patients were classified as 'ever-smokers' if they had smoked more than 100 lifetime cigarettes. The latest CD4 count that was obtained within 3 months of onset of the illness was recorded for each episode. The study was approved by the Research Ethics Committee of National Taiwan University Hospital and informed consent was waived.

Definitions

If patients had been hospitalized more than once due to different pulmonary complications, each hospitalization was regarded as an independent episode. Moreover, patients might have more than one diagnosis during each episode. Recurrence of pre-existing diseases was excluded.

Pneumocystosis was diagnosed if: (1) *P. jirovecii* was identified by cytology of sputum or BAL specimen, or histopathology of lung biopsy specimen (confirmed cases); (2) the PCR assay for *Pneumocystis* 16S rRNA of sputum or BAL specimen was positive, plus a typical clinical history and image findings of interstitial pneumonitis (probable cases); and (3) patients presented with a typical clinical history and interstitial pneumonitis, for which anti-pneumocytosis therapy was initiated (presumptive cases). Patients were diagnosed to have CMV pneumonitis if: (1) the lung biopsy demonstrated pneumonitis and cytopathic effect consistent with CMV (confirmed cases); and (2) the chest radiography revealed interstitial pneumonitis and CMV was detected in the serum or respiratory specimens by PCR assays with clinical response to anti-CMV treatment with ganciclovir or foscarnet (probable cases). Bacterial pneumonia was diagnosed when patients presented with consistent respiratory symptoms, infiltrates by chest radiography, growth of typical respiratory pathogens, or positive results of pneumococcal or legionella antigen assays of urine specimens. In patients without microbiologic confirmation, bacterial pneumonia was diagnosed by the presence of respiratory symptoms, infiltrates by chest radiography, and favorable clinical response to antibiotic therapy. Tuberculosis (TB) was confirmed in patients with positive cultures of sputum specimens for *Mycobacterium tuberculosis*; or probable TB was diagnosed if chest radiography showed pulmonary infiltrates with or without cavitation, or miliary infiltrates, in addition to clinical response to anti-TB therapy. Nontuberculous mycobacterial infection was diagnosed if patients had positive culture results for nontuberculous mycobacteria (NTM) from at least two separate expectorated sputum specimens or at least one BAL specimen, with exclusion of other diagnoses. Diagnosis of crypotococcosis, aspergillosis, or penicillosis of the lung was made when patients presented with pulmonary infiltrates by chest radiography plus positive serologic, mycobiologic, or histopathologic studies of clinical specimens. Diagnoses of malignant diseases were based on histpathologic examinations of tissue biopsies. Pulmonary hypertension was confirmed by echocardiography, while pulmonary embolism by CT of the lungs. Lung edema was diagnosed when patients presented with a consistent clinical history plus chest radiography.

Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). The χ^2 test or Fisher's exact test was used for categorical variables, and the one-way analysis of variance for continuous data. All tests were two-tailed and differences were considered statistically significant at $p < 0.05$.

Results

During the study period, 218 episodes that occurred in 197 HIV-infected adult patients were identified. Thirteen episodes were excluded due to non-pulmonary diseases (five) or recurrent episodes (eight), and two others were excluded because of lacking CD4 count data in last three months. A total of 203 episodes in 190 patients were included for analysis.

The baseline characteristics of all patients are shown in Table 1. The mean CD4 count was 123×10^6 cells/L. Ninety-four episodes (46.3%) occurred in patients with a CD4 count $<50 \times 10^6$ cells/L, 71 (35.0%) between 50 to 200×10^6 cells/L, and 38 (18.7%) $>200 \times 10^6$ cells/L; the mean age of these three groups was 38, 39, and 49 years, respectively ($p < 0.001$). Almost all (96.6%) of the patients were male, with homosexual or bisexual contact as the most common route for HIV transmission. While 125 patients were previously diagnosed as having HIV infection, only 51 (40.8%) were receiving cART for >30 days before presentation, among who 40 (78.4%) had achieved successful viral suppression (defined as plasma HIV RNA level <400 copies/mL). Two-fifths (41.4%) of the patients were ever-smokers, and 10.8% had pre-existing pulmonary diseases. Nearly half of the patients had been healthy before without any pulmonary or systemic diseases.

The etiologies of pulmonary complications are shown in Table 2. In 38 episodes, more than one etiology was identified (two etiologies in 34 episodes, three in two, and four in two). *P jirovecii* pneumonia was the most common etiology, which accounted for more than half of the complications in patients with a CD4 count $<200 \times 10^6$ cells/L. Bacterial infections were the second common cause of pulmonary complications (18.7% of all cases), and the proportion was higher among patients with a CD4 count $>200 \times 10^6$ cells/L ($p < 0.001$). Of note, the proportion of pneumococcal pneumonia was similar in patients with different CD4 count categories. On the other hand, legionellosis and empyema were more commonly seen in patients with a CD4 count $>200 \times 10^6$ cells/L compared with those with a CD4 count $<200 \times 10^6$ cells/L ($p = 0.03$ and 0.001, respectively). CMV pneumonitis was diagnosed in 26 episodes (12.8%), for which seven (26.9%) were confirmed by histopathology of lung biopsy specimens. CMV pneumonitis were seen exclusively in patients with a CD4 count $<200 \times 10^6$ cells/L ($p = 0.01$). Pulmonary TB was diagnosed in 8.4% of the patients, which accounted for a significantly higher proportion among patients with a CD4 count $>50 \times 10^6$ cells/L: 1.1%, 14.1%, and 15.8% of the cases in patients with a CD4 cell count <50, 50 to 200, and $>200 \times 10^6$ cells/L, respectively (CD4 count <50 vs. 50 to 200, $p = 0.001$; CD4 count <50 vs. >200, $p = 0.002$). Other less common infectious etiology of pulmonary complications included *M avium* complex (MAC) infection, NTM infection other than MAC (both 3.0%), cryptococcosis (2.5%), aspergillosis, and penicilliosis marneffei (both 1.5%).

Ten patients (4.9%) were diagnosed to have malignancies involving the lungs, which included non-Hodgkin's lymphoma (six), Kaposi's sarcoma (one), multicentric Castleman's disease (one), non—small-cell lung cancer (one), and metastatic squamous cell carcinoma of unknown primary origin (one). Lung edema resulting from congestive heart failure or impaired renal function was diagnosed in 3.4% of the cases, which was almost exclusively seen in patients with a CD4 count $>200 \times 10^6$ cells/L ($p = 0.003$). The etiology of pulmonary complication remained unidentified in 7.9% of the cases.

Fig. 1 demonstrates the relationship between CD4 counts and pulmonary complications with a proportion ≥2.5% of all episodes. Pneumocystosis, CMV pneumonitis,

Table 1 Baseline characteristics of 190 HIV-infected patients with 203 episodes of pulmonary complications

Variables	All episodes	Episodes occurring in patients with different CD4 count categories			*p*
		$<50 \times 10^6$ cells/L	50-200 $\times 10^6$ cells/L	$>200 \times 10^6$ cells/L	
Number of episodes, *n* (%)	203	94 (46.3)	71 (35.0)	38 (18.7)	
Age, mean (SD), years,	40 (12)	38 (9)	39 (9)	49 (16)	**<0.001**
Male gender, *n* (%)	196 (96.6)	90 (95.7)	70 (98.6)	36 (94.7)	0.48
Risk behaviors for HIV transmission, *n* (%)					
Homosexual/bisexual	151 (74.4)	73 (77.7)	59 (83.1)	19 (50.0)	
IDU	10 (4.9)	0	4 (5.6)	6 (15.8)	
Both homosexual and IDU	3 (1.5)	1 (1.1)	2 (2.8)	0	
Others or unknown	39 (19.2)	20 (21.3)	6 (15.8)	13 (34.2)	
Previously diagnosed with HIV infection, *n* (%)	125 (61.6)	45 (47.9)	44 (62.0)	36 (94.7)	**<0.001**
Latest CD4 cell count, $\times 10^6$ cells/L					
mean (SD)	123 (175)	20 (14)	94 (36)	434 (190)	**<0.001**
<50, *n* (%)	94 (46.3)				
50–200	71 (35.0)				
201–350	18 (8.9)				
>350	20 (9.9)				
Latest plasma HIV RNA load, mean (SD), $\log_{10}$ copies/ml,	4.4 (1.6)	5.1 (1.0)	4.7 (1.3)	2.4 (1.4)	**<0.001**
Patients with data, *n*	189	87	65	37	
<400 copies/ml, *n* (%)	40 (21.2)	3 (3.4)	8 (12.3)	29 (78.4)	
On cART	51 (25.1)	7 (7.4)	13 (18.3)	31 (81.6)	
On TMP/SMX among patients with a CD4 count $<200 \times 10^6$ cells/L, *n* (%)	22 (13.3)	13 (13.8)	9 (12.7)	—	
Ever-smoker, *n* (%)	84 (41.4)	37 (39.4)	29 (40.8)	18 (47.4)	0.70
Pulmonary disease at baseline, *n* (%)					
COPD	4 (2.0)	0	1 (1.4)	3 (7.9)	**0.01**
Asthma	4 (2.0)	2 (2.1)	2 (2.8)	0	0.83
Bronchiectasis	2 (1.0)	2 (2.1)	0	0	0.67
Tuberculosis	9 (4.4)	4 (4.3)	2 (2.8)	3 (7.9)	0.44
Non-tuberculous mycobacteriosis	4 (2.0)	2 (2.1)	1 (1.4)	1 (2.6)	>0.99
Systemic diseases at baseline, *n* (%)					
Diabetes mellitus	10 (4.9)	1 (1.1)	1 (1.4)	8 (21.1)	**<0.001**
Hypertension	10 (4.9)	2 (2.1)	2 (2.8)	6 (15.8)	**0.007**
Cardiovascular diseases	8 (3.9)	0	2 (2.8)	6 (15.8)	**<0.001**
Chronic HBV infection	42 (20.7)	19 (20.2)	18 (25.4)	5 (13.2)	0.32
Chronic HCV infection	7 (3.4)	1 (1.1)	1 (1.4)	5 (13.2)	**0.003**
Renal disease	4 (2.0)	1 (1.1)	0	3 (7.9)	**0.02**
Solid-organ malignancy	5 (2.5)	0	3 (4.2)	2 (5.3)	0.06
Hematological malignancy	6 (3.0)	2 (2.1)	2 (2.8)	2 (5.3)	0.58
Hematological disease	5 (2.5)	2 (2.1)	1 (1.4)	2 (5.3)	0.50
Autoimmune disease	2 (1.0)	2 (2.1)	0	0	0.67
None	101 (49.8)	51 (54.3)	37 (52.1)	13 (34.2)	0.10

cART = combination antiretroviral therapy; COPD = chronic obstructive pulmonary disease; HBV = hepatitis B virus; HCV = hepatitis C virus; IDU = injecting drug user; SD = standard deviation; TMP/SMX = trimethoprim/sulfamethoxazole.
P values marked in bold if <0.05.

NTM infections, cryptococcosis, and non-Hodgkin's lymphoma occurred mostly or exclusively in patients with a CD4 count $<200 \times 10^6$ cells/L, whereas bacterial infections, pulmonary TB, and lung edema could be seen in patients with higher CD4 cell counts.

HRCT of the chest was performed in 73.4% of the cases ($n = 149$), and the predominantly interstitial pattern was the most common radiographic finding that was seen in 65.8% of the cases ($n = 98$). In patients presenting with interstitial pneumonitis, the majority (92.9%) had pneumocystosis only (65 cases) or pneumocystosis with other concomitant etiologies (26 cases; Table 3). The etiologies of the remaining cases included CMV pneumonitis (two) and lung edema (one). Four patients did not have a definite diagnosis.

Table 2 Etiology and clinical outcome of 190 HIV-infected patients with 203 episodes of pulmonary complications

Etiology, *n* (%)	Total episodes $n = 203$	Episodes occurring in patients with different categories of CD4 counts			*p*
		$<50 \times 10^6$ cells/L ($n = 94$)	50-200 $\times 10^6$ cells/L ($n = 71$)	$>200 \times 10^6$ cells/L ($n = 38$)	
Pneumocystis pneumonia	106 (52.2)	65 (69.1)	39 (54.9)	2 (5.3)	**<0.001**
Bacterial infection	38 (18.7)	10 (10.6)	10 (14.1)	18 (47.4)	**<0.001**
(1) Bacterial pneumonia	32 (15.8)	9 (9.6)	10 (14.1)	13 (34.2)	**0.002**
Pneumococcal infection	9 (4.4)	3 (3.2)	3 (4.2)	3 (7.9)	0.49
Legionellosis	2 (1.0)	0	0	2 (5.3)	**0.03**
Nocardiosis	2 (1.0)	2 (2.1)	0	0	0.27
(2) Empyema	6 (3.0)	1 (1.1)	0	5 (13.2)	**0.001**
Cytomegalovirus pneumonitis	26 (12.8)	18 (19.1)	8 (11.3)	0	**0.01**
Tuberculosis	17 (8.4)	1 (1.1)	10 (14.1)	6 (15.8)	**0.002**
MAC infection	6 (3.0)	3 (3.2)	3 (4.2)	0	0.66
Other NTM infection	6 (3.0)	4 (4.3)	1 (1.4)	1 (2.6)	0.75
Cryptococcosis	5 (2.5)	0	4 (5.6)	1 (2.6)	**0.04**
Aspergillosis	3 (1.5)	3 (3.2)	0	0	0.30
Penicillium marneffei pneumonia	3 (1.5)	3 (3.2)	0	0	0.30
Non-Hodgkin's lymphoma	6 (3.0)	5 (5.3)	1 (1.4)	0	0.29
Kaposi's sarcoma	1 (0.5)	1 (1.1)	0	0	>0.99
Multicentric Castleman's disease	1 (0.5)	0	0	1 (2.6)	0.19
Lung cancer	1 (0.5)	0	0	1 (2.6)	0.19
Metastatic cancer	1 (0.5)	0	0	1 (2.6)	0.19
Pulmonary hypertension	2 (1.0)	0	1 (1.4)	1 (2.6)	0.29
Pulmonary embolism	1 (0.5)	0	1 (1.4)	0	0.54
Lung edema	7 (3.4)	1 (1.1)	1 (1.4)	5 (13.2)	**0.003**
Inconclusive	16 (7.9)	8 (8.5)	4 (5.6)	4 (10.5)	0.63
Outcome, *n* (%)					
Respiratory failure	40 (19.7)	27 (28.7)	8 (11.3)	5 (13.2)	**0.01**
ICU admission	42 (20.7)	25 (26.6)	10 (14.1)	7 (18.4)	0.14
In-hospital mortality	31 (15.3)	22 (23.4)	6 (8.5)	3 (7.9)	**0.01**

ICU = intensive care unit; MAC = *Mycobacterium avium* complex; NTM infection = non-tuberculous mycobacterial infection.
P values marked in bold if <0.05.

In terms of clinical outcomes (Table 2), 19.7% of the patients developed respiratory failure and 20.7% had been admitted to the intensive care units. The in-hospital mortality rate was 15.3%. Patients with a CD4 count $<50 \times 10^6$ cells/L were more likely to develop respiratory failure and had a higher in-hospital mortality rate than those with a CD4 count $>50 \times 10^6$ cells/L ($p = 0.01$ for both comparisons).

Of the 106 patients who developed PCP in the cART era, 54.7% were newly diagnosed as having HIV infection; 19.8% had never received cART after HIV infection was diagnosed; and 21.7% had interrupted cART due to various reasons. The latest CD4 counts of the patients who never received cART were all $<200 \times 10^6$ cells/L, except one who had a CD4 count of 228×10^6 cells/L. Only four patients (3.7%) were receiving cART when PCP developed: one patient with multi-drug resistant HIV-1 infection after experiencing multiple failures to cART who discontinued trimethroprim-sulfamethoxazole 4 months prior to this episode due to impaired renal function; the other three patients who had not been prescribed prophylaxis for pneumocystosis and were receiving cART with successful viral suppression had latest CD4 counts $<200 \times 10^6$ cells/L (34, 133, and 170×10^6 cells/L, respectively). Of note, two of the three patients had received chemotherapy containing corticosteroids for non-Hodgkin's lymphoma within one month prior to the episodes.

Discussion

In this observational study, we found that *P jirovecii* pneumonia remained the most common cause of pulmonary complications in HIV-infected Taiwanese patients in the era of cART, especially those with a CD4 count $<200 \times 10^6$ cells/L. Bacterial infections and tuberculosis were the second and fourth common etiology, which accounted for a larger proportion among patients with higher CD4 counts. CMV pneumonitis was the third common etiology and occurred exclusively in patients with a CD4 count $<200 \times 10^6$ cells/L.

The incidence of pneumocystosis has declined markedly after the introduction of trimethoprim/sulfamethoxazole prophylaxis and cART[6,15,16]; nevertheless, pneumocystosis continues to be a common presenting opportunistic illness in HIV-infected individuals who are unaware of their HIV infection, those who fail to access HIV care, and those who

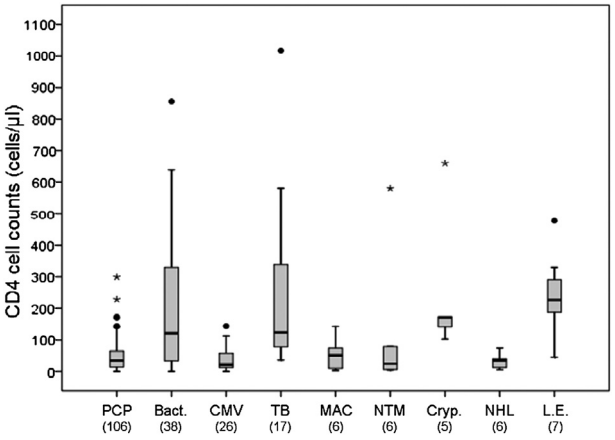

Figure 1. Relationship between CD4 cell counts and the types of pulmonary complications. Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), minimum and maximum except outliers (lower and upper whiskers) of CD4 cell counts for pulmonary complications. Asterisks and dots are outliers >3.0 and 1.5 interquartile range. The case number for each etiology is shown in the bracket. PCP = *Pneumocystis* pneumonia; Bact. = bacterial infection; CMV = cytomegalovirus infection; TB = tuberculosis; MAC = *Mycobacterium avium* complex infection; NTM = non-tuberculous mycobacterial infection; Cryp. = cryptococcosis; NHL = non-Hodgkin's lymphoma; L.E. = lung edema.

fail to adhere to antiretroviral therapy or antimicrobial prophylaxis.[15] In our study, pneumocystosis remained the most common etiology of pulmonary complications in HIV-infected Taiwanese patients, and the aforementioned reasons can be cited for the majority of our patients who developed this complication. More emphasis is needed in Taiwan to increase awareness of HIV infection among persons at risk and health care providers,[17] facilitate early diagnosis of HIV infection, retain HIV-infected patients in care, and provide timely and appropriate antimicrobial prophylaxis and cART for those who meet the criteria.

Table 3 Etiology of pulmonary complications with an interstitial pattern on high-resolution computed tomography of the chest

Etiology, *n* (%)	Total episodes *n* = 98
Pneumocystis pneumonia	91 (92.9)
Isolated	65 (66.3)
With concomitant etiology	26 (26.5)
CMV pneumonitis	15 (15.3)
CMV pneumonitis and *Penicillium marneffei* pneumonia	1 (1.0)
CMV pneumonitis and aspergillosis	1 (1.0)
CMV pneumonitis, aspergillosis, and bacterial infection	1 (1.0)
Bacterial infection	5 (5.1)
NTM infection	2 (2.0)
Cryptococcosis	1 (1.0)
CMV pneumonitis	20 (20.4)
Isolated	2 (2.0)
With concomitant etiologies	18 (18.4)
Lung edema	1 (1.0)
Inconclusive	4 (4.1)

CMV = cytomegalovirus; NTM infection = nontuberculous mycobacterial infection.

In our study, few patients developed pneumocystosis while receiving cART with successful viral suppression. They were not prescribed with trimethoprim/sulfamethoxazole for prophylaxis while their CD4 counts had not increased to $>200 \times 10^6$ cells/L. There is an increasing number of studies suggesting that discontinuation of prophylaxis for pneumocystosis may be safe in patients with CD4 counts of 101 to 200 $\times$ 10^6 cells/L and viral suppression.[18,19] However, this strategy should warrant cautious judgment when applied to all patients, especially those who have additional risk factors for pneumocystosis, such as lymphoproliferative malignancies and use of corticosteroids.[20]

Bacterial pneumonia occurs more frequently in HIV-infected patients, and the incidence increases as the CD4 count decreases.[21,22] Despite the overall reduction in the incidence of bacterial pneumonia after the introduction of cART, it remains a common pulmonary complication in HIV-infected persons,[23] which was also seen in the study. Of note, pneumococcal pneumonia could occur at any stage of HIV infection,[24] and HIV-infected patients have a higher risk for invasive pneumococcal diseases than the general population even after the introduction of cART.[25,26] As a result, other preventive interventions for pneumococcal disease such as pneumococcal vaccination are important.

The incidence of CMV end-organ diseases such as retinitis and colitis was >20%/year in HIV-infected patients with a CD4 count $<100 \times 10^6$ cells/L.[27,28] However, CMV as a pulmonary pathogen has been considered uncommon; only 0.24% to 8% of HIV-infected patients received a diagnosis of CMV pneumonitis in previous studies.[29,30] The definite diagnosis of CMV pneumonitis remains controversial. The presence of CMV in BAL specimens by culture or cytology is neither a sensitive nor a specific test for CMV pneumonitis.[31–34] Lung biopsy is likely to be more specific for CMV pneumonitis, but the procedure is invasive and may be insensitive due to the patchy nature of the disease. In our study, the definition of CMV pneumonitis was similar to that of the AIDS Clinical Trials Group (ACTG) Protocol 360 Study,[30] but only patients who responded to anti-CMV treatment were defined as probable cases. CMV pneumonitis occurred in almost 20% of the patients with a CD4 count $<50 \times 10^6$ cells/L, and the actual incidence could be higher because severely immunocompromised patients with CMV pneumonitis might not respond to therapy or their critical illness might preclude them from invasive diagnostic procedures.

TB was the fourth common etiology of pulmonary complications, and accounted for 8.4% of the cases in this study. TB can occur at any stage of HIV infection. [35,36] Interestingly, TB accounted for a significantly lower proportion among patients with a CD4 count $<50 \times 10^6$ cells/L than those with a CD4 count $>50 \times 10^6$ cells/L in our study (1.1% vs. 14.7%). In patients with low CD4 counts, TB tends to become disseminated and have atypical or minimal changes on chest radiography when the patients present for clinical care.[34,35]

As a result, some of the patients with disseminated TB may not be included in this study, although in our stepwise diagnostic approach, acid-fast smears and TB cultures of respiratory tract specimens were routinely performed in patients with fever and respiratory symptoms. The lower prevalence of TB may also be because of a significantly higher case number of interstitial pneumonitis and a higher mortality rate in the patients with CD4 $<50 \times 10^6$ cells/L. The higher mortality may preclude us from detecting concomitant TB at presentation in this subgroup.

In patients with a low CD4 count, other opportunistic infections and neoplasms such as infections due to NTM, aspergillosis, penicilliosis, cryptococcosis, non-Hodgkin's lymphoma, and Kaposi's sarcoma were also seen in our study, although less frequently. On the other hand, some rare diseases including pulmonary hypertension, multicentric Castleman's disease, and bronchogenic cancer occurred in patients with a higher CD4 cell count. These disease entities may warrant clinicians' attention since their pathogenesis is associated with HIV infection and/or the incidences are higher in HIV-infected patients than in uninfected people.[37–39]

Our study has several limitations. First, this is a single center study conducted at a referral hospital in Taiwan. As a result, the disease severity of the patients may be higher than the HIV population in general in Taiwan. Second, the definite diagnosis of certain pulmonary diseases, such as CMV pneumonitis and neoplasms, mainly relied on histopathology. Therefore, under-diagnosis may have occurred. Last, limited by the sample size, we were not able to analyze the association between the etiologies of pulmonary complications and many other factors such as plasma HIV RNA level, cART status, virological and immunological responses to cART, and other co-morbidities.

In conclusion, pneumocystosis remained the most common cause in HIV-1-infected patients with lower CD4 cell counts in the cART era in Taiwan. The etiology of pulmonary complications was different between patients with CD4 counts $<200 \times 10^6$ cells/L and those with CD4 $>200 \times 10^6$ cells/L.

Conflicts of interest

All authors declare that they have no conflicts of interest relevant to this article.

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