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RESPIRATORY INFECTIONS (F ARNOLD, SECTION EDITOR)

Treating HIV-Positive/Non-AIDS Patients for Community-Acquired Pneumonia with ART

Catia Cillóniz[1] · Antonella Ielpo[2] · Antoni Torres[1]

Abstract

Purpose of Review This article reviews the most recent publications on community-acquired pneumonia (CAP) in the HIV-infected population on antiretroviral therapy (ART), focusing on epidemiology, prognostic factors, etiology, and antimicrobial therapy. The data discussed here were mainly obtained from a non-systematic review using Medline and references from relevant articles.

Recent Findings CAP remains a major cause of morbidity and mortality among HIV-infected patients and incurs high health costs despite the introduction of ART.

Summary HIV-infected patients are generally known to be more susceptible to bacterial pneumonia. *Streptococcus pneumoniae* is the most frequently reported pathogen in HIV-infected patients on ART, who present a higher rate of bacteremia than non-HIV-infected patients. Several studies have also examined microbial etiology and prognostic factors of CAP in HIV-infected patients on ART. Despite the high rate of bacterial pneumonia in these patients, mortality rates are not higher than in patients without HIV infection.

Keywords Community-acquired pneumonia · Treatment · HIV infection

Introduction

According to the World Health Organization (WHO), at the end of 2016, there were approximately 36.7 million people living with human immunodeficiency virus (HIV): 25.6 million in Africa, 3.5 million in Southeast Asia, 3.3 million in the Americas, 2.4 million in Europe, 1.5 million in the Western Pacific, and 360,000 in the Eastern Mediterranean. By mid-2017, approximately 20.9 million people living with HIV were receiving active antiretroviral therapy (ART), including seven out of every 10 pregnant women living with HIV [1]. In 2016, 1.8 million people became newly infected with HIV [2]. The introduction of active ART has changed the epidemiology of HIV infection and acquired immune deficiency syndrome (AIDS) worldwide [3, 4]. However, community-acquired pneumonia (CAP) remains a frequent cause of morbidity and mortality among HIV-infected patients on ART, and incurs high health costs [4–6]. Some associated factors that contribute to the high incidence of CAP in HIV-infected patients on ART are active or passive smoking, alcohol abuse, and intravenous drug use [7••].

Although ART reduces viral replication and systemic inflammation and improves immune response, the risk of pneumonia remains high in these patients in part because they present altered immunity and their immune activation persists even when they receive therapy [6]. The incidence of CAP in HIV-infected patients on ART is reported to be between 2.5 and 8 cases per 1000 patients per year [8]. The risk of CAP in HIV-infected patients on ART and the probability of mixed infections or pneumonia caused by intracellular pathogens is inversely associated with the CD4 cell count [6, 7••, 9].

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✉ Catia Cillóniz
catiacilloniz@yahoo.com

✉ Antoni Torres
atorres@clinic.cat

[1] Department of Pulmonary Medicine, Institut Clinic del Tórax, Hospital Clinic of Barcelona – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB) - SGR 911- Ciber de Enfermedades Respiratorias (Ciberes), C/ Villarroel 170, 08036 Barcelona, Spain

[2] Department of Medicine and Surgery, Respiratory Disease, and Lung Function Unit, University of Parma, Parma, Italy

Mortality in HIV-infected patients on ART with CAP ranges from 6 to 9% [9, 10]; in patients with severe CAP, however, it may be above 30% [11, 12]. *Streptococcus pneumoniae* (pneumococcus) is the main pathogen involved in CAP in both HIV-infected patients on ART and the general population [9, 13••, 14•]. HIV is a known risk factor for invasive pneumococcal disease (IPD); even when receiving ART, HIV-infected patients on ART had a 20-fold increased risk of IPD [7••, 15, 16].

Vaccination (pneumococcal conjugate [PCV13] and polysaccharide vaccines [PPV23]) represents one of the most important preventive strategies for CAP in HIV-infected patients on ART [17]. Implementation of programs to help patients comply with ART and early diagnosis of suspected HIV-infected patients are key measures for improving CAP management.

Global Epidemiology of CAP in HIV-Infected Adult Patients

The introduction of ART changed the global epidemiology of pulmonary infection in the HIV-infected population [18] by reducing the incidence of opportunistic pulmonary infections. In high-income countries, such as Europe and the USA, bacterial pneumonia (especially pneumococcal pneumonia) is the predominant lung disease in the HIV-infected population on ART [4, 9].

A Brazilian study of CAP in HIV-infected adult patients receiving ART for at least 60 days reported an incidence of pneumonia of 3.07 cases per 100 persons-years. Viral load and CD4 cell counts were identified as predictive factors for pneumonia. Uncontrolled HIV infection (detectable viral load) doubled the risk for pneumonia, while time-updated increases in CD4 cell counts represented a protective factor [19]. Analyzing more than 10,000 patients in 34 countries, the EuroSIDA cohort study reported an incidence of 0.53 cases per 100 persons-year and identified low CD4 cell count (200–349 cells/μl), current smoking, and higher viral load as risk factors for pneumonia [20]. Similarly, Mussini et al. [21] reported an incidence of 0.56 cases of pneumonia per 100 persons-year and found the probabilities of first episode of bacterial pneumonia at 3, 5, 10, and 14 years after ART initiation to be 2%, 2.9%, 4.3%, and 5.7% respectively. The factors associated with the first episode of bacterial pneumonia were low nadir $CD4^+$, low current CD4, high $CD8^+$, low hemoglobin, unfavorable virological outcome, older age, male gender, non-Italian nationality, smoking, and longer time to ART initiation.

In a 10-year study of survival of HIV-infected patients admitted to the ICU in the UK between 1999 and 2009 [22], it was observed that respiratory disease remains the main cause of ICU admission. The proportion of patients on ART prior to ICU admission increased from 37% in the early period (1999–2005) to 60% in the late period (2006–2009). In patients newly diagnosed with HIV, the rates of survival to ICU and hospital discharge were 69% and 57% respectively. In patients with known HIV diagnosis, survival to ICU and hospital discharge was 80% and 74% respectively.

Another UK study [23] of the implementation of automated HIV testing for pneumonia patients admitted to the ICU reported that prior to this measure, the HIV testing rate in patients with pneumonia within 2 weeks of admission was 29%. After the implementation of automated HIV testing to all admitted patients, 80% of ICU patients with pneumonia were tested for HIV infection within 48 h and 73% with 24 h. Adopting universal testing for HIV in patients with pneumonia admitted to ICU is mandatory in order to reduce morbidity and mortality.

Microbial Etiology of CAP in HIV-Infected Patients

Despite advances in microbiological tests, microbial diagnosis is achieved in only 40–50% of CAP cases [9, 13••]. The bacterial etiology of pneumonia is similar in HIV-infected patients on ART and in the uninfected population [24, 25]. Factors that have an impact on microbial etiology in CAP are the characteristics of the population, the geographical area (developed or developing countries), and the methodology applied to microbial diagnosis [6, 26].

A recent prospective observational study of 331 adult CAP cases in HIV-infected patients from Spain [13••] described the microbial etiology in this population. The most frequently detected microorganisms were *S. pneumoniae* (30%), *P. jirovecii* (13%), mixed etiology (11%), respiratory viruses (5%), *Haemophilus influenzae* (2%), *Staphylococcus aureus* (2%), and *Legionella pneumophila* (1%). *S. pneumoniae* was the most frequent microorganism in the group with a CD4+ cell count of ≥ 200 cell/mm^3 and *P. jirovecii* in the group of patients with a CD4+ cell count of < 200 cells/mm^3 and in patients with HIV-RNA ≥ 200 copies/mL. The authors also reported that ≤ 5 days of symptoms (OR 2.6, 95% CI 1.5–4.4), C-reactive protein level ≥ 22 mg/dL (OR 4.3, 95% CI 2.3–8.2), and hepatitis C-virus co-infection (OR 2.3, 95% CI 1.4–3.9) were predictors of bacterial CAP, whereas a WBC count $\leq 4000 \times 10^9$ cells/L (OR 3.7, 95% CI 1.2–11.5), LDH ≥ 598 U/L (OR 12.9, 95% CI 4.2–39.7), and multilobar infiltration (OR 5.8, 95% CI 1.9–19.5) were predictors of *P. jirovecii*. In that study, HIV infection had been diagnosed prior to hospital admission in 83% of patients, and 51% of patients were on ART; the other 17% were diagnosed with HIV infection during the pneumonia episode (Fig. 1).

Pneumococcal pneumonia in HIV-infected patients frequently presents with bacteremia and invasive pneumonia

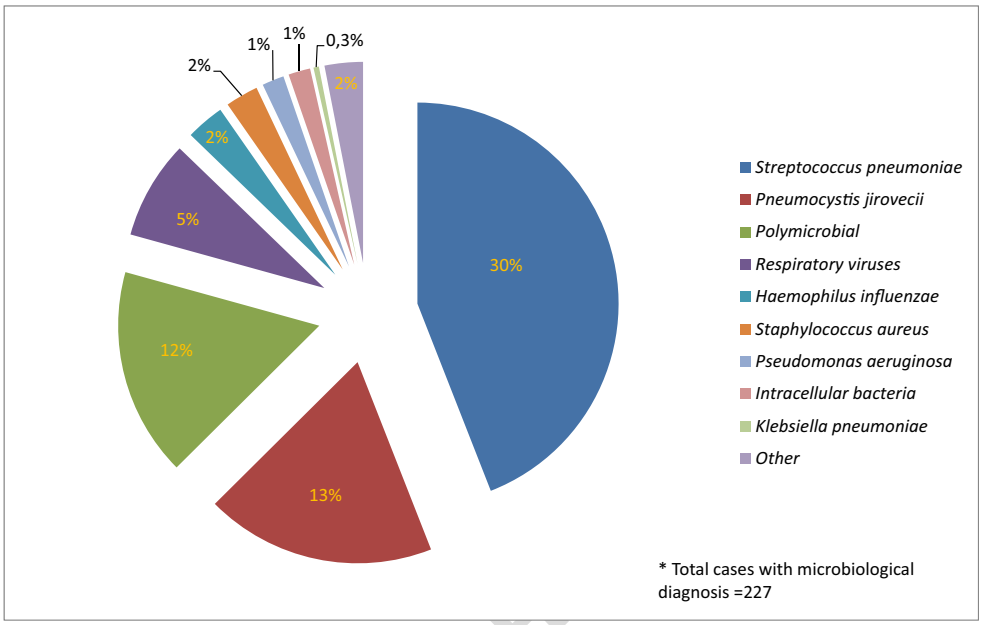

Fig. 1 Microbial etiology in HIV-infected patients with CAP

[7••, 9]. In an earlier Spanish study of the microbial etiology of CAP in HIV-infected patients, 15% of the study population presented bacteremia, and pneumococcus was the main pathogen involved [13••]. In a study of 129 HIV-infected adult patients with CAP, the factors that predicted bacteremia were positive urinary antigen detection and the absence of ART [27].

Pseudomonas aeruginosa is also a cause of pneumonia in HIV-infected patients and is reported in fewer than 6% of CAP cases [13••, 28]. Risk factors associated with *P. aeruginosa* CAP in HIV-infected patients are previous antibiotic therapy, neutropenia, and a low CD4 count [29].

Legionella pneumophila accounts for approximately 9% of all adult HIV-associated pneumonias [10]. Other intracellular pathogens causing CAP in HIV-infected patients include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Coxiella burnetii* [30•]. A recent published case-control study that compared the clinical presentation and outcomes (length of hospital stay, ICU admission, and 30-day mortality) of *L. pneumophila* pneumonia in HIV-infected patients (32 cases) and non-HIV-infected patients (96 controls) reported that clinical presentation and outcomes in HIV-infected patients with *Legionella* pneumonia did not differ from patients without HIV infection. The authors suggest that *Legionella* infection affected with more frequently patients with correct immunological status [31].

Severity of CAP and Site of Care

To determine the site of care, microbiological testing and the choice of empiric antibiotic therapy, it is important to assess the pneumonia severity (Fig. 2). Severity scores for predicting short-term mortality have been developed in order to allow more objective decisions regarding hospitalization to be taken in the general population [32, 33]. The most frequent scores are the Pneumonia Severity Index (PSI), recommended by the IDSA/ATS guidelines, and the CURB-65 criteria recommended by the BTS guidelines. However, few studies have validated these severity scores in the HIV-infected population [10, 34]. In 2008, evaluating the PSI score in HIV-infected patients with CAP, Curran et al. [10] reported that it accurately predicted high-risk pneumonia and mortality. The authors suggested that the combination of CD4 cell count value and PSI risk class would help to identify patients requiring hospitalization. More recently, a study investigating the use of CURB65 in HIV-infected patients reported that a higher CURB65 score and a CD4 count lower than 200 cells/mL were both associated with worse outcomes [34]. The authors concluded that the CURB65 score plus CD4 cell count could be used in HIV-infected patients with CAP.

An interesting study assessing the predictive value of analytical markers of full blood count that can be assessed in the emergency department in 160 HIV-infected patients with CAP (49% of them on ART) reported that higher red blood cell distribution width (RDW) (OR = 1.2, 95% CI 1.1–1.4, p = 0.013) and a lower number of lymphocytes (OR 2.2, 95% CI 1.1–2.2, p = 0.035) were independent predictors of admission to ICU in the multivariate analysis. The small number of cases analyzed was a limitation, but the combination of severity scores and laboratory data such as RDW and lymphocytes may be a good predictor for prognosis in HIV-infected patients with CAP [35].

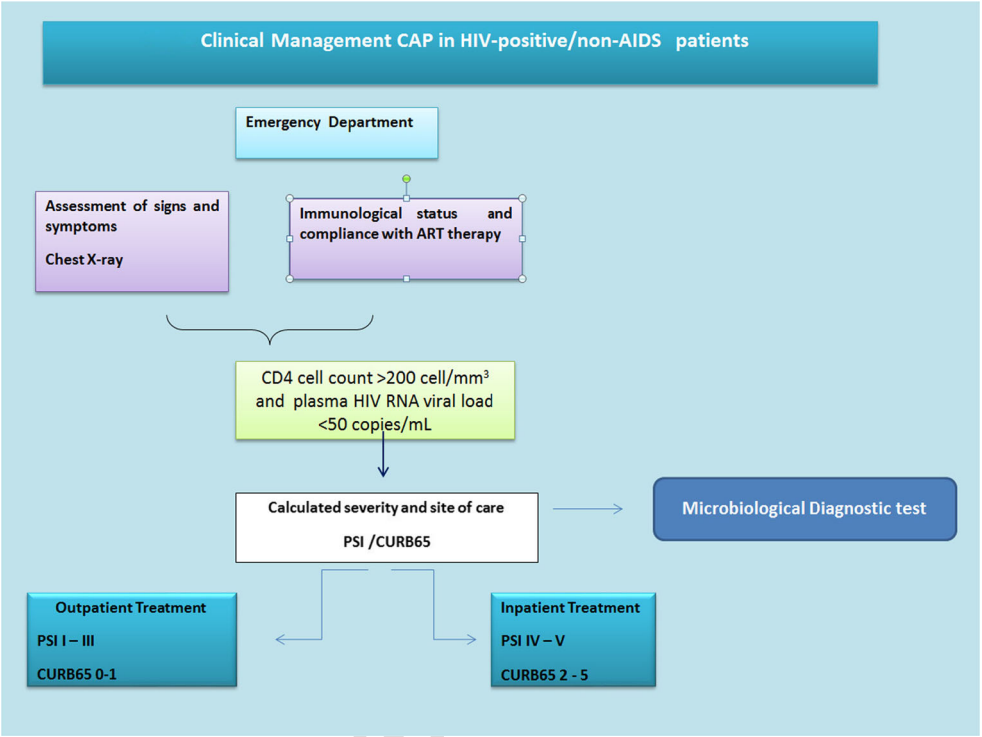

Fig. 2 Clinical management CAP in HIV-positive/non AIDS patients

Microbial Diagnosis of CAP

Microbiological diagnosis of CAP continues to be based on respiratory samples or blood culture. The most important application of these methods is in the determination of antibiotic susceptibility patterns that allow the selection of appropriate antimicrobial therapy, which is an important factor for reducing mortality [36].

In general, international guidelines recommend standard microbiological investigation [37, 38]. In the case of patients with low to mild pneumonia, microbiological diagnosis is optional. Extensive microbiological diagnosis is recommended in cases of severe pneumonia or in cases that do not respond to empiric antibiotic therapy. However, if clinically indicated, an extensive microbiological diagnosis should be performed (Fig. 3).

Microbiological test	Outpatient	Inpatient low severity	Inpatient non ICU moderate severity	Inpatients ICU high severity
Sputum culture	None routinely	X	X	X
Pneumococcal urinary antigen test		None routinely	X	X
Legionella urinary antigen test			X	X
Blood culture			X	X
Invasive respiratory tract sample culture				X
Others				X
Specific guidelines recommendations:				
*Outpatients with failure of antibiotic therapy: sputum culture, urinary antigen test for *Legionella pneumonia and Streptococcus pneumoniae.*				
*Positive urinary antigen test for *pneumococcus* or *Legionella*: sputum and blood culture for positive urinary antigen test for pneumococcus and sputum culture for positive urinary antigen test for *Legionella.*				
*Severe obstructive lung disease: sputum culture				
*Severe obstructive lung disease: sputum culture Cavitary infiltrates: sputum culture (bacterias, fungal and mycobacterias) and blood culture.				
*Active alcoholism: sputum and blood culture, urinary antigen test for pneumococcus and *Legionella.*				
* Severe CAP admitted to intensive care unit (ICU): sputum and blood culture, urinary antigen test for pneumococcus and *Legionella,* tracheal aspirate or bronchoalveolar lavage culture.				
* Epidemiological factor or specific risk factors suggesting pathogen: urinary antigen test for *Legionella* (Legionnaires disease), influenza test during influenza season				

Fig. 3 International guideline recommendation for microbiological diagnostic test in CAP

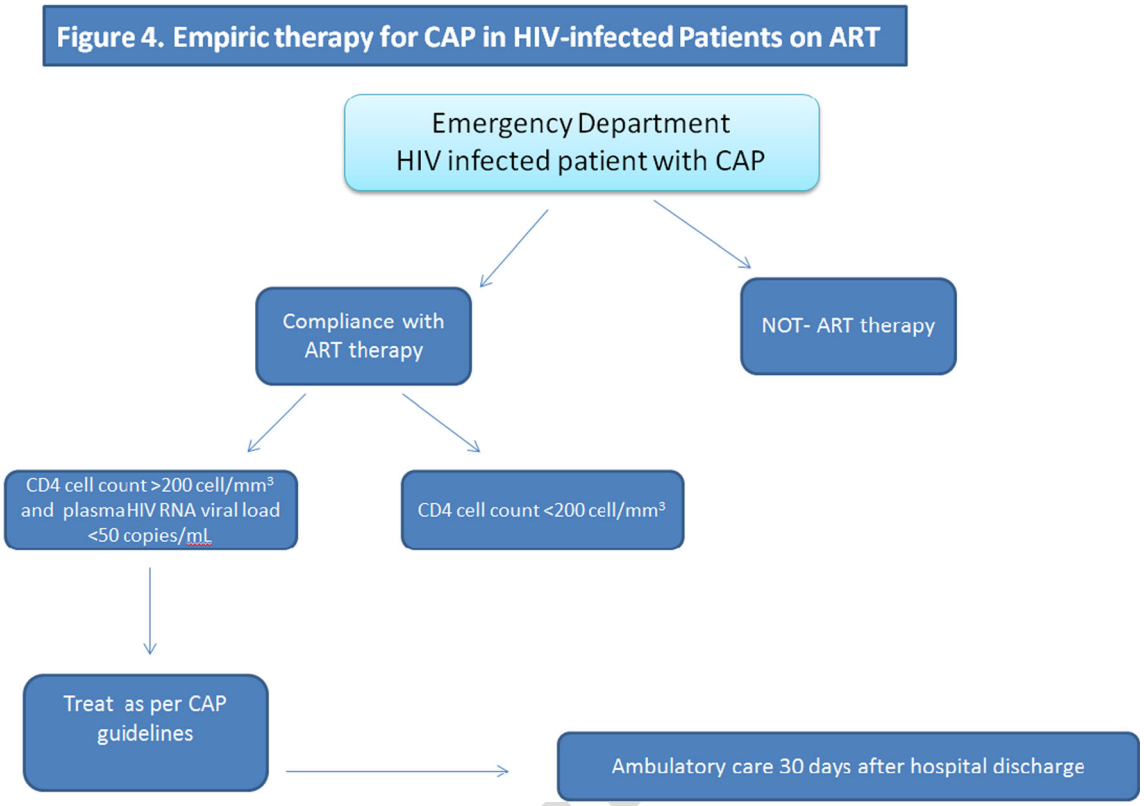

Fig. 4 Empiric therapy for CAP in HIV-infected patients on ART

Blood cultures, sputum staining, sputum culture, and urinary antigen testing for *Legionella* and pneumococcus should be carried out in patients with severe CAP. Since influenza viruses present in seasonal epidemics, rapid antigen or direct fluorescent antibody testing is recommended to guide decisions regarding antiviral therapy and may help to reduce the use of antibacterial agents.

In recent years, the development and implementation of molecular diagnostic tests for pneumonia have been major advances in the microbiological diagnosis of respiratory pathogens. These technologies achieve rapid results (within 1–2 h) and may be useful in the decision management of patients, especially with regard to the early initiation of appropriate antimicrobial therapy, a factor associated with mortality. The rapid identification of antibiotic resistant pathogens is also central to timely isolation of patients. However, the main limitations of these technologies are their reduced ability to differentiate between colonization and infection and their cost-effectiveness [39].

Microbiome

A new challenge for microbiologists and clinicians has arisen with the study of the pulmonary microbiome, which has changed our current concept of pneumonia [40]. It is now known that the lungs are a dynamic microbiological ecosystem, and the new data show us that pneumonia involves a dysbiosis or alteration of the lung microbiome [39, 41•].

An interesting study addressed by Iwai et al. [42••] compared oral and airway microbiota in patients with and without HIV-infection. The authors reported that HIV-infected patients with pneumonia have an increased abundance of phylogenetically distinct taxa, which included Firmicutes and Prevotellaceae compared with the presence of Proteobacteria-enriched communities in non-HIV-infected patients with pneumonia. A second interest study published by the same authors compared the lung microbiome between HIV-infected patients from Ugandan with pneumonia to pneumonia patients from San Francisco. The authors reported that the microbiome composition of lower airway of HIV-infected patients with pneumonia in Uganda was significantly different from those in San Francisco. The author suggested that these differences may be due to the clinical status, age, and/or pneumonia type across the geographically distinct cohorts. The profile of microbiome in Uganda patients was enriched by Proteobacteria, being *Pseudomonas aeruginosa* the pathogen more frequently detected. On the other hand, lung microbiome in patients from San Francisco was enriched for Firmicutes and Actinobacteria [43].

Q3 t1.1 **Table 1** International guidelines for the management and treatment for community-acquired pneumonia

	Pneumonia severity	Low severity	Moderate severity	High severity
t1.3	GNAC guidelines	• Moxifloxacin or levofloxacin: 5 to 7 days • Amoxicillin or amoxicillin-clavulanate (7 days) + macrolide (azithromycin 3–5 days or clarithromycin 7 days) • Cefditoren is an alternative with is not possible use amoxicillin or quinolones	• Third-generation (e.g., cefotaxime or ceftriaxone) cephalosporin or • Amoxicillin-clavulanate + macrolide (azithromycin or clarithromycin) • Moxifloxacin or fluoroquinolone monotherapy	• Non-antipseudomonal cephalosporin in high dose (ceftriaxone 2 g/24 h, cefotaxime 2 g/6–8 h) + macrolide (azithromycin 500 mg/day or clarithromycin 500 mg/12 h) • Alternative: moxifloxacin (400 mg/24 h) or levofloxacin (500 mg/12 h) instead of macrolides
t1.4	BTS guidelines	• CURB65 scores 0–1 • Treat with oral amoxicillin or doxycycline or clarithromycin	• CURB65 score 2 • Treat with oral/intravenous amoxicillin + clarithromycin or doxycycline, moxifloxacin, or levofloxacin	• CURB65 scores 3–5 • Treat with co-amoxiclav plus clarithromycin/benzylpenicillin plus levofloxacin or ciprofloxacin/or cephalosporin plus clarithromycin
t1.5	ATS/IDSA guidelines	• PSI OR CURB65 score to guide outpatient treatment • Treat with macrolide or doxycycline: patients with low risk of drug-resistant pneumococcus • Treat with fluoroquinolone or ß-lactam + macrolide: patients with high risk of drug-resistant pneumococcus	• Direct admission to ICU: septic shock requiring vasopressor support and /or respiratory failure requiring intubation and ventilation. • ß-Lactam plus a macrolide or fluoroquinolone	
t1.6	ERS/ESCMID guidelines	• CURB65 to guide outpatient treatment • Treatment: *Aminopenicillin ± macrolide *Aminopenicillin/b-lactamase inhibitor ± macrolide *Non-antipseudomonal cephalosporin II or III + macrolide *Cefotaxime or ceftriaxone ± macrolide *Penicillin G ± macrolide	• ICU admission: acute respiratory failure, severe sepsis, or septic shock and radiographic extension of infiltrates/severely decompensated comorbidities • No risk factors for *P. aeruginosa:* non-antipseudomonal cephalosporin III + macrolide or non-antipseudomonal cephalosporin III + moxifloxacin or levofloxacin • Risk factors for *P. aeruginosa:* antipseudomonal cephalosporin or acyl ureidopenicillin/ß-lactamase inhibitor or carbapenem (meropenem preferred) plus ciprofloxacin or plus macrolide + aminoglycoside (gentamicin, tobramycin, or amikacin)	

References: [35, 36, 39, 40]

The new investigations about the lung microbiome in HIV-infected patients have provided novel insights and new knowledge about the mechanisms of microbial pathogenesis in pneumonia in this population.

Initial Empiric Therapy

When a HIV-infected patient with CAP is admitted to the emergency department, clinicians should check the immunological status (CD4+ cell/count) and compliance with ART. If patients are on ART and have a CD4 lymphocyte count of > 200 cells/mm^3, the empiric antibiotic therapy for CAP is similar to that administered in the general population [13••] and complies with the international guidelines recommendations for CAP [37, 38, 44, 45]. All patients will be visited within 30 days after hospital discharge and followed up on an outpatient basis (Fig. 4).

Initial empiric therapy for CAP should be guided by the site of care, age, previous use of antibiotics within the previous 90 days, the presence of comorbidities (risk of resistant pathogens), and drug intolerance.

Empiric antiviral therapy for influenza may be necessary when the clinical and epidemiological criteria are met. Several studies reported that 1 to 6% of patients hospitalized with H1N1 were HIV-infected [46, 47]. In an American study, HIV patients with influenza experienced similar rates of ICU admission (29% vs. 34%) and mortality (13% vs. 13%) to those of non-HIV patients [46]. Ormsby et al. [48] suggested that the 2009 H1N1 infection was more severe in HIV-infected patients with late and advanced HIV disease than in well-controlled patients on ART.

Two groups of antiviral drugs are currently available for influenza: M2-protein-inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir). These antivirals should be administered within 48 h of symptom onset. In cases of severe pneumonia, medication is recommended even 48 h after symptom onset.

Empiric antibiotic therapies recommended by international guidelines are summarized in Table 1 [37, 40, 41•, 44].

Drug interactions between ART and CAP antibiotic therapy represent an important issue for clinicians. However, penicillins, betalactam inhibitors, and levofloxacin do not interact with ART. For its part, moxifloxacin has a low interaction with atazanavir and lopinavir which are protease inhibitors. As moxifloxacin has been shown to prolong the QT interval, clinicians should exercise caution with its use, especially in the case of patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances). Caution is also required in these patients regarding the use of azithromycin since it may cause abnormal changes in the electrical activity of the heart, and since the interactions between atazanavir, lopinavir and saquinavir (protease inhibitors), and rilpivirine/FTC/TAF (NNRTIS) are low.

Clarithromycin presents more drug interaction with all classes of antiretrovirals (protease inhibitors, NNRTIS, entry and integrase inhibitors, and nucleoside/tide analogues) because it can lead to a prolonged QT interval. In patients with long QT syndrome, cardiac disease, or in patients taking other QT-prolonging medications, this can increase the risk of life-threatening arrhythmias [49]. So the use of azithromycin is preferred. For more information on drug-drug interaction, consult

https://www.hiv-druginteractions.org/checker

Conclusions

Despite the advent of ART, pneumonia remains a major cause of disease in the HIV-infected population. Pulmonary infections are also the main cause of ICU admission. *Streptococcus pneumoniae* (pneumococcus) remains the most frequently detected cause of CAP in HIV-positive/non-AIDS on ART. The clinical presentation and management of CAP are similar in HIV-infected patients on ART and in uninfected patients, and outcomes in HIV virologically suppressed patients on ART with > 350 CD4+ T cell counts/mm^3 are similar to those in the general population. The general recommendation is that these patients do not need special treatment, admission, or sites of care. Treatment of HIV-positive/non-AIDS patients with CAP is also similar to that in the general population and should follow international guidelines.

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Compliance with Ethical Standards

Conflict of Interest Catia Cillóniz, Antonella Ielpo and Antoni Torres no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Q1. Please check if the affiliations are presented correctly
Q2. Please check if the reference citations captured in the sentence that begins with “If patients are on ART and have a CD4 lymphocyte…” are correct
Q3. Please check if Table 1 is presented/captured correctly