Taylor & Francis
Taylor & Francis Group

Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: http://www.tandfonline.com/loi/ierz20

Community-acquired bacterial pneumonia in adult HIV-infected patients

Catia Cillóniz, Carolina García-Vidal, Asunción Moreno, José M. Miro & Antoni Torres

To cite this article: Catia Cillóniz, Carolina García-Vidal, Asunción Moreno, José M. Miro & Antoni Torres (2018): Community-acquired bacterial pneumonia in adult HIV-infected patients, Expert Review of Anti-infective Therapy, DOI: 10.1080/14787210.2018.1495560

To link to this article: https://doi.org/10.1080/14787210.2018.1495560

Accepted author version posted online: 05 Jul 2018.

Publisher: Taylor & Francis

Journal: *Expert Review of Anti-infective Therapy*

DOI: 10.1080/14787210.2018.1495560

Review

Community-acquired bacterial pneumonia in adult HIV-infected patients

Catia Cillóniz[1], Carolina García-Vidal[2], Asunción Moreno[2], José M. Miro[2], Antoni Torres[1*]

[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) Barcelona, Spain.

[2]Infectious Diseases Service, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain.

***Corresponding author:**

Antoni Torres

Department of Pulmonary Medicine, Hospital Clinic of Barcelona

C/ Villarroel 170, 08036 Barcelona, Spain

Phone: (+34) 93-227-5779, FAX: (+ 34) 93-227-9813

Email: atorres@clinic.cat

Abstract

Introduction: Despite active antiretroviral therapy (ART), community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality among HIV-infected patients, and incurs high health costs.

Areas covered: This article reviews the most recent publications on bacterial CAP in the HIV-infected population, focusing on epidemiology, prognostic factors, microbial etiology, therapy, and prevention. The data discussed here were mainly obtained from a non-systematic review using Medline, and references from relevant articles.

Expert Commentary: HIV-infected patients are more susceptible to bacterial CAP. Although ART improves their immune response and has reduced CAP incidence, these patients continue to present increased risk of pneumonia in part because they show altered immunity and because immune activation persists. The risk of CAP in HIV-infected patients and the probability of polymicrobial or atypical infections are inversely associated with the CD4 cell count. Mortality in HIV-infected patients with CAP ranges from 6% to 15% but in well-controlled HIV-infected patients on ART the mortality is low and similar to that seen in HIV-negative individuals. Vaccination and smoking cessation are the two most important preventive strategies for bacterial CAP in well-controlled HIV-infected patients on ART.

Keywords: Community-acquired pneumonia, bacterial pneumonia, HIV-infection

1. Introduction

Community-acquired pneumonia (CAP) remains a major complication in human immunodeficiency virus (HIV)-infected patients, even in the era of combined antiretroviral therapy (ART)(1–5). Although the introduction of ART has drastically changed the epidemiology of pulmonary infections in HIV-infected patients, not all patients receive ART or show good compliance. In addition, the number of patients with unknown HIV infection remains high.

In 2016, the Global Health Observatory (GHO) reported that 36.7 million people worldwide were living with HIV, almost 21 million people were receiving antiretroviral therapy by mid-2017 and approximately 1 million had died of HIV-related disease(1).

Progressive CD4+ T-cell loss and changes in immunological status in untreated HIV-infected persons comprise the main risk factors for developing other infectious diseases such as pneumonia, which often require admission to an intensive care unit (ICU)(6).

Several studies have examined the microbial etiology and prognostic factors of CAP in HIV-infected patients(4–6). In general, HIV-infected persons have a 10-fold higher risk of developing bacterial pneumonia than HIV-negative persons(7,8). However, despite the high rate of bacterial pneumonia in HIV-infected patients, mortality rates are no higher than in patients without HIV infection(5,9,10).

The aim of this article is to review the most recent relevant studies focusing on epidemiology, risk factors, etiology, treatment, prognosis and prevention of CAP in HIV-infected patients.

2. Methods

This article reviews the most recent publications relative to Community-Acquired Bacterial Pneumonia in Adult HIV-infected Patients, with a focus on epidemiology, risk factors, microbial etiology, microbiome, antibiotic therapy, prognosis and prevention. The data discussed in this review were mainly obtained from a non-systematic review using Medline, and references from relevant articles.

Titles and abstracts were initially screened to identify relevant citations, which were then reviewed in full by all authors. All authors confirmed the inclusion of the identified publications.

3. Epidemiology

The Global Burden of Disease study (2016) reported that lower respiratory tract infections are the third most common cause of death worldwide, exceeded only by ischemic heart disease and cerebrovascular disease(1). Similarly, statistics released by the World Health Organization (WHO) in 2015 indicated that 3.2 million of the 56.4 million deaths worldwide in 2015 were caused by lower respiratory tract infections (LRTI), rendering them the most deadly communicable disease and the third leading cause of mortality(11). Bacterial CAP, *Pneumocystis* infection, and tuberculosis (TB) are the most frequent pulmonary infections in HIV-infected patients(6). The distribution of prevalence of these respiratory infections is associated with specific geographical areas. For example, in low- and middle-income regions, TB remains the main infection related to HIV-infected patients, whereas in high-income regions, bacterial CAP is most frequent in the HIV-infected population.

An interesting study of pneumonia in individuals with and without HIV infection reported that its incidence in HIV-infected patients in the pre-ART era was 5.06 hospitalizations per 100 person-years, compared with 3.46 hospitalizations per 100 person-years in patients without infection. In the post-ART era the incidence was 1.97 hospitalizations per 100 person-years in HIV-infected patients, and 0.59 hospitalizations per 100 person-years in HIV-infected patients with CD4 cell count >500 cell/ul; in patients without HIV infection, it was 0.63 hospitalizations per 100 person-years(12).

The use of ART is clearly changing the epidemiology of bacterial CAP in HIV-infected patients. However, HIV infection remains a risk factor for pneumonia even in persons with high CD4+ cell counts.

For example, in an epidemiological study of bacteraemic pneumococcal pneumonia, Grau et al.(13) reported an incidence of 2.41 episodes per 100 patient-years in pre-ART era patients, compared with 0.82 episodes per 100 patient-years in patients with ART.

In an interesting RCT performed in the US(14), which compared the risk of bacterial pneumonia in HIV-infected patients with intermittent ART therapy and in patients with virologically suppressed HIV infection and receiving continuous ART, the authors reported that HIV-infected patients with predominantly off-ART therapy were over twice as likely to develop bacterial pneumonia (risk rate 2.8 per 100 person-years for those with fewer than 250 CD4 cells) compared with virologically-suppressed HIV-infected patients (risk of 1.0 per 100 person-years for those with 500 or more CD4 cells) in the multivariate analysis.

As with the general population, *Streptococcus pneumoniae* (pneumococcus) is the main cause of bacterial CAP in HIV-infected patients. Pneumococcus is diagnosed in approximately 30% to 40% of CAP cases in HIV-infected patients with a defined etiology(4,15). In a recently published study on lower respiratory tract infection (LRTI) in a cohort of 2669 HIV-infected adults on ART, Lamas et al.(16) reported a LRTI incidence of 3.07 cases/100 patient-years. CAP was diagnosed in 14% (384) of cases. The same authors also reported that higher CD4 counts and undetectable viral loads were protective factors for CAP in the multivariate analysis, as were pneumococcal and influenza vaccinations. Despite effective ART, bacterial CAP is still frequent in HIV-

infected patients(17,18), and mortality rates may be rising due to the prevalence of comorbidities in CAP patients(19). A prospective study(7) analyzing more than 18,000 patients in 34 countries over the period 2006 to 2011 reported a pneumonia incidence of 0.53 cases/100 person-years. Similarly, in an Italian study, Mussini et al.(20) reported an incidence of bacterial CAP of 0.56 cases/100 person-years.

More recently a study by O'Connor et al.(21) that investigated the effect of immediate initiation of ART on risk of severe bacterial infections in HIV-infected patients with CD4 cell counts >500 cells per ml, and involved intercontinental patient data, reported that the incidence of severe bacterial infection including pneumonia ranges from 0.5 to 2.8 per 100 person-years according to geographical region. Bacterial pneumonia was present in 1.02% of the 4,685 patients: 0.6% of patients who received immediate ART presented bacterial pneumonia whereas 1.44% of patients in whom ART initiation was deferred presented bacterial CAP.

In conclusion, CAP remain a major clinical problem in HIV-infected patients, even though we observed a reduced incidence after ART scale-up, and remains frequent even in HIV-infected patients on ART with high CD4+ cell counts. Overall, HIV-infected patients have a ten times higher risk of developing pneumonia than uninfected patients(19,22).

4. Risk factors for CAP

The specific risk factors for CAP in HIV-infected patients include active and passive smoking, alcoholism, older age (older than 65 years), intravenous drug use, comorbidities (chronic obstructive pulmonary disease, chronic liver disease, cardiovascular disease, chronic renal disease), low CD4 cell counts, detectable HIV viral

load, previous episode of pneumonia, and lower socioeconomic status (Table 1)(23). The prevalence of smoking in HIV-infected patients in general is very high – between 42% and 46% in US and European studies, compared to 21% to 26% in the general population(24–26). Also, excessive alcohol consumption is common among HIV-infected people and increases the risk of pulmonary disease such as pneumonia. Alcohol affects both innate and adaptive immune responses and causes immunosuppression; this explains why chronic alcohol consumption increases the incidence of bacterial and viral pneumonias in these patients.

A study including data from 34 European countries(7) reported that the factors predisposing HIV-infected patients to develop severe bacterial non-AIDS infections were the presence of previous comorbidities, a previous episode of pneumonia, and malnutrition in the adjusted multivariate analysis.

An American study (27) reported that 10.8% of the approximately 50,000 incident HIV infections that occur annually in the USA affect people ≥50 years old. Immunosenescence refers to age-related immunological changes that reduce the efficiency of the adaptive and innate immune system, and it is responsible for deterioration in the response to infection and an increase in pathological disorders in the elderly population(28).

Smoking impacts on the immune system's capacity to mount an appropriate immune and inflammatory response to infections such as CAP, and this effect has also been observed in passive smokers(22,29,30). Some studies have suggested that there is an association between smoking and a poor virological and immunological response to ART(31–34). This was confirmed in a recent study by Hile et al.(35), who studied the

association between tobacco smoking and biomarkers of HIV disease progression, and found that recent tobacco smoking was independently associated with unsuppressed viral load (OR = 1.38) and a low CD4 cell count (OR = 1.12) in multivariate analyses controlling for sociodemographic and clinical characteristics.

It has been reported that approximately 25% of HIV-infected patients have chronic obstructive pulmonary disease(36). In a recent age and sex-matched study on airway obstruction in 351 HIV-infected and 702 uninfected study participants, all smokers over 40 years of age, the authors found that HIV infection was independently associated with lower FEV1/FVC ratios in a multivariate analysis. They also reported that HIV was associated with an increased prevalence of airway obstruction, as measured by a prebronchodilator FEV1/FVC ratio less than 0.70 and a FEV1 value less than 80% of the theoretical value(37).

In conclusion, the risk factors for CAP in HIV-infected patients are: smoking, alcoholism, advanced age, intravenous drug use, previous comorbidities, low CD4 cell counts, detectable HIV viral load, previous episode of pneumonia, and lower socioeconomic status.

5. Principal pathogens involved in HIV-infected patients with CAP

Despite advances in microbiological tests, microbial diagnosis is only achieved in approximately 50% of CAP cases. It is known that the bacterial etiology of pneumonia is similar in HIV-infected on ART and in uninfected patients(6,38). In a prospective observational study of 331 consecutive adult CAP cases in HIV-infected patients from Spain, Cillóniz et al.(4) described the microbial etiology in this population. According to these authors, *S. pneumoniae* (30%), *P. jirovecii (13%),* mixed etiology (11%), respiratory viruses (5%), *Haemophilus influenzae* (2%), and *Staphylococcus aureus* (2%)

were the most frequently detected microorganisms in the study population (Figure 1). Of these, *S. pneumoniae* was the most frequently observed microorganism in the group with a CD4+ cell count of ≥ 200 cell/mm^3, while *P. jirovecii* was the most frequently occurring microorganism in the group with a CD4+ cell count of < 200 cell/mm^3 and in patients with HIV-RNA ≥ 200 copies/mL. The authors also reported that days of symptoms ≤5 (OR 2.6, 95% CI 1.5–4.4), cotrimoxazole prophylaxis (OR 2.0, 95% CI 1.2–3.4), 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 in the multivariate analysis, whereas female sex (OR 0.2, 95% CI 0.1–0.9), current smoking (OR 0.4, 95% CI 0.1–0.9), cotrimoxazole prophylaxis (OR 0.1, 95% CI 0.04–0.5), WBC count ≤ 4,000 x10^9 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 the multivariate analysis. In this study HIV infection had been diagnosed prior to hospital admission in 83% of the patients and 51% of the patients were on ART; the remaining 17% of the patients were diagnosed with HIV infection during the pneumonia episode.

In a study from Brazil in which the majority of patients had never used, had abandoned, or reported irregular use of ART, and 73% of patients presented < 200 CD4 cells/mm^3, the microbial etiology of 224 CAP cases in whom microbial diagnosis was plausible in 64% of cases was as follows(39): *Pneumocystis jirovecii* was the main agent, detected in 36% of cases, followed by *Mycobacterium tuberculosis* (20%), *S. pneumoniae* and Rhinovirus (15% each), influenza virus (10%), *Mycoplasma pneumoniae* (8%), and *Chlamydophila pneumoniae* (5%). The authors also reported

mixed infections, diagnosed in 34% of cases. These two studies showed differences in the distribution of pathogens in bacterial CAP according to the use of ART therapy.

Data from South Africa showed that underlying HIV infection is the most important risk condition for LRTI hospitalization with a prevalence higher than 90% in adults aged between 25 to 44 years. It has also been reported that between 18% to 40% of CAP patients may test positive for tuberculosis, with over 50% of tuberculosis cases being in HIV-infected persons. The microbial etiology in HIV-infected patients with CAP may differ from HIV-uninfected individuals, with pneumococcus and tuberculosis being more frequent pathogens in HIV-infected patients. *Pneumocystis* infection was diagnosed in approximately 22% of HIV-infected adults admitted with CAP in sub-Saharan Africa(40).

Pneumococcal CAP in HIV-infected patients frequently presents with bacteremia and invasive pneumonia(3,6). In a Spanish study on the microbial etiology of CAP in HIV-infected patients, 15% of the study population presented bacteremia, and pneumococcus was the main pathogen involved(4). In a study analyzing 129 HIV-infected patients with CAP, Perello et al.(41) reported that 24% of patients presented bacteremia, and that the predictors of bacteremia were positive urinary antigen detection and the absence of ART in the multivariate analysis.

Albrich et al.(42,43) have published two interesting studies on the nasopharyngeal colonization density of pneumococcus, measured by quantitative ART-PCR, and its relationship with diagnosis, severity, and outcomes of pneumococcal CAP in HIV-infected patients. In their first study, a pneumococcal density cut-off of over 8000 copies/mL for HIV-infected patients with CAP showed higher sensitivity and specificity

for diagnosed pneumococcal pneumonia. The second study demonstrated a correlation between nasopharyngeal colonization density and pneumococcal bacteremia, survival, and prognostic biomarkers in pneumonia.

The main gram-negative bacterium involved in pneumonia in HIV-infected patients is *Haemophilus influenzae,* reported in under 7% of CAP cases in HIV-infected patients(4,6).

Although pneumonia caused by *Legionella* is more common in patients with immunosuppressive conditions, it is rarely described in HIV-infected patients(44). *Legionella pneumophila* accounts for approximately 20% of all adult HIV-associated pneumonias, compared with 15% in the general population(45), and most information on this population is based on case reports(46–48). In a recent multicenter case-control study (32 cases and 96 controls) conducted in Spain on the clinical presentation and outcomes of *L. pneumophila* CAP, no differences were found in clinical presentation or outcomes between cases and controls. The protective factors identified for developing *L. pneumophila* pneumonia in HIV-infected patients were undetectable viral load, higher CD4 cell counts, and use of ART in the multivariate analysis(49).

Other intracellular pathogens causing CAP in HIV-infected patients include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Coxiella burnetii*(45). A recent study from Portugal of the microbial etiology of CAP in HIV-infected patients reported that *M. pneumoniae* was responsible for 8% and *C. pneumoniae* for 7% of CAP cases(39). Some studies have reported that the pulmonary infection rates of *M.*

pneumoniae and *C. pneumoniae* are inversely proportional to the CD4 cell counts in HIV-infected patients(45,50).

Despite the notable advances achieved with ART, HIV infection is a major risk factor for increased susceptibility to viral infection and for severe clinical presentation and worse outcomes. Respiratory viruses, especially influenza virus, represent a serious clinical event in HIV-infected patients above all in those with lower CD4 cell counts. Influenza is complicated in these patients with pneumonia or viral-bacterial co-infection. In the absence of ART, HIV patients have an increased risk of hospitalization, mortality, and prolonged illness due to influenza infection when compared with the general population(51,52). During the H1N1 influenza pandemic of 2009, between 1% and 6% of the hospitalized cases were HIV-infected patients. A study from Mexico describing the clinical course of infection by 2009 (H1N1) influenza virus at different stages of HIV found the infection to be more severe in HIV-infected patients with late and advanced HIV disease than in well-controlled patients on ART(53). In a Spanish study of more than 600 HIV-infected patients on ART with influenza A H1N1, the severity of influenza A H1N1 infection in HIV-infected patients on ART did not increase, and influenza A H1N1 infection did not have a major effect on HIV infection(54).

In conclusion, the distribution of pathogens in bacterial CAP differs according to the use of ART. Overall, *S. pneumoniae*, *P. jirovecii, H. influenza* and respiratory viruses remain the most common pathogens causing CAP in HIV-infected patients.

6. Microbiome in HIV-infected patients

New culture-independent methods have shown that the lungs, previously thought to be sterile, instead host a diversity of microbial communities collectively known as the

"lung microbiome". These communities exist in the absence of infection and are modified by several external and internal factors. In a recently published study on the potential role of airway microbiota in dictating immune responses and infection outcomes in 182 HIV-associated pneumonia cases, Shenoy et al.(55) reported that compositionally and structurally distinct lower airway microbiomes were associated with discrete local host immune responses, peripheral metabolic reprogramming, and different mortality rates. Similarly, in a study on the relationship between respiratory microbiota and metabolic profiles in bronchoalveolar lavage (BAL) fluid from 39 HIV-infected outpatients and 20 HIV-uninfected outpatients, Cribbs et al.(56) reported that specific metabolic profiles in BAL samples correlated with bacterial organisms that are known to play a role in the pathogenesis of pneumonia in HIV-infected patients.

In another interesting study, Iwai et al.(57) investigated respiratory bacterial communities associated with acute pneumonia in HIV-infected patients. The authors compared oral and airway samples in a cohort of HIV-infected patients during the course of antimicrobial therapy for pneumonia, and compared the airway microbiota of HIV-infected and uninfected patients with acute pneumonia on antimicrobial therapy. The oral bacterial burden was 2.80 x 10^6 copies per 20 ng of DNA, whereas the airway bacterial burden was 5.43 x 10^3 copies per 20 ng of DNA. In oral samples, 1,754 taxa, representing 42 phyla and 153 families, were detected in at least one of the 15 HIV-infected patients. In airway samples 1,654 taxa representing 41 phyla and 152 distinct families were detected in at least one of the 15 samples; of those, 194 taxa were detected in more than 80% of patients including members of the *Sphingomonadaceae*, *Campylobacteraceae*, and *Helicobacteracea.* Twenty-two taxa belonging to the phyla *Actinobacteria*, *Bacteroidetes*, *Chloroflexi*, *Cyanobacteria*,

Firmicutes, and *Natronoanaerobium* were common to the oral and airways niche in all patients and included *Streptococcus bovis* and *Chryseobacterium* species. These data suggest that HIV-infected patients exhibit a relatively high abundance of a large number of phylogenetically distinct taxa, which include pathogenic organisms, suggesting that recurrent pneumonia in the HIV-infected population may be related to the presence of these species.

In the near future, better knowledge and understanding of the lung (and gut) microbiome will shed light on the physiopathology, treatment, and prevention of CAP.

7. Assessment of severity and making site-of-care decisions

Several instruments such as the Pneumonia Severity Index (PSI) and the CURB-65 (Confusion, Urea, Blood Pressure and Age 65) criteria to predict short-term mortality have been developed to render hospitalization decisions more objective in the general population(58,59). In addition, the IDSA/ATS 2007 criteria(60), has been developed to determine ICU admission in the general population. However, few studies have evaluated the applicability of these instruments in the HIV-infected population(61,62). Curran et al.(61) evaluated the PSI score and reported that it accurately predicted high-risk pneumonia and mortality. The authors also suggested that combining the CD4 cell count and PSI score would help physicians decide which patients required hospitalization. The study by Albrich et al.(42), which analyzed the association between nasopharyngeal *S. pneumoniae* densities in HIV-infected patients from South Africa with markers of severity and poor outcomes, reported no correlation between CURB-65 and mortality in these patients. However, the study by Almeida et al.(62) investigated the use of CURB65 in HIV-infected patients, and reported that a higher

CURB65 score and a CD4 count lower than 200 cells/mL were both associated with worse outcomes. They concluded that the CURB65 score plus CD4 cell count could be used in HIV-infected patients with CAP.

In conclusion, the combined use of severity scores such as PSI or CURB65 and CD4 cell count should help clinicians to determine the severity of bacterial CAP in HIV-infected patients (Figure 2).

8. Antibiotic therapy

Antibiotic therapy in HIV-infected patients with CAP does not differ significantly from that administered to the general population. Nevertheless, current pneumonia guidelines do not specifically include the HIV-infected population(60,63), suggesting that treatment should be similar to that for the general population. Although HIV-infected patients on ART show an improved immune response, CD4 reconstitution, and viral suppression, these patients are still at higher risk of pneumonia in part because they show altered immunity and because immune activation persists even when receiving ART(7).

The empiric antibiotic therapy for CAP should cover the main pathogens that cause pneumonia, including *S. pneumoniae* and intracellular bacteria (*C. pneumoniae, C. burnetii, M. pneumoniae* and *L. pneumophila*) and should be modified according to the antibiotic susceptibility report. Current international guidelines suggest the use of macrolide or doxycycline in healthy outpatients without risk of drug-resistant *S. pneumoniae*, and a fluoroquinolone or β-lactam plus macrolide in outpatients with risk of drug-resistant *S. pneumoniae*.

A β-lactam plus a macrolide, or a β-lactam plus a fluoroquinolone, or a fluoroquinolone alone should be as empiric treatment for hospitalized patients (in the ICU or general ward), but fluoroquinolone monotherapy should be restricted to non-ICU patients(40,60). However, few randomized controlled trials (RCT) have investigated these antibiotic regimens and most of the information available comes from retrospective observational analyses.

In a recent randomized controlled trial published by Figueiredo-Mello et al.(64) on the use of ceftriaxone monotherapy versus ceftriaxone plus macrolide in HIV-infected patients with CAP, it was observed that the combination did not improve patient outcomes. However, in that study not all patients who met the inclusion criteria were enrolled in the trial. In addition, the first dose of the assigned regimen was administered within the first 48 hours of hospitalization; these circumstances may have influenced the results of the study.

In contrast, a prospective observational international multicenter study that included 844 adult HIV-infected and uninfected patients with pneumococcal bacteremia found that combination therapy was associated with a lower 14-day mortality rate in only severely ill patients (23% versus 55%; p = 0.015)(65) but there were no significant differences between the two groups. A potential explanation for these results is the fact that macrolides not only inhibit bacterial protein synthesis, but are also potent inhibitors of the production of pneumolysin and reduce the adherence of pneumococcus to respiratory epithelium.

In regions where *M. tuberculosis* is common we must exercise caution regarding fluoroquinolone monotherapy, since its use in *M. tuberculosis* cases may render the

sputum culture negative due to the rapid clearance of the pathogen in the sputum sample and the development of fluoroquinolone resistance in the isolates.

9. Drug interactions between ART and CAP antibiotic therapy

Drug-drug interactions (DDI) present significant risks to patients and are a challenge for health care providers. However, there is no interaction between ART families and penicillins, beta-lactams inhibitors or levofloxacin. Moxifloxacin has a low interaction with atazanavir and lopinavir (protease inhibitors): it has been shown to prolong the QT interval, and so care should be taken especially in patients with pre-existing risk factors (bradycardia, long congenital QT, electrolyte imbalances, and so on).

Azithromycin may cause abnormal changes in the electrical activity of the heart and can induced QTc interval prolongation and *Torsade de pointes*. This adverse event should be taken into account when antiretrovirals can increase its exposure (like ritonavir-boosted protease inhibitors) or can also increase QT interval (rilpivirine). Azithromycin is mainly eliminated via biliary excretion and animal data suggest this may occur via P-glycoprotein and MRP2. Ritonavir-boosted regimens could potentially increase azithromycin exposure (inhibition of P-glycoprotein and MRP2); however, no a priori dosage adjustment is recommended for azithromycin. Cobicistat is not expected to inhibit hepatic P-gp and MRP2 at clinically relevant concentrations and can be given concomitantly with azithromycin. Rilpivirine (an NNRTIs drug) should be used with caution when co administered with a drug with a known risk of Torsade de Pointes. In healthy subjects, supra-therapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval.

Clarithromycin can also prolong the QT interval and increase the risk of life-threatening arrhythmias. Clarithromycin is metabolized by CYP3A4 and its concentrations are increased due to inhibition of CYP3A4 by ritonavir or cobicistat-based ART regimens. Ritonavir increases clarithromycin AUC and Cmax by 77% and 31%, respectively. Clarithromycin should be avoided in patients with long QT syndrome, cardiac disease, or in patients taking other QT-prolonging medications, such as rilpivirine. Because clarithromycin has many and different types of DDI with all classes of antiretrovirals (protease inhibitors, NNRTIs, entry and integrase inhibitors and nucleoside/tide analogues [NRTI]), it is preferable to use azithromycin instead of clarithromycin because of its better DDI profile.

We recommend these two links for more updated information on DDI between the antimicrobials used to treat pulmonary infections and antiretroviral drugs:

https://www.hiv-druginteractions.org/checker (English Web site);

http://www.interaccionesvih.com/interaccions.html (Spanish Web site)

10. Prognosis of Bacterial CAP in HIV-infected patients

In a recent study of 806 patients admitted to the medical and surgical ICUs at Groote Schuur Hospital, Cape Town, South Africa over the course of one year (66), 77 were HIV-positive (9.6%), and the main cause of ICU admission was CAP. The same authors reported that ICU mortality was 25% and hospital mortality was 35%. These data clearly demonstrate that CAP is a major cause of morbidity and mortality among HIV-infected persons, especially in those not receiving ART – a very frequent situation in the geographical region where this study was conducted.

Bacterial CAP mortality in HIV-infected patients in the post-ART era has been reported to range between 6% and 15% (4,7). Despite the high rate of bacterial pneumonia in HIV-infected patients, mortality rates are not higher than in non-HIV-infected patients(5,10,19,67). The risk factors reported associate with higher mortality are neutropenia, a CD4 cell count of < 100 cells per mm^3, a Karnofsky score of ≤ 50, LDH ≥ 598 U/L, mechanical ventilation, a partial pressure of oxygen < 70 mmHg, shock, and radiographic progression of disease(4,19,38).

In a retrospective study from Italy, the authors studied 84 bacterial CAP episodes in 76 HIV-infected inpatients. The proportion of patients receiving ART was 42% whereas 58% of HIV-infected patients were not treated. Although the time to clinical stability was longer in patients without ART (1.9 ± 7.9 vs. 7.6 ± 5.4 days; p = 0.01), the author did not observe differences in mortality between HIV-infected patients with or without ART (44% vs. 55%) because of the small sample size(19).

In a case-control study from the USA that aimed to determine differences in clinical outcomes between hospitalized HIV-positive and HIV-negative patients with CAP, Christensen et al. (11) found no differences in time to clinical stability, length of hospitalization, or mortality, and concluded that clinical outcomes for hospitalized patients with CAP may not be influenced by HIV infection. Patients were matched for age and the mortality risk was determined by the PSI score. However, two main limitations in this study should be noted: the small sample size, and the lack of data on the CD4 cell count for 36% of the population. Additionally, Bordon et al. (67) reported that clinical outcomes for HIV-infected patients with CAP were not predicted by CD4+ cell counts or HIV-RNA levels in a cohort of North American patients.

The data on clinical presentation and outcomes of pneumococcal CAP in HIV-infected patients are conflicting. Clinical variables in HIV-infected patients are difficult to compare with those of non-HIV-infected patients, as bacterial pneumonia often occurs at later ages in non-HIV-infected patients than in the HIV population(68,69). In 2007, a study investigated the clinical and laboratory features, hospital course and outcome of HIV with non-HIV patients with bacteraemic pneumococcal pneumonia. In the analysis of 768 cases with bacteraemic pneumococcal CAP, 14-day mortality was 16% in the HIV patients and 13.9% in the non-HIV patients (a non-significant difference). When adjustments were made for age and severity of pneumonia, HIV patients had significantly higher 14-day mortality, with a significant trend towards increased 14-day mortality in those with lower CD4 counts(15).

However, a recent Spanish study on clinical outcomes of pneumococcal CAP in virologically suppressed, HIV-infected patients on ART with a CD4+ T-cell count > 350 cells/mm^3 compared with uninfected patients with CAP found similar outcomes between HIV-infected and uninfected patients with pneumococcal CAP(9).

Recent years have witnessed changes in the demography of the HIV-infected population, especially as regards age. In a recent study by Barakat et al.(70) comparing clinical outcomes in HIV-infected and uninfected older men hospitalized for CAP, the authors use the Veterans Aging Cohort Study (VACS) Index, which is a validated predictor of all-cause mortality in HIV-infected patients and also predicts 30-day mortality for both HIV-infected and uninfected patients admitted to the ICU(70–72).

The VACS Index score was significantly higher among the HIV-infected patients compared with the uninfected patients [mean 32.7 (SD 19.4) versus 27.2 (SD 17.5; p <

0.001], and the majority of the HIV-infected patients had CD4 counts < 500 cells/μL and HIV viral loads < 500 copies/mL and were on ART. The median VACS Index score was 58, and the adjusted mortality rate was 18.4 (95% CI 6.6, 51.3)/1000 person-months for those on ART versus 73.6 (95% CI 24.8, 218.5)/1000 person-months for those not on ART. The authors concluded that the VACS Index was associated with adverse clinical outcomes. ART was associated with a lower 30-day mortality and length of hospital stay(70) in the multivariate analysis.

11. Prevention

Several interventions can reduce the risk of CAP in HIV-infected adults, especially smoking cessation, reduced alcohol consumption, ART initiation in patients with CAP, early diagnosis of HIV infection, and programs to help with ART compliance in non-compliant patients(23,70).

The risk and severity of pneumococcal pneumonia and influenza complications are higher in HIV-infected individuals(73). Vaccination constitutes an important strategy to ensure the health of HIV-infected persons, and an annual influenza vaccination — regardless of CD4 count — is the main recommendation for HIV-infected patients given by advisory groups in Europe(74–76) and the US (77–79), and by the WHO.

The European AIDS Clinical Society (EACS) advises the administration of pneumococcal vaccination for all HIV-positive persons(75) as follows: One dose of conjugated 13-valent vaccine (PCV-13) for all individuals, even when pre-vaccinated with PPV-23 polysaccharide vaccine. No general recommendation has been given for a booster dose. The Advisory Committee on Immunization Practice (ACIP) and the Infectious

Diseases Society of America (IDSA) guidelines(78,80) recommend PCV13 followed by PPSV23 in HIV-infected patients.

In a recently published randomized clinical trial investigating immunological response to PCV13 followed by PPSV23 versus PPSV23 in HIV-infected adults, Sadlier et al.(81) found that combining PCV13 with PPSV23 elicited a greater magnitude of IgG and (OPA) immune response compared to PPSV23 alone in HIV-infected individuals with a CD4 count > 200 cells/mm^3 over the study period. The result of this study supports the current pneumococcal vaccination recommendations in the United States and Europe for HIV-infected persons.

In previously unvaccinated individuals, the recommendation is one dose of PCV13 followed by one dose of PPV23 ≥ 8 weeks later (preferably when the CD4 count ≥ 200 cells/mm^3), repeating the PPV23 dose 5 years later. In persons previously vaccinated with PPV23, the recommendation is to give PCV13 at ≥ 1 year later followed 5 years later by PPV23(82).

12. Conclusions

Community-acquired pneumonia in HIV-infected patients is a major cause of morbidity, and mortality. However, the management and outcomes of bacterial CAP in HIV-infected persons on ART are similar to those in uninfected persons, suggesting that the management should be the same for both populations.

13. Expert commentary

Recent studies have reported that despite ART, bacterial CAP remains a major cause of disease, health costs, and mortality in the HIV-infected population, especially in high-income countries. However, in middle and low-income countries tuberculosis remains

the main cause of pulmonary disease and bacterial pneumonia is the second most important cause of lung infections. Despite improvements in the accessibility to ART it is not yet available to millions of HIV-infected people, especially in developing countries.

Since pneumococcal pneumonia is the most frequently occurring bacterial infection in HIV-infected persons on ART and is associated with higher mortality rates, preventive strategies such as smoking cessation programs and vaccination campaigns are essential. Also, we recommend that since HIV is diagnosed in many cases of CAP, all suspected cases of CAP should be tested for HIV.

Early identification of HIV infection is mandatory, especially in those geographical areas most affected by this pandemic, in order to start effective ART therapy and improve the quality of life of affected persons.

14. Five-year view

CAP in the HIV-infected population is a major health problem worldwide. Since HIV-infected patients are surviving longer than those who were ill before the advent of ART, we will observe changes in the epidemiology of CAP. In future clinical practice, multidisciplinary specialist teams will be required for the management of HIV-infected patients with pneumonia in order to improve patient outcomes. Further clinical research is needed in order to provide more complete information that will help management of CAP in this specific population. Furthermore, continuous smoking cessation programs and vaccination campaigns will effectively help prevent bacterial CAP in the HIV-infected population. National and international guidelines should be based on current knowledge of pneumonia in HIV-infected patients in order to disseminate research data worldwide

15. Key issues

- Despite ART, bacterial pneumonia remains a major cause of disease in the HIV-infected population.
- *Streptococcus pneumoniae* is the most frequently detected pathogen causing bacterial CAP in HIV-infected patients on ART. Tuberculosis and *Pneumocystis* infection are the prevalent pathogens in geographical areas with a lower rate of HIV diagnosis and no ART therapy.
- The clinical presentation and management of bacterial CAP is similar in HIV-infected patients on ART and uninfected patients.
- In HIV virologically suppressed patients on ART with > 350 CD4+ T-cell count/mm^3 clinical outcomes are similar to the general population. We recommend that such patients do not need treatment, admission, or care sites that differs from that of the general population.
- Bacterial CAP prevention measures such as smoking cessation and vaccination campaigns are crucial in the HIV-infected population.

Funding

The study was funded by the CERCA Programme, Ciber de Enfermedades Respiratorias (CibeRes CB06/06/0028), research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and Strategic plan for research and innovation in health (PERIS).

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors were involved in the content development of the manuscript, reviewed all drafts and approved the final version.

References

Reference annotations

*** Of interest**

**** Of considerable interest**

1. WHO | World Health Statistics 2016: Monitoring health for the SDGs [Internet]. WHO. [cited 2017 Dec 19]. Available from: http://www.who.int/gho/publications/world_health_statistics/2016/en/

2. Brown J, Lipman M. Community-Acquired Pneumonia in HIV-Infected Individuals. Curr Infect Dis Rep. 2014 Mar;16(3):397.

3. ** Feldman C, Anderson R, Rossouw T. HIV-related pneumococcal disease prevention in adults. Expert Rev Respir Med. 2017 Mar;11(3):181–99.

   ** Important review article about pneumococcal disease in HIV infected patients

4. ** Cilloniz C, Torres A, Polverino E, Gabarrus A, Amaro R, Moreno E, et al. Community-acquired lung respiratory infections in HIV-infected patients: microbial aetiology and outcome. Eur Respir J. 2014 Jun;43(6):1698–708.

   ** Important data of a study performed in a high-income setting exemplifies how bacterial agents have taken over P. jirovecci as the main microbial etiology of CAP.

5. * Cillóniz C, Torres A, Manzardo C, Gabarrús A, Ambrosioni J, Salazar A, et al. Community-Acquired Pneumococcal Pneumonia in Virologically Suppressed HIV-Infected Adult Patients: A Matched Case-Control Study. Chest. 2017 ug;152(2):295-303.

   *Important study about clinical presentation and outcome of pneumocccal CAP in HIV infected patients virologically suppresed.

6. Feldman C, Anderson R. HIV-associated bacterial pneumonia. Clin Chest Med. 2013 Jun;34(2):205–16.

7. * Søgaard OS, Reekie J, Ristola M, Jevtovic D, Karpov I, Beniowski M, et al. Severe bacterial non-aids infections in HIV-positive persons: incidence rates and risk factors. J Infect. 2013 May;66(5):439–46.

   * Important data from the large EuroSIDA cohort

8. Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. Lancet Infect Dis. 2004 Jul;4(7):445–55.

9. Malinis M, Myers J, Bordon J, Peyrani P, Kapoor R, Nakamatzu R, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2010 Jan;14(1):e22-27.

10. Christensen D, Feldman C, Rossi P, Marrie T, Blasi F, Luna C, et al. HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2005 Aug 15;41(4):554–6.

11. The top 10 causes of death [Internet]. World Health Organization. [cited 2018 Apr 26]. Available from: http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

12. Sogaard OS, Lohse N, Gerstoft J, Kronborg G, Ostergaard L, Pedersen C, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008 Nov 15;47(10):1345–53.

13. Grau I, Pallares R, Tubau F, Schulze MH, Llopis F, Podzamczer D, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med. 2005 Jul 11;165(13):1533–40.

14. Gordin FM, Roediger MP, Girard P-M, Lundgren JD, Miro JM, Palfreeman A, et al. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. Am J Respir Crit Care Med. 2008 Sep 15;178(6):630–6.

15. Feldman C, Klugman KP, Yu VL, Ortqvist A, Choiu CCC, Chedid MBF, et al. Bacteraemic pneumococcal pneumonia: impact of HIV on clinical presentation and outcome. J Infect. 2007 Aug;55(2):125–35.

16. Lamas CC, Coelho LE, Grinsztejn BJ, Veloso VG. Community-acquired lower respiratory tract infections in HIV-infected patients on antiretroviral therapy: predictors in a contemporary cohort study. Infection. 2017 Dec;45(6):801–9.

17. Kunisaki KM. Will expanded ART use reduce the burden of HIV-associated chronic lung disease? Curr Opin HIV AIDS. 2014 Jan;9(1):27–33.

18. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit Care Med. 2011 Feb 1;183(3):388–95.

19. Madeddu G, Porqueddu EM, Cambosu F, Saba F, Fois AG, Pirina P, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. Infection. 2008 Jun;36(3):231–6.

20. Mussini C, Galli L, Lepri AC, De Luca A, Antinori A, Libertone R, et al. Incidence, timing, and determinants of bacterial pneumonia among HIV-infected patients: data from the ICONA Foundation Cohort. J Acquir Immune Defic Syndr 1999. 2013 Jul 1;63(3):339–45.

21. O'Connor J, Vjecha MJ, Phillips AN, Angus B, Cooper D, Grinsztejn B, et al. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per µL: secondary outcome results from a randomised controlled trial. Lancet HIV. 2017 Mar;4(3):e105–12.

22. Almirall J, Bolíbar I, Serra-Prat M, Roig J, Hospital I, Carandell E, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J. 2008 Jun;31(6):1274–84.

23. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013 Nov;68(11):1057–65.

24. Bénard A, Mercié P, Alioum A, Bonnet F, Lazaro E, Dupon M, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. PloS One. 2010 Jan 26;5(1):e8896.

25. Mdodo R, Frazier EL, Dube SR, Mattson CL, Sutton MY, Brooks JT, et al. Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. Ann Intern Med. 2015 Mar 3;162(5):335–44.

26. Frazier EL, Sutton MY, Brooks JT, Shouse RL, Weiser J. Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009-2014. Prev Med. 2018 Mar 14;111:231–4.

27. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV incidence in the United States, 2006-2009. PloS One. 2011;6(8):e17502.

28. Yanagi S, Tsubouchi H, Miura A, Matsuo A, Matsumoto N, Nakazato M. The Impacts of Cellular Senescence in Elderly Pneumonia and in Age-Related Lung Diseases That Increase the Risk of Respiratory Infections. Int J Mol Sci. 2017 Feb 25;18(3).

29. Almirall J, Serra-Prat M, Bolíbar I, Palomera E, Roig J, Hospital I, et al. Passive smoking at home is a risk factor for community-acquired pneumonia in older adults: a population-based case-control study. BMJ Open. 2014 Jun 13;4(6):e005133.

30. Chinnapaiyan S, Unwalla HJ. Mucociliary dysfunction in HIV and smoked substance abuse. Front Microbiol. 2015;6:1052.

31. Feldman JG, Minkoff H, Schneider MF, Gange SJ, Cohen M, Watts DH, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. Am J Public Health. 2006 Jun;96(6):1060–5.

32. Yuan Y, L'italien G, Mukherjee J, Iloeje UH. Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort. HIV Med. 2006 Apr;7(3):156–62.

33. Pacek LR, Crum RM. A Review of the Literature Concerning HIV and Cigarette Smoking: Morbidity and Mortality, Associations with Individual- and Social-Level Characteristics, and Smoking Cessation Efforts. Addict Res Theory. 2015 Feb;23(1):10–23.

34. Reynolds NR. Cigarette smoking and HIV: more evidence for action. AIDS Educ Prev Off Publ Int Soc AIDS Educ. 2009 Jun;21(3 Suppl):106–21.

35. Hile SJ, Feldman MB, Alexy ER, Irvine MK. Recent Tobacco Smoking is Associated with Poor HIV Medical Outcomes Among HIV-Infected Individuals in New York. AIDS Behav. 2016 Aug;20(8):1722–9.

36. Lalloo UG, Pillay S, Mngqibisa R, Abdool-Gaffar S, Ambaram A. HIV and COPD: a conspiracy of risk factors. Respirol Carlton Vic. 2016 Oct;21(7):1166–72.

37. Makinson A, Hayot M, Eymard-Duvernay S, Ribet C, Raffi F, Pialoux G, et al. HIV is associated with airway obstruction: a matched controlled study. AIDS Lond Engl. 2017 Nov 10;

38. Raju R, Peters BS, Breen RAM. Lung infections in the HIV-infected adult. Curr Opin Pulm Med. 2012 May;18(3):253–8.

39. Figueiredo-Mello C, Naucler P, Negra MD, Levin AS. Prospective etiological investigation of community-acquired pulmonary infections in hospitalized people living with HIV. Medicine (Baltimore). 2017 Jan;96(4):e5778.

40. Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017 Jun;9(6):1469–502.

41. Perelló R, Miró O, Marcos MA, Almela M, Bragulat E, Sánchez M, et al. Predicting bacteremic pneumonia in HIV-1-infected patients consulting the ED. Am J Emerg Med. 2010 May;28(4):454–9.

42. Albrich WC, Madhi SA, Adrian PV, van Niekerk N, Telles J-N, Ebrahim N, et al. Pneumococcal colonisation density: a new marker for disease severity in HIV-infected adults with pneumonia. BMJ Open. 2014;4(8):e005953.

43. Albrich WC, Madhi SA, Adrian PV, van Niekerk N, Mareletsi T, Cutland C, et al. Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012 Mar 1;54(5):601–9.

44. Benito N, Moreno A, Miro JM, Torres A. Pulmonary infections in HIV-infected patients: an update in the 21st century. Eur Respir J. 2012 Mar 1;39(3):730–45.

45. * Head BM, Trajtman A, Rueda ZV, Vélez L, Keynan Y. Atypical bacterial pneumonia in the HIV-infected population. Pneumonia Nathan Qld. 2017;9:12.

* Important review about the intracellular pathogens causing CAP in HIV patients

46. Robbins NM, Kumar A, Blair BM. Legionella pneumophila infection presenting as headache, confusion and dysarthria in a human immunodeficiency virus-1 (HIV-1) positive patient: case report. BMC Infect Dis. 2012 Sep 22;12:225.

47. Franzin L, Dal Conte I, Cabodi D, Sinicco A. Culture proven Legionella pneumophila pneumonia in a HIV-infected patient: case report and review. J Infect. 2002 Oct;45(3):199–201.

48. Sandkovsky U, Sandkovsky G, Suh J, Smith B, Sharp V, Polsky B. Legionella pneumonia and HIV: case reports and review of the literature. AIDS Patient Care STDs. 2008 Jun;22(6):473–81.

49. Cillóniz C, Miguel-Escuder L, Pedro-Bonet ML, Falcó V, Lopez Y, García-Vidal C, et al. Community-Acquired Legionella Pneumonia in HIV-Infected Adult Patients: A Matched Case-Control Study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2018 Apr 12;

50. Boschini A, Smacchia C, Di Fine M, Schiesari A, Ballarini P, Arlotti M, et al. Community-acquired pneumonia in a cohort of former injection drug users with and without human immunodeficiency virus infection: incidence, etiologies, and clinical aspects. Clin Infect Dis Off Publ Infect Dis Soc Am. 1996 Jul;23(1):107–13.

51. Sheth AN, Althoff KN, Brooks JT. Influenza susceptibility, severity, and shedding in HIV-infected adults: a review of the literature. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011 Jan 15;52(2):219–27.

52. Cohen C, Simonsen L, Sample J, Kang J-W, Miller M, Madhi SA, et al. Influenza-related mortality among adults aged 25-54 years with AIDS in South Africa and the United States of America. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012 Oct;55(7):996–1003.

53. Ormsby CE, de la Rosa-Zamboni D, Vázquez-Pérez J, Ablanedo-Terrazas Y, Vega-Barrientos R, Gómez-Palacio M, et al. Severe 2009 pandemic influenza A (H1N1) infection and increased mortality in patients with late and advanced HIV disease. AIDS Lond Engl. 2011 Feb 20;25(4):435–9.

54. Martínez E, Marcos MA, Hoyo-Ulloa I, Antón A, Sánchez M, Vilella A, et al. Influenza A H1N1 in HIV-infected adults. HIV Med. 2011 Apr;12(4):236–45.

55. Shenoy MK, Iwai S, Lin DL, Worodria W, Ayakaka I, Byanyima P, et al. Immune Response and Mortality Risk Relate to Distinct Lung Microbiomes in Patients with HIV and Pneumonia. Am J Respir Crit Care Med. 2017 Jan 1;195(1):104–14.

56. Cribbs SK, Uppal K, Li S, Jones DP, Huang L, Tipton L, et al. Correlation of the lung microbiota with metabolic profiles in bronchoalveolar lavage fluid in HIV infection. Microbiome. 2016 Jan 20;4:3.

57. Iwai S, Fei M, Huang D, Fong S, Subramanian A, Grieco K, et al. Oral and airway microbiota in HIV-infected pneumonia patients. J Clin Microbiol. 2012 Sep;50(9):2995–3002.

58. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan 23;336(4):243–50.

59. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003 May;58(5):377–82.

60. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007 Mar 1;44 Suppl 2:S27-72.

61. Curran A, Falcó V, Crespo M, Martinez X, Ribera E, Villar del Saz S, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. HIV Med. 2008 Oct;9(8):609–15.

62. Almeida A, Almeida AR, Castelo Branco S, Vesza Z, Pereira R. CURB-65 and other markers of illness severity in community-acquired pneumonia among HIV-positive patients. Int J STD AIDS. 2016 Oct;27(11):998–1004.

63. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009 Oct;64 Suppl 3:iii1-55.

64. Figueiredo-Mello C, Naucler P, Negra MD, Levin AS. Ceftriaxone versus ceftriaxone plus a macrolide for community-acquired pneumonia in hospitalized patients with HIV/AIDS: a randomized controlled trial. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2017 Jun 23;

65. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med. 2004 Aug 15;170(4):440–4.

66. Mkoko P, Raine RI. HIV-positive patients in the intensive care unit: A retrospective audit. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2017 Sep 22;107(10):877–81.

67. Bordon J, Kapoor R, Martinez C, Portela D, Duvvuri P, Klochko A, et al. CD4+ cell counts and HIV-RNA levels do not predict outcomes of community-acquired pneumonia in hospitalized HIV-infected patients. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2011 Dec;15(12):e822-827.

68. Mayaud C, Parrot A, Cadranel J. Pyogenic bacterial lower respiratory tract infection in human immunodeficiency virus-infected patients. Eur Respir J Suppl. 2002 Jul;36:28s-39s.

69. Heffernan RT, Barrett NL, Gallagher KM, Hadler JL, Harrison LH, Reingold AL, et al. Declining incidence of invasive Streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. J Infect Dis. 2005 Jun 15;191(12):2038–45.

70. Barakat LA, Juthani-Mehta M, Allore H, Trentalange M, Tate J, Rimland D, et al. Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia. HIV Med. 2015 Aug;16(7):421–30.

71. Justice AC, Modur SP, Tate JP, Althoff KN, Jacobson LP, Gebo KA, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. J Acquir Immune Defic Syndr 1999. 2013 Feb 1;62(2):149–63.

72. Akgün KM, Tate JP, Pisani M, Fried T, Butt AA, Gibert CL, et al. Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era. Crit Care Med. 2013 Jun;41(6):1458–67.

73. * Pulmonary Complications of HIV [Internet]. European Respiratory Society; 2014. 277 p. Available from: http://books.ersjournals.com/content/9781849840552/9781849840552

* Important data about pulmonary complication in HIV population

74. Geretti AM, Brook G, Cameron C, Chadwick D, French N, Heyderman R, et al. British HIV Association Guidelines on the Use of Vaccines in HIV-Positive Adults 2015. HIV Med. 2016 Aug;17 Suppl 3:s2–81.

75. EACS Guidelines [Internet]. [cited 2017 Dec 11]. Available from: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

76. Frésard A, Gagneux-Brunon A, Lucht F, Botelho-Nevers E, Launay O. Immunization of HIV-infected adult patients - French recommendations. Hum Vaccines Immunother. 2016;12(11):2729–41.

77. Kim DK, Riley LE, Harriman KH, Hunter P, Bridges CB, Advisory Committee on Immunization Practices. Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017. Ann Intern Med. 2017 Feb 7;166(3):209–19.

78. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Feb;58(3):309–18.

79. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Jan;58(1):1–10.

80. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012 Oct 12;61(40):816–9.

81. Sadlier C, O'Dea S, Bennett K, Dunne J, Conlon N, Bergin C. Immunological efficacy of pneumococcal vaccine strategies in HIV-infected adults: a randomized clinical trial. Sci Rep. 2016 Sep 1;6:32076.

82. Crum-Cianflone NF, Sullivan E. Vaccinations for the HIV-Infected Adult: A Review of the Current Recommendations, Part I. Infect Dis Ther. 2017 Sep;6(3):303–31.

Table 1. Risk factors associated with bacterial CAP in HIV-infected patients

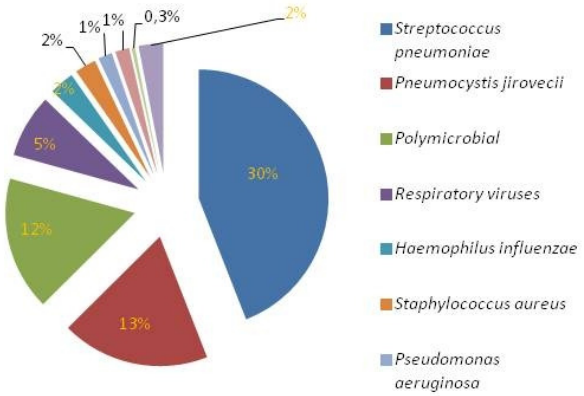
Risk factors	Evidence	Suggested Intervention
***Smoking (current and passive)**	*Risk of CAP increased in current, former and passive smokers	* Smoking cessation
***Abuse of alcohol consumption**	*Higher consumption of alcohol (≥80 g/L) is a risk factor for CAP. Alcohol exposure (chronic heavy drinking) affects all components of the adaptive immune system.	* Reduce alcohol consumption
***Injecting drug use**	*High incidence of bacterial CAP due to poor adherence to ART and lower socioeconomic status	* Programs to control drug use
***Older age**	*CAP incidence increases significantly with advanced age. Immunological changes that decreased efficiency of the adaptive and innate immune systems: "immunosenescence".	
***Malnutrition**	* Underweight is associated with increased risk of CAP	* Dietary advice
***Detectable viral load and lower CD4 cell count**	*Suppressed HIV loads are associated with a lower incidence of CAP.	*Compliance with ART and following periodical control
***Comorbidities**	*Chronic respiratory diseases, chronic cardiovascular disease, diabetes mellitus, chronic liver or renal disease increase the risk of CAP	

Not vaccinated against influenza and *Streptococcus pneumoniae	*Recommendations of international societies	*Ensure compliance with vaccination

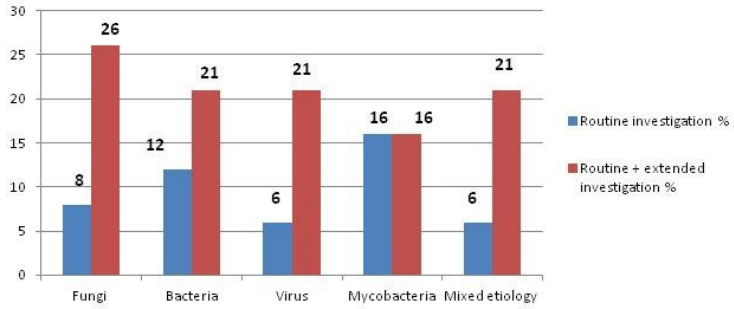
References: 2,3,9,13,14,15,17,18,19,20,22,23,24,25,27,28,29,30,62,63,66,67,68,70,71

Figure 1. Microbial Etiology in HIV-infected patients with CAP

1.- Total cases with microbiological diagnosis =227



2.- Total cases with microbiological diagnosis= 92



Reference:
1.-Cilloniz et al. Eur Respir J. 2014 Jun;43(6):1698-708

2.-Figueiredo-Mello et al. Medicine (Baltimore). 2017 Jan;96(4):e5778.

Figure 2. Bacterial CAP in HIV-infected Patients