

Community-Acquired Pneumonia (Last updated October 10, 2019; last reviewed January 12, 2022)

Epidemiology

Bacterial respiratory diseases, including sinusitis, bronchitis, otitis, and pneumonia, are among the most common infectious complications in patients with HIV, occurring with increased frequency at all CD4 T lymphocyte cell (CD4) counts.¹ This chapter will focus on the diagnosis, prevention, and management of bacterial community-acquired pneumonia (CAP) in patients with HIV.

In general, although data are limited, hospital-acquired pneumonia and ventilator-associated pneumonia do not differ in terms of microbiology, clinical course, treatment, or prevention in persons with HIV as compared to persons without HIV with similar HIV-unrelated comorbidities. Therefore, they will not be addressed in these guidelines.

Bacterial pneumonia is a common cause of HIV-associated morbidity. Recurrent pneumonia, considered two or more episodes within a 1-year period, is an AIDS-defining condition. The incidence of bacterial pneumonia in individuals with HIV has decreased progressively with the advent of combination antiretroviral therapy (ART).²⁻⁷ In one study, the incidence of bacterial pneumonia declined from 22.7 episodes per 100 person-years before the introduction of ART to 9.1 episodes per 100 person-years by 1997 after ART was introduced. Since then, the incidence of bacterial pneumonia among people with HIV in developed countries has continued to drop. In the Strategic Timing of AntiRetroviral Treatment (START) study, the incidence rate of serious bacterial infections overall was 0.87 per 100 person-years, and approximately 40% of these infections were due to bacterial pneumonia.⁴ Recurrent bacterial pneumonia as an AIDS-defining illness is also less frequently encountered in individuals on ART; however, its exact incidence is hard to evaluate because surveillance data for it are not collected systematically as for other opportunistic infections.⁸

Despite ART, bacterial pneumonia remains more common in individuals with HIV than in those who do not have HIV.⁹⁻¹¹ Bacterial pneumonia may be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4 count. Bacterial pneumonia in individuals with HIV results from multiple risk factors, particularly immune defects. A CD4 count decrease, especially when below 100 cells/mm³ continues to be a major risk factor for pneumonia due to routine bacterial pathogens. Other immune defects include quantitative and qualitative B-cell abnormalities that result in impaired pathogen-specific antibody production, abnormalities in neutrophil function or numbers, and abnormalities in alveolar macrophage function.^{12,13} Lack of ART or intermittent use of ART increases the risk for pneumonia, likely due to uncontrolled HIV viremia.¹⁴

Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include tobacco, alcohol, and/or injection drug use; and chronic viral hepatitis.^{3,10,15,16} Chronic obstructive pulmonary disease (COPD), malignancy, renal insufficiency, and congestive heart failure are emerging as risk factors for pneumonia, particularly in the population of older adults with HIV.¹⁷ Risk for CAP can also increase with obesity,⁴ an emerging health problem in people living with HIV.

Microbiology

In individuals with HIV, *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia, the same as in individuals without HIV.¹⁸⁻²⁴ *Staphylococcus aureus* (*S. aureus*) and *S. pneumoniae* are among the most common etiologies of pneumonia in association with influenza infection.^{25,26} Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia* species have been reported as infrequent causes of CAP in individuals with HIV.^{21,27} However, when more extensive testing such as serology to detect IgM antibodies and/or positive polymerase chain reaction (PCR) of respiratory secretions was performed, additional infections due to *Mycoplasma* and *Chlamydia* were detected.²⁸ Respiratory viruses are also a

common cause of CAP. Although virally-induced CAP is less studied in individuals with HIV, data from a Centers for Disease Control and Prevention (CDC) study of the epidemiology of CAP in adult patients in five hospitals in Nashville and Chicago showed that respiratory viruses were detected in nearly a quarter of the adults with CAP (23% had one or more respiratory viruses and 3% had both respiratory viruses and bacteria).²⁹

The frequency of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *S. aureus* as community-acquired pathogens is higher in individuals with HIV than in those without HIV based on studies in the early combination ART era.^{22,30} Many of these patients often had poorly controlled HIV or the presence of other concomitant risk factors that contributed to the risk for *P. aeruginosa* or *S. aureus*. Patients with advanced HIV disease (CD4 count ≤ 50 cells/mm³) or underlying neutropenia, as well as pre-existing lung disease such as bronchiectasis or severe COPD have an increased risk of infection with *P. aeruginosa*. Other risk factors for infection include the use of corticosteroids, severe malnutrition, hospitalization within the past 90 days, residence in a health care facility or nursing home, and chronic hemodialysis.³¹

S. aureus should be considered in patients with recent viral infection (particularly influenza), a history of injection drug use, or severe, bilateral, necrotizing pneumonia. Risk factors for *S. aureus* pneumonia in patients with HIV include receipt of antibiotics prior to hospital admission, comorbid illnesses, and recent health care contact.³² Community outbreaks of methicillin-resistant *S. aureus* (MRSA) infection have also been seen among men who have sex with men.³³ Studies of patients without HIV have identified hemodialysis, known prior colonization or infection with MRSA, as well as recurrent skin infections to be risk factors for MRSA pneumonia.³¹ Notably, nasal carriage and colonization of skin sites with MRSA is more common in individuals with HIV than in those without HIV, and is more likely in patients recently incarcerated and/or hospitalized.^{34,35}

Clinical Manifestations

The clinical and radiographic presentation of bacterial pneumonia in individuals with HIV, particularly in those with higher CD4 count and HIV viral suppression, is similar to that in individuals without HIV.³⁶ Patients with pneumonia caused by bacteria such as *S. pneumoniae* or *Haemophilus* species characteristically have acute onset (3–5 days) of symptoms, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum, and dyspnea.³⁷ The presence of fever, tachycardia, and/or hypotension can be indicators of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia, and in such cases, clinicians should strongly consider hospitalizing the patient.

Patients with bacterial pneumonia typically have signs of focal consolidation, such as egophony, and/or pleural effusion on lung examination. In contrast, lung examination often is normal in those with *Pneumocystis* pneumonia (PCP), and if abnormal, reveals inspiratory crackles. In patients with bacterial pneumonia, the white blood cell (WBC) count usually is elevated. The elevation may be relative to baseline WBC count in those with advanced HIV. Neutrophilia or a left shift in WBC differential may be present.

Individuals with bacterial pneumonia characteristically exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. The frequency of these typical radiographic findings, however, may depend on the underlying bacterial pathogen. Those with pneumonia due to *S. pneumoniae* or *Haemophilus* typically present with consolidation, whereas cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*.

In individuals with HIV the incidence of bacteremia accompanying pneumonia is greater than in individuals without HIV, especially when infection is due to *S. pneumoniae*.³⁸ In data from CDC, the incidence of invasive pneumococcal disease, inclusive of bacteremia, was significantly higher in individuals with HIV; rates were 173 cases per 100,000 in those with HIV infection, compared to 3.8 per 100,000 in younger adults aged 18–34 years and 36.4 per 100,000 among those aged ≥ 65 years in the general population.³⁹ Similarly, in a study from Kenya, the rate of pneumococcal bacteremia was significantly higher in individuals with HIV infection (rate ratio of HIV-positive versus HIV-negative adults, 19.7, 95% CI, 12.4–31.1).⁴⁰ With

the introduction of ART and pneumococcal conjugate vaccines for both the general pediatric population and individuals living with HIV, this disparity in incidence rates of bacteremia between people with and without HIV has narrowed but has not been eliminated.⁴¹⁻⁴⁵ Risk factors associated with bacteremia include lack of ART, low CD4 count (particularly <100 cells/mm³), as well as alcohol abuse, current smoking, and comorbidities, particularly liver disease.⁴²

Disease severity and arterial oxygenation should be assessed in all patients with pneumonia. Noninvasive measurement of arterial oxygen saturation by pulse oximetry is an appropriate screening test. Arterial blood gas analysis is indicated for patients with evidence of hypoxemia suggested by noninvasive assessment and for patients who have tachypnea and/or respiratory distress. The use of severity scoring systems for pneumonia and their application to patients with HIV are discussed in the Treating Disease section.

Although some studies suggest that bacterial pneumonia is associated with increased mortality in individuals with HIV,^{22,46,47} others do not.^{36,48-50} Independent predictors of increased mortality in a prospective, multicenter study of individuals with HIV with community-acquired bacterial pneumonia were CD4 count <100 cells/mm³, radiographic progression of disease, and presence of shock.⁵¹ In that study, multilobar infiltrates, cavitory infiltrates, and pleural effusion on baseline imaging were all independent predictors of radiographic progression of disease. However, in patients on ART with controlled HIV viremia, and high CD4 counts (>350 cells/mm³), the clinical courses and outcomes of pneumonia appear to be similar to those in patients without HIV.³⁶

As in patients without HIV, pneumonia may have an impact on longer term outcomes of patients with HIV. This includes greater long-term mortality, as hospitalization for pneumonia has been associated with increased mortality up to one year later.⁵² Pneumonia has also been associated with impaired lung function and risk of subsequent lung cancer in individuals with HIV.⁵³⁻⁵⁵

Diagnosis

General Approach

Patients with clinical symptoms and signs suggestive of CAP should have posteroanterior and lateral chest radiographs; evidence of pneumonia can also be found on chest computed tomography (CT) scan, but routine use of chest CT scan for this purpose is not recommended. Lung ultrasound can also be used to aid in the diagnosis pneumonia. If previous radiographs are available, they should be reviewed to assess for new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate by chest radiograph or other imaging technique in conjunction with compatible clinical symptoms and signs.

The differential diagnosis of pneumonia in individuals with HIV is broad and a confirmed microbiologic diagnosis should be pursued. Microbial identification can allow clinicians to target the specific pathogen(s) and discontinue broad spectrum antibiotic therapy and/or empiric therapy that targets non-bacterial pathogens. Given the increased incidence of *Mycobacterium tuberculosis* (*M. tuberculosis*) in individuals with HIV, a tuberculosis (TB) diagnosis should always be considered in patients with HIV who have pneumonia. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (i.e., respiratory isolation for hospitalized patients), and two to three sputum specimens should be obtained for acid fast bacilli evaluation (including TB PCR; see [Mycobacterium tuberculosis Infection and Disease](#)). Bronchoscopy with bronchoalveolar lavage should be considered, especially if the differential diagnosis includes opportunistic pathogens such as *Pneumocystis jirovecii*.

Procalcitonin (PCT) testing has been proposed as a tool to distinguish between bacterial and viral respiratory infections. One study from Africa specifically evaluated the usefulness of PCT testing to distinguish CAP due to bacteria (non-TB), *M. tuberculosis*, and PCP in persons with HIV. In general, PCT levels associated with bacterial pneumonia are higher than those associated with viral or fungal pneumonias, but levels can also be elevated in non-bacterial pulmonary infections.⁵⁶ Specific PCT thresholds have not been established or validated in HIV-associated bacterial pneumonia. Thus, given the lack of data, the use of PCT to guide

decisions regarding etiology of pneumonia, initiation of anti-bacterial treatment, or duration of treatment in patients with HIV is not recommended.

Recommended Diagnostic Evaluation in Community-Acquired Pneumonia

Guidelines for microbiologic testing for diagnosis of CAP in individuals without HIV generally also apply to persons with HIV.⁵⁷

- In patients with HIV with CAP who are well enough to be treated as outpatients, routine diagnostic tests to identify a bacterial etiologic diagnosis are optional, especially if the microbiologic studies cannot be performed promptly.
- In patients with HIV hospitalized for CAP, a Gram stain of expectorated sputum and two blood cultures are recommended, particularly in those with severe pneumonia, in those who are not on ART; or in those who are known to have a CD4 count <350 cells/mm³ (and especially if <100 cells/mm³) prior to hospitalization. Specimens should ideally be obtained before initiation of antibiotics, or within 12 hours to 18 hours of such initiation.
- Urinary antigen tests for *L. pneumophila* and *S. pneumoniae* are recommended in hospitalized patients, particularly those with severe CAP. In addition, lower respiratory tract secretions should be cultured for *Legionella* on selective media or undergo *Legionella* nucleic acid amplification testing in adults with severe CAP. *Legionella* testing should also be done in patients with HIV with non-severe CAP when indicated by epidemiological factors, such as association with a *Legionella* outbreak or recent travel.
- Microbiologic diagnostic testing is indicated whenever epidemiologic, clinical, or radiologic clues prompt suspicion of specific pathogens that could alter standard empirical management decisions.
- If available, rapid MRSA nasal testing should be performed, particularly in patients with risk factors for MRSA or in a high prevalence setting, as results can direct empiric antibiotic therapy.⁵⁸

Gram stain and culture of sputum is recommended in all hospitalized patients meeting the criteria stated above and is optional in individuals with HIV and CAP not meeting these criteria. In general, Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained prior to (or not more than 12–18 hours after) initiation of antibiotics, and quality performance measures for collection, transport, and processing of samples can be met. Sputum cultures in patients with HIV have been shown to identify a bacterial etiology in up to 30% to 40% of good quality specimens^{47,59} although yield is less in other studies.^{14,28} Correlation of sputum culture with Gram stain can help in interpretation of sputum culture data. For intubated patients, an endotracheal aspirate sample should be obtained promptly after intubation, or bronchoscopy may be indicated.

Blood cultures are more likely to be positive in individuals with HIV than in those without HIV. Patients with HIV, particularly those with lower CD4 counts, are at increased risk of invasive infection with *S. pneumoniae*. Given concerns for drug-resistant *S. pneumoniae*,^{60,61} as well as *S. aureus* and/or other drug-resistant pathogens, blood cultures are recommended for patients with HIV who meet the criteria as noted above, and are optional for those who do not meet the criteria listed.

Diagnostic thoracentesis should be performed in all patients with pleural effusion if concern exists for accompanying empyema, and pleural fluid should be sent for microbiologic studies. Therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion. Given the increased risk of invasive pneumococcal disease in patients with HIV, clinicians should be vigilant for evidence of extra-pulmonary complications of infection.

Preventing Exposure

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community. General precautions to maintain health, such as adhering to hand hygiene and

cough etiquette and refraining from close contact with individuals who have respiratory infections, should be emphasized for patients with HIV as for other patient populations.

Preventing Disease

Vaccination against *S. pneumoniae* and influenza, use of ART, and lifestyle modifications are all important measures in preventing bacterial pneumonia. Multiple observational studies have reported benefits of pneumococcal polysaccharide vaccine (PPV) in persons with HIV.^{16,62-68} Several studies also have documented an association between vaccination and a reduced risk of pneumococcal bacteremia.^{42,67} One randomized placebo-controlled trial of PPV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia.⁶⁹ Follow-up of this cohort confirmed the increase in pneumonia in vaccinated participants, but notably also showed a decrease in all-cause mortality.⁷⁰ However, subsequent observational studies have demonstrated that PPV vaccination provides people with HIV moderate protection against pneumococcal disease.⁷¹

The 13-valent pneumococcal conjugate vaccine (PCV13) is recommended by the Advisory Committee on Immunization Practices for use in adults with immunocompromising conditions, including HIV infection.³⁹ A randomized, double-blind, placebo-controlled trial of 7-valent PCV among adults with HIV in Malawi demonstrated 74% efficacy against vaccine-type invasive pneumococcal disease, with clear evidence of efficacy in those with CD4 counts <200 cells/mm³.⁷²

Adults and adolescents with HIV who have never received any pneumococcal vaccine should receive a single dose of PCV13 regardless of CD4 count (**AI**).³⁹ Patients with CD4 counts >200 cells/mm³ should receive a dose of 23-valent PPV (PPV23) at least 8 weeks later (**AI**).^{62-68,73,74} While individuals with HIV with CD4 counts <200 cells/mm³ can also be offered PPV23 at least 8 weeks after receiving PCV13 (**CIII**) (e.g., when there are concerns with retention in care), PPV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm³ while on ART (**BIII**). Clinical evidence supporting use of PPV23 in persons with CD4 counts <200 cells/mm³ appears strongest in patients who also have HIV RNA <100,000 copies/mL;^{73,74} evidence also suggests benefit for those who start ART before receiving PPV vaccination.^{67,75}

The duration of the protective effect of PPV23 is unknown; a single revaccination with PPV is recommended if ≥5 years have elapsed since the first dose of PPV23 was given (**BII**).⁶⁶ A final dose of PPV23 is recommended after age 65 years, and should be given ≥5 years after any doses that were given before age 65 years (**BII**). Typically, no more than three doses of PPV23 are given in a lifetime.

PCV13 should also be given to patients with HIV who have already received PPV23 (**AII**).⁷⁶ However, in such cases, adult patients should wait ≥1 year after their most recent dose of PPV23 before receiving a single dose of PCV13 (**BIII**);³⁹ adolescents aged <19 years should wait ≥8 weeks (**BIII**). Subsequent doses of PPV23 should be given according to the schedule outlined above (i.e., ≥5 years between doses of PPV23 with no more than 3 lifetime doses).

Inactivated or recombinant influenza vaccine should be administered annually during influenza season to all individuals with HIV (**AII**).⁷⁷ This recommendation is pertinent to prevention of bacterial pneumonia, which can occur as a complication of influenza. Influenza and pneumococcal vaccines can be administered during the same visit. Use of live attenuated influenza vaccine is contraindicated and **is not recommended** in individuals with HIV (**AIII**).

Use of high-dose inactivated influenza vaccine is associated with decreased incidence of influenza and greater antibody response in adults without HIV aged ≥65 years.⁷⁸ One study found greater immunogenicity in individuals with HIV aged ≥18 years who were given high-dose influenza vaccine compared with standard-dose inactivated vaccine.⁷⁹ While providers can also give the high-dose influenza vaccine to their patients with HIV aged ≥65 years (**CIII**), there are no data on the efficacy of high-dose influenza vaccine in individuals with HIV. Currently, the high-dose vaccine is trivalent rather than quadrivalent, offering

protection against one rather than two Influenza B viruses and two Influenza A viruses.

The incidence of *H. influenzae* type b infection in adults with HIV is low. Therefore, *H. influenzae* type vaccine is not usually recommended for adult use **(BIII)**⁷⁵ unless a patient also has anatomic or functional asplenia.

Several factors are associated with a decreased risk of bacterial pneumonia in HIV, including use of ART and trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis.⁴⁷ In many studies, daily administration of TMP-SMX for PCP prophylaxis reduced the frequency of bacterial respiratory infections.^{9,80,81} This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of TMP-SMX (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, in the United States, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(AIII)**. Similarly, clarithromycin or azithromycin should not be prescribed solely for preventing bacterial respiratory infection **(AIII)**.

A decreased absolute neutrophil count (e.g., <500 cells/mm³) is associated with an increased risk of bacterial infections, including pneumonia, although this risk has been demonstrated primarily in persons with malignant neoplasms. To reduce the risk of such bacterial infections, clinicians should take steps to reverse neutropenia, such as by stopping myelosuppressive drugs **(CIII)**. Studies of granulocyte-colony stimulating factor in persons with HIV have failed to document benefit.^{82,83}

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes, using injection drugs, and consuming alcohol.^{9,68,84-86} Clinicians should encourage cessation of these behaviors, refer patients to appropriate services, and/or prescribe medications to support quitting. Data demonstrate that smoking cessation can decrease the risk of bacterial pneumonia.¹⁵

Treating Disease

General Approach to Treatment

The basic principles of antibiotic treatment of CAP are the same for patients with HIV as for those who do not have HIV.⁵⁷ As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should preferably be collected before antibiotic therapy is initiated or within 12 hours to 18 hours of antibiotic initiation. However, antibiotic therapy should be administered promptly, without waiting for the results of diagnostic testing. Empiric therapy varies based on geographic region and common pathogens in these regions, and should take into account local resistance patterns, results of MRSA rapid swab testing if done, and individual patient risk factors, including severity of immunocompromise (recent CD4 cell count, HIV viral load) and use of ART.

In patients with HIV, providers must also consider the risk of opportunistic lung infections, such as PCP, that would alter empiric treatment. In settings where the prevalence of TB is high, initiation of empiric therapy for both bacterial pneumonia and TB may be appropriate for patients in whom both diagnoses are strong considerations and after diagnostic studies are undertaken. Because respiratory fluoroquinolones are also active against *M. tuberculosis*, they should be used with caution in patients with suspected TB who are not being treated with concurrent standard four-drug TB therapy. Thus, patients with TB who are treated with fluoroquinolones in the absence of standard four-drug TB therapy may have an initial, but misleading response, that could delay diagnosis of TB and initiation of appropriate multidrug TB therapy, increasing the risk of drug-resistant TB and TB transmission.

Assessing Severity of Disease and Treatment Location

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. In addition to considerations regarding ability to take oral medications, adherence, and other confounding factors (e.g., housing, comorbid diseases), severity of illness is a key factor that helps to guide decisions regarding treatment location for CAP—outpatient versus inpatient, including intensive care unit

(ICU). Notably, no prospective randomized clinical trials have assessed the performance of the [Pneumonia Severity Index \(PSI\)](#) for CAP or other severity scores (e.g., the Infectious Diseases Society of America [IDSA]/American Thoracic Society [ATS] [ATS/IDSA] severity criteria⁵⁷ or [CURB-65 Score for Pneumonia Severity](#)) to guide decisions regarding inpatient or outpatient treatment location for persons with HIV. However, the PSI, CURB-65, the ATS/IDSA severity criteria, and other scoring systems appear to be valid for predicting mortality in patients with HIV with CAP, especially when used in combination with CD4 count.^{51,87,88} One study suggested that the site of care decision be dictated by considering the PSI score and CD4 count together.⁸⁷ Mortality was increased in patients with higher PSI risk class; however, even in those without an increased mortality risk by PSI, a CD4 count <200 cells/mm³ was associated with an increased risk of death.⁸⁷ This led to the suggestion to hospitalize CAP patients with CD4 counts <200 cells/mm³ and to use the PSI to help guide decision-making in those with higher CD4 counts.⁸⁹ However, other studies have found the PSI was predictive of outcomes independent of CD4 count.⁹⁰ Furthermore, CD4 count or HIV RNA level are not clearly associated with short-term outcomes of CAP.⁹¹ Other HIV-specific scoring systems such as the [Veterans Aging Cohort Study \(VACS\) Index](#), although originally designed to predict overall mortality, may also be useful in predicting ICU admission and mortality. In a study of older patients with and without HIV with CAP, a higher VACS Index was associated with greater 30-day mortality, readmission, and length of stay.⁹²

Therefore, in general, validated clinical prediction scores for prognosis can be used in patients with HIV in conjunction with clinical judgement to guide treatment location for CAP. Low risk patients for whom there are no other concerns regarding adherence or complicating factors can be treated as outpatients. Patients with severe CAP, including those presenting with shock or respiratory failure, usually require a higher level of care, typically ICU admission. Additionally, severe CAP criteria can include PSI risk class of III or IV or CURB-65 scores ≥ 3 . Patients with ≥ 3 of the ATS/IDSA minor severity criteria for CAP⁵⁷ often require ICU or higher level of care as well.

Empiric Antibiotic Therapy by Treatment Setting and Severity of Diseases

There is a general paucity of clinical trials evaluating different antibiotic regimens for treating CAP in populations with HIV and a lack of evidence that treatment response to antibiotics is different in individuals with HIV than in those without HIV. Therefore, treatment recommendations for CAP in individuals with HIV are generally consistent with those for persons without HIV.

Outpatient Community-Acquired Pneumonia Treatment

Individuals with HIV who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide (**AI**), or an oral respiratory fluoroquinolone (**AI**). Preferred beta-lactams are high-dose amoxicillin or amoxicillin-clavulanate; alternatives are cefpodoxime or cefuroxime. Preferred macrolides are azithromycin or clarithromycin. Preferred oral respiratory fluoroquinolones are moxifloxacin or levofloxacin. An oral respiratory fluoroquinolone (moxifloxacin or levofloxacin) should be used as an alternative to a beta lactam in patients who are allergic to penicillin. If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative (**BIII**) in addition to a beta-lactam.

Empirical monotherapy with a macrolide for outpatient CAP is not routinely recommended in patients with HIV for two reasons (**BIII**). First, increasing rates of pneumococcal resistance have been reported with macrolide-resistant rates up to 30%,⁹³ prompting concerns for possible treatment failure. In this regard, local drug resistance patterns, if available, can help inform treatment decisions. Second, patients who are already receiving a macrolide for MAC prophylaxis may have resistance due to chronic exposure and should also not receive macrolide monotherapy for empiric treatment of bacterial pneumonia. However, macrolides can be used as part of a combination CAP regimen.

Non-Severe Community-Acquired Pneumonia Inpatient Treatment

Individuals with HIV who are being treated as inpatients should receive an intravenous (IV) beta-lactam

plus a macrolide (**AI**) or an IV respiratory fluoroquinolone (**AI**). Monotherapy with a macrolide is not recommended in the inpatient setting. The role for dual therapy with a macrolide is somewhat controversial based on prior observational studies and two prospective clinical trials in patients without HIV with CAP that evaluated outcomes in those treated with beta-lactam monotherapy and those treated with dual-therapy including a macrolide.^{94,95} In one study, beta-lactam monotherapy was not found to be non-inferior to beta-lactam/macrolide combination therapy. Notably, in the monotherapy arm, patients who had more severe CAP, as indicated by a PSI \geq IV, or who had atypical pathogens were less likely to reach clinical stability. There were also more 30-day readmissions among the patients on monotherapy.⁹⁴ While there was a trend towards improved outcomes in those on dual therapy, the difference between arms was not statistically significant. In a pragmatic, cluster-randomized, cross-over trial of non-ICU hospitalized patients with CAP, beta-lactam monotherapy was found to be non-inferior to beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy.⁹⁵ However in this study, the diagnosis of CAP did not require radiographic confirmation, illness was mild, and there were cross-overs between groups. Only one study thus far has compared a cephalosporin (ceftriaxone) to dual therapy with a cephalosporin (ceftriaxone) plus macrolide in 225 persons with HIV with CAP, finding no difference between in-hospital or 14-day mortality between the groups; most patients had lower severity of disease, with only 7% of the cohort having a CURB-65 score >2 and 17% with a PSI risk class $>III$.⁹⁶ Given the heterogeneity and limitations of recent studies and scarce data in patients with HIV, the recommendation for patients with HIV who are hospitalized with non-severe CAP remains to administer either beta-lactam/macrolide combination therapy, or a single drug regimen of a respiratory fluoroquinolone (**AI**).

Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Preferred macrolides are azithromycin and clarithromycin. Preferred respiratory fluoroquinolones are moxifloxacin or levofloxacin. If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative (**BIII**) in addition to a beta-lactam. Clinical and Laboratory Standards Institute and Food and Drug Administration (FDA) changes in the penicillin breakpoints for treatment of non-meningitis pneumococcal disease imply IV penicillin is an acceptable option for treatment of pneumococcal disease in patients with HIV (**BIII**).⁹⁷ In patients who are allergic to penicillin, an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) alone should be used (**AI**). As noted, fluoroquinolone monotherapy should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy.

Severe Community-Acquired Pneumonia Treatment

Patients with severe CAP should not receive empiric monotherapy, even with a fluoroquinolone, because of the range of potential pathogens and the desirability of prompt and microbiologically active therapy (**AI**). In one study, the use of dual therapy (usually with a beta-lactam plus a macrolide) was associated with reduced mortality in patients with bacteremic pneumococcal pneumonia, including those admitted to the ICU.⁹⁸ Patients with severe pneumonia should be treated with an IV beta-lactam plus either IV azithromycin (**AI**) or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) (**AI**). Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. In patients who are allergic to penicillin, aztreonam plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used (**BIII**).

Most CAP pathogens can be treated adequately with recommended empiric regimens. The increased incidence of *P. aeruginosa* and *S. aureus* (including community-acquired MRSA) as causes of CAP are exceptions. Both pathogens occur in specific epidemiologic patterns with distinct clinical presentations for which empiric antibiotic coverage may be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empiric treatment if results are negative.

The addition of corticosteroids for treating CAP has not been studied in individuals with HIV. Data from studies in persons without HIV with CAP suggest that corticosteroids may decrease a composite outcome of mortality, time to clinical stability, and length of hospital stay,⁹⁹ except in influenza pneumonia, where corticosteroids increase mortality.¹⁰⁰ The optimal regimen including dose, duration, and formulation of

corticosteroid, and the patient population with bacterial non-influenza related CAP most likely to benefit from the additional use of corticosteroids remain uncertain. Selecting patients without HIV with severe CAP and increased inflammation as defined by C-reactive protein levels >150 mg/mL is one strategy for treatment of CAP that has been shown to be beneficial.¹⁰¹ Overall, the use of corticosteroids in patients with HIV with severe CAP is not routinely recommended (**CIII**) given the lack of data specifically in populations with HIV. If providers administer corticosteroids to patients with HIV with severe CAP, they must ensure that no other contraindications to steroids exist; in patients who have no contraindications and have persistent shock despite fluid resuscitation, following Surviving Sepsis Guidelines¹⁰² and administering hydrocortisone 200 mg IV daily for 3 to 7 days (or tapering once vasopressors are no longer needed) is reasonable (**CIII**).

Empiric Pseudomonas aeruginosa Treatment

If risk factors for *Pseudomonas* infection are present, an antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (750-mg dose) should be used (**AI**). Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Alternative therapeutic agents that are recommended are an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin (**BII**) or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (**BII**). In patients who are allergic to penicillin, aztreonam is recommended to be used in place of the beta-lactam (**BII**).

Empiric Staphylococcus aureus Treatment

A nasal swab for MRSA can help inform decision-making whether initial empiric coverage should include MRSA. In studies of patients without HIV, negative test results have a high negative predictive value for pneumonia due to MRSA. If the nasal swab is negative for MRSA and the pneumonia is not severe and no other risk factors or features suggestive of MRSA pneumonia are present, empiric coverage for MRSA may be withheld (**BII**).⁵⁸

However, in patients who have risk factors for *S. aureus* infection, vancomycin or linezolid should be added to the antibiotic regimen (**AII**). Empiric coverage for MRSA should also be added if a rapid nasal swab is positive for MRSA, although the positive predictive value for pneumonia is only moderate, and therapy should be de-escalated if cultures are negative (**BIII**). Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) or the use of linezolid alone, is recommended by many experts if severe necrotizing pneumonia is present to minimize bacterial toxin production (**CII**).

Telavancin is an alternative agent that can be used for *S. aureus* pneumonia (**BIII**); it is currently FDA-approved for treatment of hospital-acquired and ventilator-associated (rather than community-acquired) pneumonia based on studies in persons without HIV infection.¹⁰³ While ceftaroline has activity against MRSA, and data suggest it can be effective for MRSA pneumonia, it has been FDA approved for treatment of community-acquired bacterial pneumonia based on two studies that did not include any MRSA isolates.¹⁰⁴ Neither telavancin or ceftaroline have been specifically studied in patients with HIV with bacterial pneumonia. Daptomycin should not be used to treat pneumonia as it is not active in the lung (**AI**).

Pathogen-Directed Therapy

When the etiology of the pneumonia has been identified based on reliable microbiological methods, antimicrobial therapy should be modified and directed at the identified pathogen (**BIII**).

Switch from Intravenous to Oral Therapy

A switch to oral therapy should be considered in patients with CAP on IV antibiotic therapy who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function. Suggested criteria for clinical stability include oral temperature <37.8°C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure ≥90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood >60 mm Hg (**BII**).⁵⁷ A longer duration of IV and overall

antibiotic therapy is often necessary in patients who have severe CAP or who have bacteremia, particularly if due to *S. pneumoniae* or *S. aureus* and complicated infection is present.

Special Considerations Regarding When to Start Antiretroviral Therapy

In patients with bacterial pneumonia who are not already on ART, ART should be initiated promptly (i.e., within 2 weeks of initiating therapy for the pneumonia) unless comorbidities make ART unwise (**AI**).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

The clinical response to appropriate antimicrobial therapy for CAP is similar in patients with and without HIV.^{36,50} A clinical response (i.e., reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) typically is observed within 48 to 72 hours after initiation of appropriate antimicrobial therapy. A review of patients with CAP found that advanced HIV infection and CD4 count <100 cells/mm³ were predictors for longer time to clinical stability (i.e., >7 days) and that patients who received ART tended to become clinically stable sooner and had better outcomes.^{89,92} The presence of bacteremia is a significant factor that impacts outcomes. Among those with pneumococcal pneumonia, longer time to clinical stability is more often seen in the setting of bacteremia. As in patients without HIV, radiographic improvement usually lags behind clinical improvement.

Immune reconstitution inflammatory syndrome (IRIS) has been rarely described in association with bacterial CAP and initiation of treatment with ART in patients with HIV. This could be secondary to a number of reasons:

- Patients with recurrent pneumonia have not been included in the study population;
- IRIS among participants with bacterial pneumonia has not been specified, *or*
- This complication has truly not been observed.^{2,105}

Only case reports describe IRIS with pneumonia due to *Rhodococcus equii*. More commonly IRIS occurs with pneumonia due to *Pneumocystis* and mycobacterial infections.

Managing Treatment Failure

Patients who do not respond to appropriate antimicrobial therapy should undergo further evaluation to search for complications secondary to pneumonia (empyema, abscess formation, metastatic infection), other infectious process, and/or noninfectious causes of pulmonary dysfunction (pulmonary embolus, COPD).

Preventing Recurrence

Patients with HIV should receive pneumococcal (**AI**) and influenza vaccines (**AII**) as recommended. Antibiotic chemoprophylaxis generally is not recommended specifically to prevent recurrences of bacterial respiratory infections because of the potential for development of drug-resistant microorganisms and drug toxicity (**AI**). Smoking cessation reduces the risk of bacterial pneumonia by approximately 27%,¹⁰⁶ and patients who smoke tobacco should be encouraged to quit and provided with the appropriate tools and referrals whenever possible (**AI**). Likewise, patients with substance use disorders (alcohol, injection or non-injection drugs) should be referred for appropriate counseling and services (**AI**). However, likely the most important intervention for prevention of bacterial pneumonia (first episode or recurrence) is initiation and adherence to ART, which is beneficial even among those with high CD4 count at time of ART initiation.⁴ Thus prompt initiation or re-initiation of ART is recommended for all patients with HIV with bacterial pneumonia (**AI**).

Special Considerations During Pregnancy

The diagnosis of bacterial respiratory tract infections in pregnant women is the same as in those who are not pregnant, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory tract infections should be managed in pregnant women as in women who are not pregnant, with certain

exceptions. Among macrolides, clarithromycin **is not recommended** because of an increased risk of birth defects seen in some animal studies. Two studies, each involving ≥ 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk of spontaneous abortion was noted in one study.^{107,108} Azithromycin did not produce birth defects in animal studies, but experience with human use in the first trimester is limited. Azithromycin is recommended when a macrolide is indicated in pregnancy (**BIII**). Arthropathy has been noted in immature animals with *in utero* exposure to quinolones. Studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.^{109,110} When indicated, quinolones can be used in pregnancy for serious respiratory infections only when a safer alternative is not available (**CIII**).¹¹¹

Doxycycline **is not recommended** for use during pregnancy because of increased hepatotoxicity and staining of fetal teeth and bones. Beta-lactam antibiotics have not been associated with teratogenicity or increased toxicity in pregnancy. Clindamycin use in pregnancy has not been associated with an increased risk of birth defects or adverse outcomes.¹¹² Aminoglycosides can be used as needed. A theoretical risk of fetal renal or eighth nerve damage exists with aminoglycoside exposure during pregnancy, but this finding has not been documented in humans, except with streptomycin (10% risk) and kanamycin (2% risk). Animal reproductive toxicity studies in rats and rabbits were negative for vancomycin, but data on first trimester exposure in humans are limited.¹¹³ A study of neonates after *in utero* exposure did not find evidence of renal or ototoxicity.¹¹⁴ Reproductive toxicity studies of telavancin in animals have shown increased rates of limb malformations in rats, rabbits, and mini pigs at doses similar to human exposure; no human data are available.¹¹³ Use of telavancin should be avoided in the first trimester if alternate agents with more experience in use in pregnancy are available. Cases of exposure to telavancin in pregnancy should be reported to the Telavancin Pregnancy Registry at 1-855-633-8479. Experience with linezolid in human pregnancy has been limited, but it was not teratogenic in mice, rats, and rabbits.

Pneumonia during pregnancy is associated with increased rates of preterm labor and delivery. Pregnant women with pneumonia after 20 weeks' gestation should be monitored for evidence of contractions (**BII**). Pneumococcal vaccine can be administered during pregnancy (**AIII**), using PPV23 for adults who have the above indications for PPV23. Although the vaccine's safety during the first trimester has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. No data are available to guide recommendations on the use of PCV13 during pregnancy but trial results are expected soon (NCT02717494).

Inactivated influenza vaccine is recommended for all pregnant women during influenza season (**AIII**). Live attenuated influenza vaccine should not be used in persons with HIV (**AIII**). Because administration of vaccines can be associated with a transient rise in plasma HIV RNA levels, vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk of perinatal transmission of HIV.

Preventing *Streptococcus pneumoniae* Infections

Indications for Pneumococcal Vaccination:

- All persons with HIV regardless of CD4 count **(AI)**

Vaccination Recommendations

For Individuals Who Have Not Received Any Pneumococcal Vaccination

Preferred Vaccination:

- One dose of PCV13 **(AI)**, followed by:
- CD4 count ≥ 200 cells/mm³: Administer PPV23 ≥ 8 weeks later **(AI)**; *or*
- CD4 count < 200 cells/mm³: PPV23 can be offered ≥ 8 weeks after receipt of PCV13 **(CIII)** or can await until CD4 count increases to > 200 cells/mm³ on ART **(BIII)**.

For Individuals Who Have Previously Received PPV23:

- One dose of PCV13 should be given to patients who have already received PPV23 **(AII)**.
- Adults (aged ≥ 19 years) should wait ≥ 1 year and adolescents (aged < 19 years) should wait ≥ 8 weeks after their most recent dose of PPV23 before receiving a single dose of PCV13 **(BIII)**.

Re-Vaccination of PPV23:

- A dose of PPV23 is recommended for individuals aged 19 through 64 years if ≥ 5 years have elapsed since their first dose of PPV **(BII)**.
- A final dose of PPV23 is recommended for individuals aged ≥ 65 years, after ≥ 5 years have elapsed since their previous PPV23 dose **(BII)**.
- Typically, no more than 3 doses of PPV23 are given in a lifetime.

Vaccine Dosing:

- PCV13: 0.5 mL IM
- PPV23: 0.5 mL IM

Preventing Influenza and Bacterial Pneumonia as a Complication of Influenza

Indication for Influenza Vaccination:

- All persons with HIV infection during influenza season **(AII)**

Vaccination:

- Inactivated, standard dose or recombinant influenza vaccine per recommendation of the season **(AII)**; *or*
- High-dose inactivated influenza vaccine may be given to individuals aged ≥ 65 years **(CIII)**.

Note: Live attenuated influenza vaccine is **contraindicated** in persons with HIV **(AIII)**.

Treating Community-Acquired Bacterial Pneumonia

Note: Empiric antimicrobial therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed below are suggested empiric therapy. The regimen should be modified as needed once microbiologic and drug susceptibility results are available. Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy.

Empiric Outpatient Therapy (Oral)

Preferred Therapy:

- An oral beta-lactam plus a macrolide (azithromycin or clarithromycin) **(AI)**

Preferred Beta-Lactams:

- High-dose amoxicillin or amoxicillin/clavulanate

Alternative Beta-Lactams:

- Cefpodoxime or cefuroxime, *or*
- A respiratory fluoroquinolone (levofloxacin or moxifloxacin)^a **(AI)**, especially for patients with penicillin allergies

Treating Community-Acquired Bacterial Pneumonia, continued

Alternative Therapy:

- A beta-lactam plus doxycycline (**BIII**)

Empiric Therapy for Hospitalized Patients with Non-Severe CAP

Preferred Therapy:

- An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) (**AI**)

Preferred Beta-Lactams:

- Ceftriaxone, cefotaxime, or ampicillin-sulbactam, *or*
- An IV respiratory fluoroquinolone (levofloxacin or moxifloxacin)^a (**AI**), especially for patients with penicillin allergies.

Alternative Therapy:

- An IV beta-lactam plus doxycycline (**BIII**)
- IV penicillin may be used for confirmed pneumococcal pneumonia (**BIII**)

Empiric Therapy for Patients with Severe CAP

Preferred Therapy:

- An IV beta-lactam plus IV azithromycin (**AI**), *or*
- An IV beta-lactam plus an IV respiratory fluoroquinolone (levofloxacin or moxifloxacin)^a (**AI**)

Preferred Beta-Lactams:

- Ceftriaxone, cefotaxime, or ampicillin-sulbactam

Alternative Therapy:

For Penicillin-Allergic Patients:

- Aztreonam (IV) plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin)^a (**BIII**)

Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia

Preferred Therapy:

- An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin IV or levofloxacin IV 750 mg/day) (**AI**)

Preferred Beta-Lactams:

- Piperacillin-tazobactam, cefepime, imipenem, or meropenem

Alternative Therapy:

- An IV antipneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus IV azithromycin (**BII**), *or*
- An IV antipneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus an IV antipneumococcal fluoroquinolone (moxifloxacin or levofloxacin) (**BII**)

For Penicillin-Allergic Patients:

- Replace the beta-lactam with aztreonam (**BII**)

Empiric Therapy for Patients at Risk of MRSA Pneumonia

Preferred Therapy:

- A nasal swab for MRSA can help inform decision of initial coverage for MRSA (see text for discussion).
- Vancomycin IV or linezolid (IV or PO) should be added to the baseline regimen (**AI**).
- Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) may be considered for severe necrotizing pneumonia to minimize bacterial toxin production (**CII**).

Recommendations for Preventing and Treating Community-Acquired Pneumonia (page 3 of 3)

Duration of Therapy:

- For most patients, 5-7 days. The patient should be afebrile for 48–72 hours and should be clinically stable before discontinuation of therapy.
- Longer duration of antibiotics is often required when severe CAP or bacteremia is present, and particularly if due to *S. pneumoniae* or complicated *S. aureus* infection.

Switch from IV to PO Therapy:

- A switch should be considered for patients who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function (**BIII**).

Other Considerations:

- Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance (up to 30%) (**BIII**), and patients receiving a macrolide for MAC prophylaxis may have resistance due to chronic exposure (**BIII**).
- Fluoroquinolones should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy (**BIII**).
- Once the pathogen has been identified by reliable microbiologic methods, antibiotic therapy should be modified to target the pathogen (**BIII**).
- If drug-resistant pathogens have not been identified by reliable microbiologic methods, antibiotic therapy can be de-escalated to cover routine causes of CAP (**BIII**).
- Antibiotics chemoprophylaxis is generally not recommended because of the potential for development of drug resistance microorganisms and drug toxicities (**AI**).

^a Respiratory fluoroquinolones (e.g., levofloxacin, moxifloxacin) are also active against *Mycobacterium tuberculosis*. In patients with undiagnosed TB, fluoroquinolones may alter response to therapy, delay TB diagnosis, and increase the risk of drug resistance. These drugs should be used with caution in patients in whom TB is suspected but who are not receiving a standard four-drug TB regimen.

Key: ART = antiretroviral therapy; CAP = community-acquired pneumonia; CD4 = CD4 T lymphocyte cell; IM = intramuscular; IV = intravenous; MAC = *Mycobacterium avium* complex; MRSA = methicillin-resistant *Staphylococcus aureus*; PCP = *Pneumocystis pneumonia*; PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; PO = orally; PPV23 = 23-Valent Pneumococcal Polysaccharide Vaccine; TB = tuberculosis

References

1. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997;155(1):72-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9001292>.
2. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19440326>.
3. Mussini C, Galli L, Lepri AC, et al. Incidence, timing, and determinants of bacterial pneumonia among HIV-infected patients: data from the ICONA Foundation Cohort. *J Acquir Immune Defic Syndr*. 2013;63(3):339-345. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23591636>.
4. O'Connor J, Vjecha MJ, Phillips AN, 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;4(3):e105-e112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28063815>.
5. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. *MMWR CDC Surveill Summ*. 1999;48(2):1-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12412613>.
6. Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med*. 2000;162(1):64-67. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10903221>.
7. Serraino D, Puro V, Boumis E, et al. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. *AIDS*. 2003;17(14):2109-2116. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14502014>.
8. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-

infected persons in the United States and Canada, 2000-2010. *J Infect Dis.* 2016;214(6):862-872. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27559122>.

9. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med.* 1995;333(13):845-851. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7651475>.
10. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis.* 2008;47(10):1345-1353. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18834317>.
11. Aston SJ, Ho A, Jary H, et al. Aetiology and risk factors for mortality in an adult Community-acquired pneumonia cohort in Malawi. *Am J Respir Crit Care Med.* 2019;200(3):359-369. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30625278>.
12. Jambo KC, Banda DH, Kankwatira AM, et al. Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. *Mucosal Immunol.* 2014;7(5):1116-1126. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24472847>.
13. Charles TP, Shellito JE. Human immunodeficiency virus infection and host defense in the lungs. *Semin Respir Crit Care Med.* 2016;37(2):147-156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26974294>.
14. Gordin FM, Roediger MP, Girard PM, et al. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med.* 2008;178(6):630-636. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18617640>.
15. Benard A, Mercie P, Alioum A, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. *PLoS One.* 2010;5(1):e8896. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20126646>.
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;45(6):801-809. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28660356>.
17. Attia EF, McGinnis KA, Feemster LC, et al. Association of COPD with risk for pulmonary infections requiring hospitalization in HIV-infected veterans. *J Acquir Immune Defic Syndr.* 2015;70(3):280-288. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26181820>.
18. Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med.* 1986;104(1):38-41. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3484420>.
19. Burack JH, Hahn JA, Saint-Maurice D, Jacobson MA. Microbiology of community-acquired bacterial pneumonia in persons with and at risk for human immunodeficiency virus type 1 infection. Implications for rational empiric antibiotic therapy. *Arch Intern Med.* 1994;154(22):2589-2596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7979856>.
20. Miller RF, Foley NM, Kessel D, Jeffrey AA. Community acquired lobar pneumonia in patients with HIV infection and AIDS. *Thorax.* 1994;49(4):367-368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8202910>.
21. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med.* 1995;152(4 Pt 1):1309-1315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7551387>.
22. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection: the Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. *Chest.* 2000;117(4):1017-1022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10767233>.
23. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. *J Infect Dis.* 2001;184(3):268-277. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11443551>.
24. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS.* 2002;16(1):85-95. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11741166>.
25. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *Chest.* 2010;138(1):130-136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20173050>.
26. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza Other Respir Viruses.* 2016;10(5):394-403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27232677>.
27. Tarp B, Jensen JS, Ostergaard L, Andersen PL. Search for agents causing atypical pneumonia in HIV-positive patients

- by inhibitor-controlled PCR assays. *Eur Respir J*. 1999;13(1):175-179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10836344>.
28. 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;96(4):e5778. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28121925>.
 29. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415-427. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26172429>.
 30. Levine SJ, White DA, Fels AO. The incidence and significance of Staphylococcus aureus in respiratory cultures from patients infected with the human immunodeficiency virus. *Am Rev Respir Dis*. 1990;141(1):89-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2297190>.
 31. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med*. 2008;168(20):2205-2210. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19001196>.
 32. Everett CK, Subramanian A, Jarisberg LG, Fei M, Huang L. Characteristics of drug-susceptible and drug-resistant Staphylococcus aureus pneumonia in patients with HIV. *Epidemiology (Sunnyvale)*. 2013;3(1). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25346868>.
 33. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant Staphylococcus aureus clone USA300 in men who have sex with men. *Ann Intern Med*. 2008;148(4):249-257. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18283202>.
 34. Popovich KJ, Hota B, Aroutcheva A, et al. Community-associated methicillin-resistant Staphylococcus aureus colonization burden in HIV-infected patients. *Clin Infect Dis*. 2013;56(8):1067-1074. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23325428>.
 35. Zervou FN, Zacharioudakis IM, Ziakas PD, Rich JD, Mylonakis E. Prevalence of and risk factors for methicillin-resistant Staphylococcus aureus colonization in HIV infection: a meta-analysis. *Clin Infect Dis*. 2014;59(9):1302-1311. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25031291>.
 36. Cilloniz C, Torres A, Manzardo C, et al. Community-acquired pneumococcal pneumonia in virologically suppressed HIV-infected adult patients: a matched case-control study. *Chest*. 2017;152(2):295-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28302496>.
 37. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of Pneumocystis carinii pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. 1998;12(8):885-893. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9631142>.
 38. Bordon JM, Fernandez-Botran R, Wiemken TL, et al. Bacteremic pneumococcal pneumonia: clinical outcomes and preliminary results of inflammatory response. *Infection*. 2015;43(6):729-738. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26424683>.
 39. Centers for Disease C, Prevention. 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;61(40):816-819. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23051612>.
 40. Feikin DR, Jagero G, Aura B, et al. High rate of pneumococcal bacteremia in a prospective cohort of older children and adults in an area of high HIV prevalence in rural western Kenya. *BMC Infect Dis*. 2010;10:186. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20573224>.
 41. Heffernan RT, Barrett NL, Gallagher KM, 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;191(12):2038-2045. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15897989>.
 42. Grau I, Pallares R, Tubau F, 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;165(13):1533-1540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16009870>.
 43. Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med*. 2006;144(1):1-9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16389249>.
 44. Cohen AL, Harrison LH, Farley MM, et al. Prevention of invasive pneumococcal disease among HIV-infected adults in the era of childhood pneumococcal immunization. *AIDS*. 2010;24(14):2253-2262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20671543>.

45. Burgos J, Penaranda M, Payeras A, et al. Invasive pneumococcal disease in HIV-infected adults: clinical changes after the introduction of the pneumococcal conjugate vaccine in children. *J Acquir Immune Defic Syndr*. 2012;59(1):31-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22156821>.
46. Osmond DH, Chin DP, Glassroth J, et al. Impact of bacterial pneumonia and *Pneumocystis carinii* pneumonia on human immunodeficiency virus disease progression. Pulmonary Complications of HIV Study Group. *Clin Infect Dis*. 1999;29(3):536-543. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10530443>.
47. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. 2006;43(1):90-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16758423>.
48. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. 2010;14(1):e22-27. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19586789>.
49. Sanders KM, Marras TK, Chan CK. Pneumonia severity index in the immunocompromised. *Can Respir J*. 2006;13(2):89-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16550266>.
50. Christensen D, Feldman C, Rossi P, 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*. 2005;41(4):554-556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16028168>.
51. Cordero E, Pachon J, Rivero A, et al. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. *Am J Respir Crit Care Med*. 2000;162(6):2063-2068. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11112115>.
52. Sogaard OS, Lohse N, Gerstoft J, et al. Mortality after hospitalization for pneumonia among individuals with HIV, 1995-2008: a Danish cohort study. *PLoS One*. 2009;4(9):e7022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19750011>.
53. Marcus JL, Leyden WA, Chao CR, et al. Immunodeficiency, AIDS-related pneumonia, and risk of lung cancer among HIV-infected individuals. *AIDS*. 2017;31(7):989-993. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28252529>.
54. Sigel K, Wisnivesky J, Crothers K, et al. Immunological and infectious risk factors for lung cancer in US veterans with HIV: a longitudinal cohort study. *Lancet HIV*. 2017;4(2):e67-e73. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27916584>.
55. Morris AM, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 2000;162(2 Pt 1):612-616. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10934095>.
56. Nyamande K, Lalloo UG. Serum procalcitonin distinguishes CAP due to bacteria, *Mycobacterium tuberculosis* and PJP. *Int J Tuberc Lung Dis*. 2006;10(5):510-515. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16704032>.
57. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44 Suppl 2:S27-72. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17278083>.
58. Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The clinical utility of methicillin-resistant staphylococcus aureus (MRSA) nasal screening to rule out MRSA pneumonia: a diagnostic meta-analysis with antimicrobial stewardship implications. *Clin Infect Dis*. 2018;67(1):1-7. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29340593>.
59. Cordero E, Pachon J, Rivero A, et al. Usefulness of sputum culture for diagnosis of bacterial pneumonia in HIV-infected patients. *Eur J Clin Microbiol Infect Dis*. 2002;21(5):362-367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12072920>.
60. Jordano Q, Falco V, Almirante B, et al. Invasive pneumococcal disease in patients infected with HIV: still a threat in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2004;38(11):1623-1628. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15156452>.
61. Hamel MJ, Greene C, Chiller T, et al. Does cotrimoxazole prophylaxis for the prevention of HIV-associated opportunistic infections select for resistant pathogens in Kenyan adults? *Am J Trop Med Hyg*. 2008;79(3):320-330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18784222>.
62. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. *J Infect Dis*. 2001;183(9):1409-1412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11294675>.
63. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency

- virus-infected patients. *J Infect Dis.* 1996;173(4):857-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8603963>.
64. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS.* 1999;13(14):1971-1975. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10513657>.
 65. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med.* 2000;160(17):2633-2638. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10999977>.
 66. Advisory Committee on Immunization P. Recommended adult immunization schedule: United States, October 2007-September 2008. *Ann Intern Med.* 2007;147(10):725-729. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17947396>.
 67. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH, Chang SC. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. *Vaccine.* 2004;22(15-16):2006-2012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15121313>.
 68. Rodriguez-Barradas MC, Goulet J, Brown S, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. *Clin Infect Dis.* 2008;46(7):1093-1100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18444830>.
 69. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet.* 2000;355(9221):2106-2111. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10902624>.
 70. Watera C, Nakiyingi J, Miiro G, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS.* 2004;18(8):1210-1213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15166540>.
 71. Pedersen RH, Lohse N, Ostergaard L, Sogaard OS. The effectiveness of pneumococcal polysaccharide vaccination in HIV-infected adults: a systematic review. *HIV Med.* 2011;12(6):323-333. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21059168>.
 72. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med.* 2010;362(9):812-822. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20200385>.
 73. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis.* 2007;45(7):e82-87. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17806042>.
 74. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998--2003. *Vaccine.* 2008;26(46):5830-5834. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18786586>.
 75. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis.* 2014;58(3):309-318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24421306>.
 76. Glesby MJ, Watson W, Brinson C, et al. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in HIV-infected adults previously vaccinated with pneumococcal polysaccharide vaccine. *J Infect Dis.* 2015;212(1):18-27. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25395187>.
 77. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep.* 2010;59(RR-8):1-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20689501>.
 78. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med.* 2014;371(7):635-645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25119609>.
 79. McKittrick N, Frank I, Jacobson JM, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons: a single-center, parallel, randomized trial. *Ann Intern Med.* 2013;158(1):19-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23277897>.
 80. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet.* 1999;353(9163):1463-1468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10232311>.
 81. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized

- pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. *N Engl J Med*. 1992;327(26):1842-1848. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1448121>.
82. Angel JB, High K, Rhame F, et al. Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. Leukine/HIV Study Group. *AIDS*. 2000;14(4):387-395. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10770541>.
 83. Keiser P, Rademacher S, Smith JW, Skiest D, Vadde V. Granulocyte colony-stimulating factor use is associated with decreased bacteremia and increased survival in neutropenic HIV-infected patients. *Am J Med*. 1998;104(1):48-55. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9528719>.
 84. Crothers K, Griffith TA, McGinnis KA, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *J Gen Intern Med*. 2005;20(12):1142-1145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16423106>.
 85. Navin TR, Rimland D, Lennox JL, et al. Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. *J Infect Dis*. 2000;181(1):158-164. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10608762>.
 86. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: A comparison of disease measurement strategies. *Med Care*. 2006;44(8 Suppl 2):S52-60. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16849969>.
 87. Curran A, Falco V, Crespo M, 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;9(8):609-615. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18557951>.
 88. 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;27(11):998-1004. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26394997>.
 89. Madeddu G, Laura Fiori M, Stella Mura M. Bacterial community-acquired pneumonia in HIV-infected patients. *Curr Opin Pulm Med*. 2010;16(3):201-207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20154625>.
 90. Chew KW, Yen IH, Li JZ, Winston LG. Predictors of pneumonia severity in HIV-infected adults admitted to an Urban public hospital. *AIDS Patient Care STDS*. 2011;25(5):273-277. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21488749>.
 91. Bordon J, Kapoor R, Martinez C, 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*. 2011;15(12):e822-827. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21885316>.
 92. Barakat LA, Juthani-Mehta M, Allore H, et al. Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia. *HIV Med*. 2015;16(7):421-430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25959543>.
 93. Centers for Disease C, Prevention. *Streptococcus pneumoniae*, 2016. 2018. Available at: <https://www.cdc.gov/abcs/reports-findings/survreports/spneu16.pdf>.
 94. Garin N, Genne D, Carballo S, et al. beta-Lactam monotherapy vs. beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med*. 2014;174(12):1894-1901. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25286173>.
 95. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med*. 2015;372(14):1312-1323. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25830421>.
 96. 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*. 2018;24(2):146-151. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28648859>.
 97. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus *Streptococcus pneumoniae*: coping with antimicrobial susceptibility in an era of resistance. *Clin Infect Dis*. 2009;48(11):1596-1600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19400744>.
 98. Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med*. 2004;170(4):440-444. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15184200>.
 99. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-

acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med.* 2015;163(7):519-528. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26258555>.

100. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care.* 2019;23(1):99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30917856>.
101. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA.* 2015;313(7):677-686. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25688779>.
102. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* 2017;43(3):304-377. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28101605>.
103. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. *Clin Infect Dis.* 2011;52(1):31-40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21148517>.
104. File TM, Jr., Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, double-blinded, multicenter Phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis.* 2010;51(12):1395-1405. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21067350>.
105. Novak RM, Richardson JT, Buchacz K, et al. Immune reconstitution inflammatory syndrome: incidence and implications for mortality. *AIDS.* 2012;26(6):721-730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22233655>.
106. De P, Farley A, Lindson N, Aveyard P. Systematic review and meta-analysis: influence of smoking cessation on incidence of pneumonia in HIV. *BMC Med.* 2013;11:15. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23339513>.
107. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *Am J Perinatol.* 1998;15(9):523-525. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9890248>.
108. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiol Drug Saf.* 2000;9(7):549-556. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11338912>.
109. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol.* 1996;69(2):83-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8902438>.
110. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother.* 1998;42(6):1336-1339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9624471>.
111. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol.* 2006;107(5):1120-1138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16648419>.
112. McCormack WM, Rosner B, Lee YH, Munoz A, Charles D, Kass EH. Effect on birth weight of erythromycin treatment of pregnant women. *Obstet Gynecol.* 1987;69(2):202-207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3543767>.
113. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A review of antibiotic use in pregnancy. *Pharmacotherapy.* 2015;35(11):1052-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26598097>.
114. Reyes MP, Ostrea EM, Jr., Cabinian AE, Schmitt C, Rintelmann W. Vancomycin during pregnancy: does it cause hearing loss or nephrotoxicity in the infant? *Am J Obstet Gynecol.* 1989;161(4):977-981. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2801848>.