



## **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 12/21/2016

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

# Bacterial Respiratory Disease (Last updated May 7, 2013; last reviewed May 7, 2013)

---

## Epidemiology

Bacterial respiratory diseases; including sinusitis, bronchitis, otitis, and pneumonia; are among the most common infectious complications in patients with HIV infection, occurring with increased frequency at all CD4 T lymphocyte cell (CD4) counts,<sup>1</sup> and some data suggest that bacterial pneumonia may occur with increased severity in this population. This chapter will focus on the diagnosis, prevention, and management of bacterial pneumonia in HIV-infected patients.

Bacterial pneumonia is a common cause of HIV-associated morbidity and recurrent pneumonia (2 or more episodes within a 1-year period) is an AIDS-defining condition. The incidence of bacterial pneumonia is higher in HIV-infected individuals than in those who are not HIV infected.<sup>2</sup> More recently, the incidence of bacterial pneumonia in HIV-infected individuals has declined. In one study, the incidence of bacterial pneumonia declined from 22.7 episodes per 100 person-years in the era before combination antiretroviral therapy (ART) to 9.1 episodes per 100 person-years by 1997.<sup>3-5</sup>

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. The high rates of bacterial pneumonia in HIV-infected individuals probably result from multiple factors, including qualitative B-cell defects that impair ability to produce pathogen-specific antibody; impaired neutrophil function or numbers, or both; and factors, such as injection drug use, that are associated with underlying HIV infection. Risk factors associated with an increased risk of bacterial pneumonia include low CD4 count ( $< 200$  cells/mm<sup>3</sup>), no or intermittent use of ART, cigarette smoking, injection drug use, and chronic viral hepatitis.

In HIV-infected individuals, as in those who are not HIV infected, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia.<sup>6-12</sup> Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia* species have been reported as infrequent causes of community-acquired bacterial pneumonia in HIV-infected individuals.<sup>9,13</sup>

The frequency of *Pseudomonas aeruginosa* and *Staphylococcus aureus* as community-acquired pathogens is higher in HIV-infected individuals than in those not HIV infected.<sup>10,14</sup> Methicillin-resistant *Staphylococcus aureus* (MRSA) infection, in particular, should be considered as a potential etiology for pneumonia, given that community outbreaks of MRSA have been seen in men who have sex with men and nasal carriage of MRSA is more common in HIV-infected individuals, particularly at lower CD4 cell counts.<sup>15</sup> Also, community-acquired MRSA pneumonia may not invariably be associated with preceding influenza illness.<sup>16</sup>

In HIV-infected patients, particularly those infected with *S. pneumoniae*, incidence of bacteremia accompanying pneumonia is increased compared with that in individuals who are not HIV infected. In one study, the estimated rate of pneumococcal bacteremia in patients with AIDS (1,094 cases per 100,000) was ~55 times that in HIV-uninfected individuals (20 cases per 100,000). This disparity narrowed but was not eliminated after the introduction of ART.<sup>17</sup> Other studies have highlighted the declining incidence of pneumococcal bacteremia in the era of ART.<sup>18</sup>

Bacterial pneumonia is associated with increased mortality in HIV-infected individuals.<sup>10,19,20</sup> In HIV-infected individuals with community-acquired bacterial pneumonia, a prospective, multicenter study documented CD4 count  $< 100$  cells/mm<sup>3</sup>, radiographic progression of disease, and presence of shock as independent predictors of increased mortality.<sup>21</sup> In that study, multilobar infiltrates, cavitary infiltrates, and pleural effusion on baseline radiograph all were independent predictors of radiographic progression of disease.

## Clinical Manifestations

Clinical and radiographic presentation of bacterial pneumonia in HIV-infected individuals is similar to that in those who are not HIV infected. Patients with pneumonias 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.<sup>22</sup> They are often febrile and the presence of fever, tachycardia, or hypotension can be an indicator of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia and clinicians should strongly consider hospitalizing such patients.

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 in those with advanced HIV. 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 presence of cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*.

Disease severity and arterial oxygenation should be assessed in all patients with pneumonia. Noninvasive measurement of arterial oxygen saturation via pulse oximetry is an appropriate screening test. Arterial blood gas analysis is indicated for those with evidence of hypoxemia suggested by noninvasive assessment and for patients who have tachypnea and/or respiratory distress. Criteria developed to assess disease severity in HIV-uninfected persons, such as the Pneumonia Severity Index (PSI) (<http://pda.ahrq.gov/clinic/psi/psicalc.asp>) appear to be valid for HIV-infected patients, especially when used in combination with CD4 count<sup>21,23</sup> (discussed in further detail in [Treating Disease](#)).

## Diagnosis

Guidelines for diagnosing and managing community-acquired pneumonia (CAP) in individuals who are not HIV infected also apply to those who are infected.<sup>24</sup> Patients with clinical symptoms and signs suggestive of CAP should have posteroanterior and lateral chest radiographs, if possible. If previous radiographs are available, they should be reviewed to assess for presence of new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate.

Given the increased incidence of *Mycobacterium tuberculosis* in HIV-infected individuals, a tuberculosis (TB) diagnosis should always be considered in HIV-infected patients who have pneumonia. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (that is, with respiratory isolation if hospitalized), and two to three sputum specimens should be obtained for acid fast bacilli evaluation. 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.

Often, the differential diagnosis of pneumonia in HIV-infected individuals is broad and a confirmed microbiologic diagnosis allows clinicians to target the specific pathogen and discontinue broad spectrum antibiotic therapy and/or empiric therapy (such as empiric PCP therapy) that targets non-bacterial pathogens.

HIV-infected patients with suspected CAP should undergo investigation for specific pathogens that would significantly alter standard (empirical) management decisions when presence of such pathogens is suspected based on epidemiologic, clinical, or radiologic clues. *P. aeruginosa* should be considered in HIV-infected patients with advanced HIV disease (that is, CD4 count  $\leq 50$  cells/mm<sup>3</sup>), pre-existing lung disease such as

bronchiectasis, or underlying neutropenia. It is also a consideration for HIV-infected patients who use corticosteroids, are severely malnourished, have been hospitalized in the past 90 days or reside in a health care facility or nursing home, or are on chronic hemodialysis. Because cavitory infiltrates are common in patients with *P. aeruginosa*, that radiographic finding also should prompt an investigation for this pathogen. *S. aureus* should be considered in patients with recent viral (or influenza) infection; a history of injection drug use; or severe, bilateral, necrotizing pneumonia.

Routine diagnostic tests to identify an etiologic diagnosis are optional for HIV-infected patients with suspected CAP who are well enough to be treated as outpatients, especially if the microbiologic studies cannot be performed promptly.

In contrast, a pre-treatment expectorated sputum specimen for Gram stain and culture and two blood cultures should be obtained from HIV-infected patients hospitalized for suspected CAP, particularly those who require intensive care.

Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures can be met for collection, transport, and processing of samples. 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. Bronchoscopy with bronchoalveolar lavage should be considered, especially if the differential diagnosis is broad and includes pathogens such as *Pneumocystis jirovecii*.

The increased incidence of bacteremia in HIV-infected patients, especially those with low CD4 cell counts, and the high specificity of blood cultures argue for their collection in such individuals. Low sensitivity of blood cultures in persons with higher CD4 counts argues against routine collection. However, patients with HIV infection are at increased risk of infection with drug-resistant pneumococci.<sup>25,26</sup> Because identification of this organism could lead to changes in management, collection of blood specimens in HIV-infected patients with CAP should always be considered.

In addition to the above tests, urinary antigen tests for *L. pneumophila* and *S. pneumoniae* should be considered.

Diagnostic thoracentesis should be considered in all patients with pleural effusion, especially if concern exists for accompanying empyema, and therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion.

## Preventing Exposure

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community.

## Preventing Disease

Vaccination against *S. pneumoniae* and influenza, use of combination ART, and lifestyle modifications are all important measures in preventing bacterial pneumonia. Multiple observational studies of pneumococcal polysaccharide vaccine (PPV) in the United States have reported benefits from such vaccination in HIV-infected persons.<sup>27-32</sup> Several studies also have documented an association between vaccination and a reduced risk of pneumococcal bacteremia.<sup>18,32</sup> One randomized placebo-controlled trial of PPV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia.<sup>33</sup> Follow-up of this cohort confirmed the increase in pneumonia in vaccinated subjects but also showed a decrease in all-cause mortality.<sup>34</sup>

A 13-valent pneumococcal conjugate vaccine (PCV13) has recently been recommended by the Advisory Committee on Immunization Practices for use in adults with immunocompromising conditions, including HIV infection.<sup>35</sup> A randomized, double-blind, placebo-controlled trial of 7-valent PCV among HIV-infected

adults in Malawi demonstrated 74% efficacy against vaccine-type invasive pneumococcal disease, with clear evidence of efficacy in those with CD4 counts <200 cells/mm<sup>3</sup>.<sup>36</sup>

HIV-infected adults and adolescents who have never received any pneumococcal vaccine should receive a single dose of PCV13 regardless of CD4 count (**AI**).<sup>35</sup> Patients with CD4 counts ≥200 cells/mm<sup>3</sup> should then receive a dose of 23-valent PPV (PPV23) at least 8 weeks later (**AII**).<sup>27-32,37-39</sup> HIV-infected patients with CD4 counts <200 cells/mm<sup>3</sup> can be offered PPV23 at least 8 weeks after receiving PCV13 (**CIII**); however, it may be preferable to defer PPV23 until after the CD4 count increases to >200 cells/mm<sup>3</sup> on ART (**BIII**). Clinical evidence supporting use of PPV23 in persons with CD4 counts <200 cells/mm<sup>3</sup> appears strongest in patients who also have HIV RNA <100,000 copies/mL;<sup>37,39</sup> evidence also suggests benefit for those who start ART before receiving PPV.<sup>32</sup>

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 (**BIII**).<sup>31</sup> A third dose of PPV23 should be given at age 65 years or later, as long as 5 years have elapsed since the most recent dose and it was given before age 65 years (**BIII**).

PCV13 should also be given in HIV-infected patients who have already received PPV23 (**AII**). However, such patients should wait at least 1 year after their most recent dose of PPV23 before receiving a single dose of PCV13 (**BIII**).<sup>35</sup> Subsequent doses of PPV23 should be given according to the schedule outlined above (i.e., at least 5 years between doses of PPV23 with no more than 3 lifetime doses).

Inactivated influenza vaccine should be administered annually during influenza season to all HIV-infected individuals (**AIII**).<sup>40</sup> This recommendation is pertinent to prevention of bacterial pneumonia, which can occur as a complication of influenza. Use of live attenuated influenza vaccine is contraindicated and **is not recommended** in HIV-infected individuals (**AIII**).

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

Several factors are associated with a decreased risk of bacterial pneumonia, including use of ART and of trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis.<sup>20</sup> In many studies, daily administration of TMP-SMX for PCP prophylaxis also reduced the frequency of bacterial respiratory infections.<sup>2,41,42</sup> This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of this drug (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection (**BIII**). Similarly, clarithromycin administered daily and azithromycin administered weekly are the drugs of choice for *Mycobacterium avium* complex (MAC) prophylaxis and may be effective in preventing bacterial respiratory infections.<sup>43,44</sup> However, these drugs also should not be prescribed solely for preventing bacterial respiratory infection (**BIII**).

A decreased absolute neutrophil count (e.g., <500 cells/mm<sup>3</sup>) is associated with an increased risk of bacterial infections, including pneumonia, although this risk has been demonstrated primarily in persons with malignancies. To reduce the risk of such bacterial infections, clinicians can consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs (**CIII**) or by administering granulocyte-colony stimulating factor (**CIII**), although these interventions have not been demonstrated to be effective in HIV-infected persons.

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes and using injection drugs and alcohol.<sup>2,38,45-47</sup> Clinicians should encourage cessation of these behaviors, and data suggest that smoking cessation can decrease the risk of bacterial pneumonia.<sup>48</sup>

## Treating Disease

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. One study suggested that the site of care decision be dictated by considering the PSI and CD4 count together.<sup>23</sup> Mortality was increased in patients with higher PSI class, but even in those without an increased mortality risk by PSI, the presence of a CD4 count  $<200$  cells/mm<sup>3</sup> was associated with an increased risk of death.<sup>23</sup> This led to the suggestion to always offer hospitalization to CAP patients with CD4 counts  $<200$  cells/mm<sup>3</sup> and to use the PSI to help guide the decision in those with higher CD4 counts.<sup>49</sup> In fact, in one series of 118 HIV-infected patients with CAP who were hospitalized, 62% fell into PSI Classes I and II, groups that are rarely hospitalized if not HIV infected.<sup>50</sup> In another study, 40% of hospitalized HIV-infected patients in low-risk PSI classes had CD4 counts  $<200$  cells/mm<sup>3</sup>.<sup>23</sup>

The basic principles of treatment of community-acquired bacterial pneumonia are the same for HIV-infected patients as for those who are not HIV infected.<sup>24</sup> As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should be taken before antibiotic therapy is initiated. Antibiotic therapy should be administered promptly, however, without waiting for the results of diagnostic testing.

### *Empiric Antibiotic Therapy by Treatment Setting and Severity of Diseases*

#### Outpatient Treatment

HIV-infected individuals who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide (**AII**) or an oral respiratory fluoroquinolone (**AII**). Preferred beta-lactams are high-dose amoxicillin or amoxicillin-clavulanate; alternatives are cefpodoxime or cefuroxime. Preferred macrolides are azithromycin or clarithromycin. Doxycycline is an alternative to the macrolide (**CIII**). Preferred oral respiratory fluoroquinolones are moxifloxacin or levofloxacin.

An oral respiratory fluoroquinolone (moxifloxacin or levofloxacin) should be used in patients who are allergic to penicillin (**AII**).

Respiratory fluoroquinolones also are active against *M. tuberculosis*. Thus, patients with TB who are treated with fluoroquinolone monotherapy may have an initial but misleading response that could delay diagnosis of TB and initiation of appropriate multidrug TB therapy and increase risk of drug-resistant TB and TB transmission. Fluoroquinolones, therefore, 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. Increasing rates of pneumococcal resistance suggest that empirical therapy with a macrolide alone **cannot be routinely recommended** (**BIII**). Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia, but macrolides can be used as part of a combination regimen.

#### Non-Intensive Care Unit Inpatient Treatment

HIV-infected individuals who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide (**AII**) or an IV respiratory fluoroquinolone (**AII**). Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Preferred macrolides are azithromycin and clarithromycin. Doxycycline is an alternative to the macrolide (**CIII**). Preferred respiratory fluoroquinolones are moxifloxacin or levofloxacin. Clinical and Laboratory Standards Institute and U.S. Food and Drug Administration changes in the penicillin breakpoints for treatment of non-meningitis pneumococcal disease imply that clinicians can consider treatment with IV penicillin in HIV-infected patients confirmed to have pneumococcal pneumonia (**BIII**).<sup>51</sup>

In patients who are allergic to penicillin, an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used (**AII**).

Because of the activity of fluoroquinolones against *M. tuberculosis* and the dangers of monotherapy in those with TB, as previously discussed, 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.

Increasing rates of pneumococcal resistance suggest that empirical therapy with a macrolide alone **cannot be recommended routinely (BIII)**. Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia, but macrolides can be used as part of a combination regimen.

### **Intensive Care Unit Treatment**

Intensive care unit patients should not receive empiric monotherapy, even with a fluoroquinolone, because the efficacy of this approach has not been established. 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 intensive care unit.<sup>52</sup> Patients with severe pneumonia who require intensive care should be treated with an IV beta-lactam plus either IV azithromycin (**AII**) or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) (**AII**). 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**).

The majority of 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 of these 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.

### **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 (**BIII**). Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Alternatives are an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin (**BIII**) or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (**BIII**). In patients who are allergic to penicillin, aztreonam can be used in place of the beta-lactam (**BIII**).

### **Empiric *Staphylococcus aureus* Treatment**

In patients who have risk factors for *S. aureus* infection, including community-acquired MRSA, vancomycin or linezolid should be added to the antibiotic regimen (**BIII**). Although not routinely recommended, the addition of clindamycin (to vancomycin, but not to linezolid) may be considered if severe necrotizing pneumonia is present to minimize bacterial toxin production (**CIII**).

### **Pathogen-Directed Therapy**

When the etiology of the pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be modified and directed at that pathogen.

### **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 (PaO<sub>2</sub>) >60 mm Hg.<sup>24</sup>

### ***Special Considerations Regarding When to Start Antiretroviral Therapy***

The presence of acute opportunistic infection (OI), including bacterial pneumonia, increases the urgency of

starting ART. In one randomized, controlled trial, use of ART early in the course of OIs, including bacterial infections, led to less AIDS progression and death compared with later onset of therapy.<sup>53</sup> Therefore, in patients not already on ART, ART should be initiated early in the course of bacterial pneumonia (**AI**).

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

The clinical response to appropriate antimicrobial therapy is similar in HIV-infected patients and individuals who are not HIV infected.<sup>54</sup> 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. The presence of advanced HIV infection, CD4 count <100 cells/mm<sup>3</sup>, and *S. pneumoniae* etiology were predictors of needing >7 days to reach clinical stability, whereas those patients receiving ART tended to become clinically stable sooner.<sup>49</sup> Usually, radiographic improvement lags behind clinical improvement.

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with bacterial respiratory disease and treatment with ART in HIV-infected patients.

### ***Managing Treatment Failure***

Patients who fail to respond to appropriate antimicrobial therapy should undergo further evaluation to search for other infectious and noninfectious causes of pulmonary dysfunction. The possibility of TB should always be considered in HIV-infected patients with pulmonary disease.

## **Preventing Recurrence**

HIV-infected patients should receive pneumococcal and influenza vaccine 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.

## **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 as in women who are not pregnant, with certain exceptions.

Clarithromycin is not recommended as the first-line agent among macrolides because of an increased risk of birth defects seen in some animal studies. Two studies, each involving at least 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.<sup>55,56</sup> 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. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.<sup>57,58</sup> Thus, when indicated, quinolones can be used in pregnancy for serious respiratory infections (**CIII**).<sup>59</sup>

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. Aminoglycosides can be used as needed. A theoretical risk of fetal renal or eighth nerve damage exists with exposure during pregnancy, but this finding has not been documented in humans, except with streptomycin (10% risk) and kanamycin (2% risk). 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**). Although its safety during the first

trimester has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Inactivated influenza vaccine also can be administered during pregnancy, and the vaccine is recommended for all pregnant women during influenza season (**AIII**). Live attenuated influenza vaccine should not be used in HIV-infected persons (**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.

## Recommendations for Preventing and Treating Bacterial Respiratory Diseases (page 1 of 3)

### Preventing *Streptococcus pneumoniae* Infections

#### *Indications for Pneumococcal Vaccination:*

- All HIV-infected persons regardless of CD4 count

#### *Vaccination Recommendations:*

##### For Individuals Who Have Not Received Any Pneumococcal Vaccination:

#### *Preferred Vaccination:*

- One dose of PCV13 (**A1**), followed by:
- For patients with CD4+ count  $\geq 200$  cells/ $\mu$ L: PPV23 should be given at least 8 weeks after receiving PCV13 (**AII**); *or*
- For patients with CD4 count  $< 200$  cells/ $\mu$ L: PPV23 can be offered at least 8 weeks after receiving PCV13 (**CIII**) or can await increase of CD4 count to  $> 200$  cells/ $\mu$ L on ART (**BIII**)

#### *Alternative Vaccination:*

- One dose of PPV23 (**BII**)

##### For Individuals Who Have Previously Received PPV23:

- One dose of PCV13 should be given at least 1 year after the last receipt of PPV23 (**AII**)

##### Re-vaccination of PPV

- A dose of PPV23 is recommended for individuals 19–64 years old if  $\geq 5$  years have elapsed since the first dose of PPV (**BIII**)
- Another dose should be given for individuals 65 years or older, if at least 5 years have elapsed since previous PPV23 dose (**BIII**)

#### *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 HIV-infected persons during influenza season (**AIII**)

#### *Vaccination:*

- Inactivated influenza vaccine per recommendation of the season (**AIII**)

**Note:** Live attenuated influenza vaccine is **contraindicated** in HIV-infected persons (**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.

#### **Empiric Outpatient Therapy (Oral)**

##### *Preferred Therapy:*

- An oral beta-lactam + a macrolide (azithromycin or clarithromycin) (**AII**), *or*
  - *Preferred beta-lactams:* high-dose amoxicillin or amoxicillin/clavulanate
  - *Alternative beta-lactams:* cefpodoxime or cefuroxime

## Recommendations for Preventing and Treating Bacterial Respiratory Diseases (page 2 of 3)

- A fluoroquinolone<sup>a</sup> (**AII**), especially for patients with penicillin allergies
  - Levofloxacin<sup>a</sup> 750 mg PO once daily (**AII**), *or*
  - Moxifloxacin<sup>a</sup> 400 mg PO once daily (**AII**)

### *Alternative Therapy:*

- A beta-lactam (**AII**) + doxycycline (**CIII**)

### *Duration of Therapy:*

- For most patients: 7–10 days; a minimum of 5 days. The patient should be afebrile for 48–72 hours, and should be clinically stable before discontinuation of therapy

### **Empiric Therapy for Non-ICU Hospitalized Patients**

#### *Preferred Therapy:*

- An IV beta-lactam + a macrolide (azithromycin or clarithromycin) (**AII**), *or*
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
- An IV fluoroquinolone<sup>a</sup> (**AII**), especially for patients with penicillin allergies
  - Levofloxacin<sup>a</sup> 750 mg IV once daily (**AII**), *or*
  - Moxifloxacin<sup>a</sup> 400 mg IV once daily (**AII**)

#### *Alternative Therapy:*

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

### **Empiric Therapy for ICU Patients**

#### *Preferred Therapy:*

- An IV beta-lactam + IV azithromycin (**AII**), *or*
- An IV beta-lactam + (levofloxacin<sup>a</sup> IV 750 mg once daily or moxifloxacin<sup>a</sup> 400mg IV daily) (**AII**)
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam

#### *Alternative Therapy:*

#### *For Penicillin-Allergic Patients:*

- Aztreonam (IV) + an IV respiratory fluoroquinolone (moxifloxacin 400 mg per day or levofloxacin 750 mg per day) (**BIII**)

### **Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia**

#### *Preferred Therapy:*

- An IV antipseudomonal, antipseudomonal beta-lactam + (ciprofloxacin IV [400 mg q8–12h] or levofloxacin IV 750 mg/day) (**BIII**)
  - *Preferred beta-lactams:* piperacillin-tazobactam, cefepime, imipenem, or meropenem

#### *Alternative Therapy:*

- An IV antipseudomonal, antipseudomonal beta-lactam + an IV aminoglycoside + IV azithromycin (**BIII**), *or*
- An IV antipseudomonal, antipseudomonal beta-lactam + an IV aminoglycoside + an IV antipseudomonal fluoroquinolone (moxifloxacin [400 mg/day] or levofloxacin [750 mg/day]) (**BIII**)

#### *For Penicillin-Allergic Patients:*

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

### **Empiric Therapy for Patients at Risk of Staphylococcus aureus Pneumonia:**

- Vancomycin IV or linezolid (IV or PO) should be added to the baseline regimen (**BIII**).
- 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 (**CIII**).

### **Other Considerations**

- Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance (**BIII**).
- Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

## Recommendations for Preventing and Treating Bacterial Respiratory Diseases (page 3 of 3)

- Once the pathogen has been identified by reliable microbiologic methods, antibiotics should be modified to treat the pathogen (BIII).
- For patients begun on IV antibiotic therapy, switching to PO should be considered when patient is clinically improved and able to tolerate oral medications.
- Antibiotics chemoprophylaxis is generally not recommended because of the potential for development of drug resistance microorganisms and drug toxicities.

<sup>a</sup> Respiratory fluoroquinolones such as levofloxacin or 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 4-drug TB regimen.

**Key to Acronyms:** PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; CD4 = CD4 T lymphocyte cell; PPV 23 = 23-Valent Pneumococcal Polysaccharide Vaccine; ART = antiretroviral therapy; IM = intramuscularly; PO = Orally; IV = Intravenously; MAC = *Mycobacterium avium* complex

## 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*. Jan 1997;155(1):72-80. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9001292>.
2. 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*. Sep 28 1995;333(13):845-851. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7651475>.
3. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. *MMWR. CDC surveillance summaries: Morbidity and mortality weekly report. CDC surveillance summaries / Centers for Disease Control*. Apr 16 1999;48(2):1-22. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12412613>.
4. 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*. Jul 2000;162(1):64-67. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10903221>.
5. Serraino D, Puro V, Boumris E, et al. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. *AIDS*. Sep 26 2003;17(14):2109-2116. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14502014>.
6. Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. Jan 1986;104(1):38-41. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3484420>.
7. 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 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=7979856&query\\_hl=62&itool=pubmed\\_DocSum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7979856&query_hl=62&itool=pubmed_DocSum).
8. Miller RF, Foley NM, Kessel D, Jeffrey AA. Community acquired lobar pneumonia in patients with HIV infection and AIDS. *Thorax*. Apr 1994;49(4):367-368. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8202910>.
9. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med*. Oct 1995;152(4 Pt 1):1309-1315. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7551387>.
10. 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*. Apr 2000;117(4):1017-1022. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10767233>.
11. 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*. Aug 1 2001;184(3):268-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11443551>.

12. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS*. Jan 4 2002;16(1):85-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11741166>.
13. Tarp B, Jensen JS, Ostergaard L, Andersen PL. Search for agents causing atypical pneumonia in HIV-positive patients by inhibitor-controlled PCR assays. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. Jan 1999;13(1):175-179. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10836344>.
14. Levine SJ, White DA, Fels AO. The incidence and significance of Staphylococcus aureus in respiratory cultures from patients infected with the human immunodeficiency virus. *The American review of respiratory disease*. Jan 1990;141(1):89-93. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2297190>.
15. 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. *Annals of internal medicine*. Feb 19 2008;148(4):249-257. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18283202](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18283202).
16. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant Staphylococcus aureus pneumonia. *Chest*. Jul 2010;138(1):130-136. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20173050](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20173050).
17. 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*. Jun 15 2005;191(12):2038-2045. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15897989>.
18. 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*. Jul 11 2005;165(13):1533-1540. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16009870>.
19. 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*. Sep 1999;29(3):536-543. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10530443>.
20. 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*. Jul 1 2006;43(1):90-98. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16758423>.
21. 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*. Dec 2000;162(6):2063-2068. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11112115>.
22. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of Pneumocystis carinii pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. May 28 1998;12(8):885-893. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9631142>.
23. 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*. Oct 2008;9(8):609-615. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18557951](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18557951).
24. 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*. Mar 1 2007;44 Suppl 2:S27-72. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17278083>.
25. 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*. Jun 1 2004;38(11):1623-1628. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15156452>.
26. 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*. Sep 2008;79(3):320-330. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18784222>.
27. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of Pneumocystis carinii pneumonia, in the United States. *J Infect Dis*. May 1 2001;183(9):1409-1412. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11294675>.
28. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. *J Infect Dis*. Apr 1996;173(4):857-862. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/8603963>.

29. 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*. Oct 1 1999;13(14):1971-1975. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10513657>.
30. 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*. Sep 25 2000;160(17):2633-2638. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10999977>.
31. Advisory Committee on Immunization P. Recommended adult immunization schedule: United States, October 2007-September 2008. *Ann Intern Med*. Nov 20 2007;147(10):725-729. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17947396>.
32. 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*. May 7 2004;22(15-16):2006-2012. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15121313>.
33. 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*. Jun 17 2000;355(9221):2106-2111. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10902624>.
34. 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*. May 21 2004;18(8):1210-1213. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15166540>.
35. 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*. Oct 12 2012;61(40):816-819. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23051612>.
36. 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*. Mar 4 2010;362(9):812-822. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20200385](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20200385).
37. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis*. Oct 1 2007;45(7):e82-87. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17806042](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17806042).
38. 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*. Apr 1 2008;46(7):1093-1100. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18444830](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18444830).
39. 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*. Oct 29 2008;26(46):5830-5834. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18786586](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18786586).
40. 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*. Aug 6 2010;59(RR-8):1-62. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20689501](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20689501).
41. 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*. May 1 1999;353(9163):1463-1468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10232311>.
42. 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*. Dec 24 1992;327(26):1842-1848. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1448121>.
43. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med*. Aug 8 1996;335(6):392-398. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8676932>.

44. Oldfield EC, 3rd, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of Mycobacterium avium complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin Infect Dis*. Mar 1998;26(3):611-619. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9524832>.
45. 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 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=16423106&query\\_hl=100&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16423106&query_hl=100&itool=pubmed_docsum).
46. Navin TR, Rimland D, Lennox JL, et al. Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. *J Infect Dis*. Jan 2000;181(1):158-164. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10608762>.
47. 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. *Medical care*. Aug 2006;44(8 Suppl 2):S52-60. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16849969>.
48. 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 <http://www.ncbi.nlm.nih.gov/pubmed/20126646>.
49. Madeddu G, Laura Fiori M, Stella Mura M. Bacterial community-acquired pneumonia in HIV-infected patients. *Curr Opin Pulm Med*. May 2010;16(3):201-207. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20154625](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20154625).
50. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. Jan 2010;14(1):e22-27. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19586789](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19586789).
51. 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*. Jun 1 2009;48(11):1596-1600. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19400744](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19400744).
52. 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*. Aug 15 2004;170(4):440-444. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15184200](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15184200).
53. 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/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19440326](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19440326).
54. 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 [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list\\_uids=16028168&query\\_hl=88&itool=pubmed\\_docsum](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16028168&query_hl=88&itool=pubmed_docsum).
55. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *American journal of perinatology*. 1998;15(9):523-525. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9890248>.
56. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiology and drug safety*. Dec 2000;9(7):549-556. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11338912>.
57. 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*. Nov 1996;69(2):83-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8902438>.
58. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. Jun 1998;42(6):1336-1339. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9624471>.
59. 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*. May 2006;107(5):1120-1138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16648419>.