Bacterial Respiratory Infections Complicating Human Immunodeficiency Virus

Charles Feldman, MB BCh, DSc, PhD[1] Ronald Anderson, PhD[2]

[1] Division of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2] Institute for Cellular and Molecular Medicine, Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Address for correspondence Charles Feldman, MB BCh, DSc, PhD, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown 2193, Johannesburg, South Africa (e-mail: charles.feldman@wits.ac.za).

Semin Respir Crit Care Med 2016;37:214–229.

Abstract

Opportunistic bacterial and fungal infections of the lower respiratory tract, most commonly those caused by *Streptococcus pneumoniae* (the pneumococcus), *Mycobacterium tuberculosis*, and *Pneumocystis jirovecii*, remain the major causes of mortality in those infected with human immunodeficiency virus (HIV). Bacterial respiratory pathogens most prevalent in those infected with HIV, other than *M. tuberculosis*, represent the primary focus of the current review with particular emphasis on the pneumococcus, the leading cause of mortality due to HIV infection in the developed world. Additional themes include (1) risk factors; (2) the predisposing effects of HIV-mediated suppression on pulmonary host defenses, possibly intensified by smoking; (3) clinical and laboratory diagnosis, encompassing assessment of disease severity and outcome; and (4) antibiotic therapy. The final section addresses current recommendations with respect to pneumococcal immunization in the context of HIV infection, including an overview of the rationale underpinning the current "prime-boost" immunization strategy based on sequential administration of pneumococcal conjugate vaccine 13 and pneumococcal polysaccharide vaccine 23.

Keywords
- community-acquired pneumonia
- host defenses
- outcome
- pneumococcal immunization
- pneumococcus
- risk factors
- severity of illness
- treatment

It has been well recognized for several years that the lung is one of the sites most severely affected as a consequence of human immunodeficiency virus (HIV) infection and most patients with HIV infection will develop a pulmonary complication during the course of their illness, of which pulmonary infections predominate.[1,2] Bacterial pneumonia is still not infrequently the first clinical manifestation of the presence of HIV infection in a patient.[1] There have, however, been significant changes in the epidemiology of pulmonary infections in HIV-infected persons over the years, initially as a consequence of the use of prophylaxis for *Pneumocystis* pneumonia (PCP) and subsequently the introduction of highly active antiretroviral therapy (HAART).[2–4] Currently, bacterial pneumonia, and especially community-acquired pneumonia (CAP) due to *Streptococcus pneumoniae*, is the most common respiratory infection in HIV-infected patients in the developed world, followed by PCP and tuberculosis (TB), while TB is the predominant complication in the developing world, followed by CAP.[2] The incidence of CAP has been said to be up to 35-fold higher in HIV-infected individuals, compared with HIV-uninfected persons of similar age, and although the incidence has decreased in HIV-infected patients with the use of HAART, it still remains higher than in HIV-uninfected persons.[3] Thus, despite significant advances in the management of patients with HIV infection, CAP still remains a cause of considerable morbidity and mortality in both the developed and developing worlds, and pneumonia per se has also been recognized to have a significant impact on both the progression of HIV disease and its outcomes.[3,4]

The topic of this review on HIV and bacterial infections of the lower respiratory tract has been covered by us in two previous reviews.[5,6] The current review therefore represents an update, encompassing not only an overview of the major

Issue Theme Pulmonary Complications of HIV Infection; Guest Editors: Laurence Huang, MD, Alison Morris, MD, MS, and Kristina Crothers, MD

DOI http://dx.doi.org/10.1055/s-0036-1572558.
ISSN 1069-3424.

causative bacterial pathogens but also incidence and risk factors, as well as the predisposing role of HIV-mediated suppression of pulmonary host defenses exacerbated by cigarette smoking. Additional topics include laboratory diagnosis, clinical strategies in the assessment of disease severity and outcome, and, finally, preventive strategies, particularly pneumococcal immunization and the rationale underpinning the current "prime-boost" vaccination strategy.

Community-Acquired Bacterial Pneumonia

Overall, bacterial pneumonia is currently the leading cause of pulmonary infection in HIV-infected patients throughout the world, with variations in incidence in different parts of the world related to the geographical location and the prevalence of specific additional risk factors in the patents.[2]

Incidence

Much has been written about the incidence of CAP in HIV-infected patients with a suggestion from a peer review of the literature that these infections may be up to 25-fold more common in HIV-infected patients than in the general community, occurring in up to 90 cases per 1,000 person-years.[7] While higher and lower rates than this have been documented in different studies,[4] it is interesting to note that a study among a cohort of former injection drug users, including cases with and without HIV infection, documented a similar rate of CAP of 90.5 per 1,000 person-years in the HIV-infected group,[8] and a study in the HAART era among HIV-infected women, with a history of either intravenous drug use and/or risky sexual behavior, documented a similar rate of 8.5 cases per 100 person-years.[9]

Clearly, variations in the reported incidences and rates of CAP in the individual studies may relate not only to different time periods in the HIV pandemic but also to the availability of various forms of prophylaxis and/or antiretroviral therapy, as well as to differing additional risk factors for CAP in the study populations.[4] One study from a single center in the Unites States, undertaken to determine whether there was a change in the spectrum of HIV-associated lung diseases since the introduction of HAART, noted that while PCP was less common in the HAART era, bacterial pneumonia was more common (odds ratio [OR], 2.41; 95% confidence interval [CI]: 1.12–5.17).[10] This is in contrast to the study by Sullivan and colleagues that showed a dramatic decrease in the incidence of bacterial pneumonia following use of antiretroviral therapy, including protease inhibitors.[11] However, these studies are not directly comparable at least in the respect that the former study included both hospital- and community-acquired bacterial pneumonias, and the latter only community-acquired infections. The authors of the former study also acknowledged that their findings really reflect a decrease in opportunistic infections rather than a direct increase in the occurrence of bacterial pneumonia.[10] Overall, therefore, it is recognized that while rates of pneumonia have been shown to decrease with use of cotrimoxazole prophylaxis and introduction of HAART, the incidence of CAP in HIV-infected patients still remains higher than in HIV-uninfected individuals.[2,4,9]

Table 1 Risk factors for, and factors protective against, CAP/bacterial pneumonia in HIV-infected patients

Risk factors	Protective factors
• HIV infection per se • Age • Socioeconomic status • Gender differences • Ethnic differences • Caregiver to young children/mothers • Smoking of cigarettes and illicit drugs • Injection drug use • Alcohol abuse • Malnutrition • Low CD4 cell count • Unsuppressed viral load • Neutropenia • Comorbid conditions • Prior episode of pneumonia • Previous episode of PCP	• Cotrimoxazole prophylaxis • HAART • Higher CD4 cell counts • Suppressed HIV viral loads • Pneumococcal vaccination

Abbreviations: CAP, community-acquired pneumonia; HAART, highly active antiretroviral therapy; PCP, *Pneumocystis* pneumonia.

Risk Factors

A myriad of articles has documented the risk factors for CAP/bacterial pneumonia in HIV-infected patients, over and above the risk from HIV per se and are shown in ►**Table 1**.[1–4,9–16] While HIV infection itself is known to be a risk factor for bacterial CAP, the exact mechanisms associated with this enhanced risk are incompletely understood and are currently being investigated.[15] Older age, and in some studies male gender, have been documented to be additional risk factors for bacterial pneumonia in HIV-infected patients.[2,16] It has also been suggested that there is a difference in the risk of bacterial pneumonia in different ethnic groups with HIV infection, possibly attributable to genetic differences.[4,7] Markers of low socioeconomic status have also been shown to be associated with an increased risk of bacterial CAP.[7,9,17] Furthermore, those in close contact with children, such as care givers of young children and even HIV-infected mothers of young children, may be at increased risk of pneumonia due to high rates of nasopharyngeal carriage of pneumococcal organisms in the children.[4,7]

While CAP in HIV-infected persons may occur at any level of immunosuppression, it has been well characterized that the risk increases with decreasing CD4 cell counts, and is greatest once the CD4 cell count falls below 200 cells/μL.[1–4,7,11–13] High and/or unsuppressed and/or detectable HIV viral loads have also been shown to increase the risk of pneumonia.[2,4,16] Neutropenia, which may result from several factors in HIV-infected persons, including HIV infection per se, or even antiretroviral therapy, is a risk factor for bacterial lower respiratory tract infections.[1]

Many studies have documented the fact that injection drug use is associated with an increased pneumonia risk in HIV-infected persons, and while this may be due to associated confounding factors, such as socioeconomic conditions and adherence to therapy, there is evidence that some of the risk

may be due to direct drug effects in certain cases, or even to the effects of drug withdrawal.[3,4,7,11,13,14] Similarly alcohol abuse has been reported to be associated with a high incidence of bacterial CAP.[14] The role of smoking as a major risk factor is addressed more fully later.

Several studies have documented that a previous episode of pneumonia or PCP appears to be a risk factor for CAP.[1,10,11,13,18] There are additional risk factors for bacterial pneumonia in HIV-infected persons, including various underlying comorbid conditions, a low Karnovsky score, and elevated baseline systemic inflammatory markers (C-reactive protein, interleukin (IL)-6, and D-dimers), but not pulmonary specific markers of inflammation (club cell secretory protein 16 and surfactant protein D).[1,7,19]

With regard to a decreased risk of bacterial pneumonia, cotrimoxazole prophylaxis has been shown, at least in some studies, to be associated with a lower risk of bacterial infections such as pneumonia, in one study being associated with a 67% reduction in the occurrence of confirmed cases of bacterial pneumonia ($p = 0.007$).[9,12,18]

HAART has been shown to decrease the risk of bacterial pneumonia.[2,9] However, it has been said that the greatest benefit may be on hospital-acquired rather than community-acquired infections.[2] In one study, a combined antiretroviral regimen containing a protease inhibitor was associated with a significantly lower risk of bacterial pneumonia (risk ratio [RR] 0.55; 95% CI: 0.31–0.94).[11] Although studies have shown that continuous rather than intermittent antiretroviral therapy has a greater impact on decreasing the risk of pneumonia,[2,4] others have documented that viral suppression is associated with a lower incidence of pneumonia.[4]

In contrast to the reduction in risk of pneumonia, as well as improved outcome following an episode of pneumonia, reported in HIV-uninfected patients taking regular statins, these benefits of statins are not evident in HIV-infected patients.[4]

HIV-Mediated Suppression of Pulmonary Host Defenses

The impact of HIV infection on susceptibility to bacterial infection, including that caused by bacterial respiratory pathogens, has been addressed extensively in several recent reviews[20–22] and is covered only briefly here. In apparent contrast to the gastrointestinal tract, which undergoes rapid and extensive depletion of the memory T-cell subset in particular, the diverse host defenses of the lungs appear more resilient in the face of this early HIV-mediated onslaught.[22] In spite of this, pulmonary host defenses are progressively weakened and eventually subdued, resulting in HIV-mediated severe impairment of adaptive primary and memory immune responses, as well as recruitment and activation of innate effector cells which are dependent on these specific immune mechanisms. The consequence is heightened susceptibility to infection by a range of respiratory bacterial pathogens, especially *S. pneumoniae* (pneumococcus) and *Mycobacterium tuberculosis*.[2] Together with the fungus, *Pneumocystis jirovecii*, these two bacterial pathogens account for approximately 75% of serious pulmonary infections in HIV-infected individuals, with the relative frequencies of each pathogen varying according to geographic region as mentioned earlier.[2]

The following are the major HIV-mediated abnormalities of pulmonary immune function which predispose to infection with bacterial respiratory pathogens:

- Destruction of $CD4^+$ T cells by several mechanisms including (1) direct cytopathic effects of HIV; (2) recognition of surface expressed viral antigens by $CD8^+$ cytotoxic T cells; (3) chronic exposure to apoptosis-inducing viral antigens; and (4) chronic immune activation with sustained exposure to proapoptotic cytokines generated by cells of both the adaptive and innate immune systems[22]
- Susceptibility of a subset of $CD4^+$ T cells known as follicular helper T (Tfh) cells to HIV infection. These cells are found in the B-cell follicles of secondary lymphoid organs, where they initiate and maintain germinal centers, driving antibody production.[23] Tfh cells appear to be particularly receptive to HIV infection, supporting efficient replication and production, as well as promoting persistence by acting as a reservoir for HIV.[23]
- Persistence of counteracting endogenous anti-inflammatory strategies to control chronic immune activation. These include sustained production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β1 generated by various cell types and mechanisms, as well as induction of immunosuppressive regulatory T cells.[22] Unwittingly, however, these also contribute to increased susceptibility for development of microbial infection.
- Apparent selective infection and phagocytic dysfunction of a discrete subset of macrophages known as small alveolar macrophages,[24] as opposed to large alveolar macrophages which retain normal phagocytic function.[25] Phagosomal proteolytic activity, on the other hand, is defective in both types of alveolar macrophage irrespective of HIV infection of these cells.[24]
- Neutropenia is commonly found in patients with advanced HIV infection[21] and may contribute to the heightened susceptibility for development of pneumonia caused by several bacterial pathogens, including *Staphylococcus aureus* in particular, as well as pneumococcus and various types of gram-negative pathogens.

While heightened susceptibility for development of pulmonary TB can be attributed predominantly to HIV-mediated severe impairment of cell-mediated immune mechanisms, in other cases, such as that of pneumococcus, abnormalities of both cell-mediated and humoral immunity are contributory.[26]

Smoking and Pulmonary Host Defenses

HIV-infected smokers appear to be particularly susceptible to the adverse health effects of smoking. This increased risk, which persists following administration of virally suppressive HAART, encompasses not only lung infections but also non–AIDS-defining conditions, including pulmonary, cardiovascular, and neoplastic disorders.[22,27–30] Even in the setting of access to reliable health care, HIV-infected smokers lose more life-years to the smoking habit, than to HIV infection per se.[31]

Smoking, like HIV infection, also compromises pulmonary immune function.[32] However, very few studies have addressed the important topic of the probable, interactive, adverse effects of HIV infection and smoking on susceptibility to serious infection with bacterial respiratory pathogens. Unlike HIV infection, however, the predisposing effects of smoking for development of bacterial pulmonary infection are operative at the levels of both the pathogen and the host. In the case of bacterial pathogens, flakes of cured tobacco, which are inhaled during smoking, contain many different potential bacterial pathogens.[33] Chronic exposure of smokers to these tobacco-associated microbes, together with cigarette smoke-mediated suppression of airway host defenses, may underpin alterations in the nasopharyngeal microbiota of smokers which are characterized by replacement of commensal bacteria with potential pathogens such as pneumococcus, *S. aureus*, and non-typeable *Haemophilus influenzae*.[34,35] Exposure to cigarette smoke has also been reported to enhance the virulence and persistence of these pathogens via upregulation of expression of bacterial adhesins and production of protective biofilm, respectively.[36–38]

The suppressive effects of smoking on airway innate and adaptive host defenses are well documented and have recently been described in detail elsewhere.[32] These include interference with the protective activities of the mucociliary escalator, alveolar macrophages, dendritic cells, natural killer (NK) cells, T lymphocytes, and B lymphocytes, due in large part to chronic exposure to the vast array of cytotoxins present in cigarette smoke.[32] Like HIV infection, smoking has also been reported to cause dysregulation of pulmonary cytokine networks, creating a chronic inflammatory milieu conducive to immunosuppression. This is nicely illustrated by the findings of two very recent studies.

In the first of these, prior experimental exposure of mice to cigarette smoke resulted in exacerbation of airway inflammatory responses following induction of experimental viral infection.[39] The proinflammatory effects of cigarette smoking in this experimental setting were attributed to altered expression of the IL-33 receptor, ST2, on cells of the innate pulmonary immune system. ST2 was found to be downregulated on "anti-inflammatory" type 2 innate lymphoid cells, and upregulated on proinflammatory macrophages and NK cells, thereby amplifying inflammatory responses.[39] In the second study, exposure of both mice and humans to cigarette smoke resulted in decreased concentrations in alveolar lining fluid of the anti-inflammatory proteins, suppressors of cytokine signaling (SOCS), SOCS1 and SOCS3.[40] These are contained in exosomes (SOCS1) and microparticles (SOCS3) released by alveolar macrophages, which, in turn, are internalized by alveolar epithelial cells, resulting in suppression of cytokine signaling, an anti-inflammatory mechanisms which is attenuated by smoking.[40]

In addition, cigarette smoke has several proinfective effects on airway epithelial cells. These include (1) upregulated expression of the platelet-activating factor (PAF) receptor on lower airway epithelial cells, thereby promoting adherence of pneumococcus via binding to cell-wall phosphorylcholine[41] and (2) disruption of epithelial tight functions and barrier integrity, favoring extrapulmonary dissemination of bacterial respiratory pathogens.[42]

The proinfective effects of cigarette smoking on both the pathogen and the host are summarized in ►**Table 2**.

Respiratory Tract Microbiome

Clearly, HIV- and smoking-mediated suppression of pulmonary host defenses would be expected to have a significant impact on the pulmonary microbiome, which, in turn, may exacerbate immune dysfunction. However, relatively few studies have addressed the issue of alterations in the lung microbiome which accompany HIV infection and their possible impact on pulmonary function and host defense. Of the few studies published to date, molecular analyses have revealed over-representation of the gram-positive bacterium, *Tropheryma whipplei*, the causative agent of Whipple's disease, and the fungus *P. jirovecii* in the bronchoalveolar lavage (BAL) fluid of asymptomatic, HIV-infected individuals relative to uninfected subjects.[43,44] Virally suppressive antiretroviral therapy resulted in attenuation of colonization of the lung by *T. whipplei*.[43] In the latter study, over-representation with *P. jirovecii* was also detected in the lungs of HIV-infected patients with chronic obstructive pulmonary disease, possibly consistent with etiologic involvement of the fungus, either directly or indirectly, in HIV-associated pulmonary dysfunction.[44]

In the case of cigarette smoking, the lung, as opposed to the oral, microbiomes of healthy non-smokers and smokers do

Table 2 Pathogen- and host-targeted proinfective effects of cigarette smoking

Pathogen	Host
• Chronic exposure to pathogen-contaminated cured tobacco[33]	• Suppression of innate and adaptive airway host defences[32]
• Transition from a commensal- to a pathogen-dominant nasopharyngeal microbiota[34,35]	• Creation of a proinflammatory pulmonary milieu due to redistribution of expression of ST2 on cells of the pulmonary innate immune system, as well as attenuation of the release of SOCS1 and SOCS3 from alveolar macrophages[39,40]
• Increased expression of bacterial adhesins[36]	• Increased expression of the PAF receptor on airway epithelium and disruption of the alveolar epithelial barrier promoting adherence and dissemination of airway pathogens, respectively[41,42]
• Induction of biofilm formation[36,37]	

Abbreviations: PAF, platelet-activating factor; SOCS, suppressors of cytokine signaling.

not differ significantly,[45] while similar studies in HIV-infected non-smokers and smokers have not been described to date.

Causative Organisms

In general, the bacterial organisms causing CAP in HIV-infected persons are very similar to those in HIV-uninfected cases.[4] As in the general population, *S. pneumoniae* is the most common cause of bacterial CAP in HIV-infected patients, accounting for approximately 20% of cases overall and 40% of those cases in which a microorganism is isolated.[2] The next most common cause is said to be *H. influenzae*, which accounts for some 10 to 15% of cases of bacterial CAP, followed by *S. aureus*.[2] Infections with *Pseudomonas aeruginosa* appear to be much less common in the HAART era.[2] In general, infections with the so-called atypical pathogens appear to be relatively less common,[2] while infections with *Rhodococcus equi* and *Nocardia* are also uncommon.[2]

Streptococcus pneumoniae

Several studies clearly attest to the fact that HIV infection is a particular risk factor for pneumococcal pneumonia and other pneumococcal infections.[46,47] An exceedingly high risk for invasive pneumococcal disease (IPD) exists in HIV-infected patients,[47–49] which appears to be 30 to 100 times greater than in HIV-uninfected patients of similar age.[47] For example, in one study, the incidence of IPD in healthy adults was 8.8 per 100,000 persons, whereas in patients with HIV/AIDS it was 422.9/100,000 persons.[48] The incidence of IPD appears to be highest among injection drug users who are HIV infected[49] and recurrent episodes of IPD are also more common in HIV-infected persons.[47,49,50] Other studies have also documented a higher incidence of pneumococcal disease (pneumonia and IPD) in injection drug users.[51] One study suggested that HIV-infected patients with CAP who were not on HAART and had a positive pneumococcal urine antigen test were more likely to have bacteremia.[52] Another reported that HIV-infected patients with comorbid conditions, high viral loads, and low CD4 cell counts were at higher risk of developing IPD.[53] Other studies have also documented that a lower CD4 cell count is a risk for both pneumococcal pneumonia and IPD.[51] These authors reported a decreased risk for pneumococcal disease following use of antiretroviral therapy and pneumococcal vaccination.[51] Another study comparing patients with bacteremic and non-bacteremic pneumococcal CAP documented, among other risk factors, that those who were bacteremic were more likely to be HIV infected.[54] Importantly, it is suggested that adults with IPD who are 15 to 44 years of age with no other apparent risk factors should be tested for HIV infection.[55]

With regard to the clinical features of pneumococcal pneumonia in HIV-infected patients, additional risk factors include cigarette smoking, intravenous drug use, a low CD4 cell count $<$200 cells/μL, and alcohol abuse.[56] While the clinical presentation of pneumococcal pneumonia in HIV-infected patients may be similar to that of HIV-uninfected patients, it is said that unusual presentations may occur depending on the degree of immunosuppression.[56] In one study of bacteremic pneumococcal pneumonia, comparing HIV-infected and -uninfected cases, the former patients tended to have respiratory symptoms (cough, sputum production, hemoptysis, pleuritic chest pain), and systemic symptoms (rigors, diarrhea, vomiting, headache) more commonly.[57] Radiological features may vary and besides a classical lobar consolidation, bilateral infiltrates may occur.[56,57] With regard to the outcome of IPD when comparing HIV-infected and HIV-uninfected patients, some studies suggested there was no difference in mortality when comparing these two groups of patients. However, in one large, multicenter, international study, when cases were stratified according to age and severity of illness, the 14-day mortality from IPD was higher in HIV-infected patients and tended to increase as the CD4 cell count decreased.[57] This is described more fully later.

With regard to some of the microbiological features of pneumococcal infection and IPD, it is first recognized that in HIV-infected patients pneumococcal infections can occur concomitantly with other infections, with dual infection with *S. pneumoniae* and *M. tuberculosis* being documented in one study.[58] Documentation of additional infections is crucial for the appropriate management of these patients and while all the cases of pneumococcal infection were documented on the basis of positive blood cultures, some of the cases required bronchoscopy to confirm the additional diagnosis of TB.[58] With regard to pneumococcal serotypes, studies have been documenting the emergence of serotype 8, a serotype not contained in the current conjugate pneumococcal vaccines, particularly among cases with IPD.[59,60] The importance of this serotype is its expression of resistance to several antimicrobial agents, commonly including levofloxacin.[59,60] Furthermore, use of cotrimoxazole prophylaxis against PCP has been associated with a higher incidence of infections with antibiotic-resistant IPD isolates, at least in some studies.[49] Interestingly, one study investigating antibiotic resistance in *P. aeruginosa* and *S. pneumoniae* in HIV-infected patients in the HAART era documented that use of HAART reduced the number of antibiotic-resistant pseudomonal pneumonia cases, but not pneumococcal pneumonia cases.[61]

There have been a considerable number of studies and reviews published describing the impact of introduction of HAART on the incidence of IPD.[3,47,49,62–67] While studies from the United States and other parts of the developed world have shown significant and sharp decreases in the incidence since the introduction of HAART,[49,63,64] it is important to be aware that the incidence is still some 35-fold higher in HIV-infected persons than in HIV-uninfected cases of similar age.[3,47] One study from South Africa documented that despite a stable prevalence of HIV infection and a progressive roll-out of HAART, the burden of IPD had not decreased in HIV-infected adults, thus highlighting not only the importance of monitoring HIV disease and the impact of the HAART program, but also to consider alternative strategies, particularly the use of the pneumococcal conjugate vaccine (PCV).[66] Another study documented a relatively stable incidence of IPD over the study period 1996–2002, which includes the modern HAART era,[62] and a third documented that despite widespread use of

HAART and the 23-valent pneumococcal vaccine, the incidence of IPD remained high in HIV-infected patients, with its associated morbidity and mortality.[65]

Haemophilus influenzae

Infections with *Haemophilus* spp., and particularly *H. influenzae*, have been documented in patients who are HIV-infected, causing either pneumonia or bacteremia, with or without pneumonia.[68–73] The most recent study of *H. influenzae* pneumonia in HIV-infected patients documented 26 cases over a 12-month period, most of whom were severely immunocompromised with 73.1% of them having a CD4 cell count below 100 cells/μL.[73] Previous studies have suggested that injection drug use is a particular risk factor for *H. influenzae* pneumonia and in the current study there was a high proportion of such individuals. These studies documented that while the presentation of the infection may be typical of other pyogenic pneumonias presenting acutely with cough, purulent sputum, and dyspnea, some patients present with a subacute illness, and more than half present with a bilateral lung infiltrate, rather than a lobar/alveolar consolidation, thus more closely resembling PCP infection.[69,73] Thus, the clinical features do not reliably suggest the diagnosis of *H. influenzae* pneumonia, which has to be considered as a possible cause of pneumonia in HIV-infected patients, especially in the setting of advanced immunocompromize,[73] and some patients present with coexisting infections, including PCP.[68] The mortality rate for *H. influenzae* infections in HIV-infected persons is the same as that with such infections in the general population,[73] although relapses can occur following antibiotic therapy.[69]

The largest study documenting *Haemophilus* spp., bacteremia in adults, some of which were nosocomial, noted that HIV infection was the most common underlying risk factor and that the HIV-infected patients were more frequently younger and presented more commonly with pneumonia than those who were HIV uninfected.[72] The mortality rate in that study was higher, at 22%, although HIV infection itself did not appear to be an independent risk factor and the authors indicated the need to take into account possible antimicrobial resistance when choosing antibiotic therapy.

Staphylococcus aureus

It is not uncommon for isolates of *S. aureus* to be cultured from respiratory tract specimens in HIV-infected patients presenting with respiratory disease, which may represent colonization, or be of indeterminate significance, or be associated with *S. aureus* pneumonia (SAP).[74] SAP appears to be mainly community-acquired and the presentation may be acute or subacute.[74,75] The patients commonly present with typical symptoms including fever, cough, chest pain, and dyspnea, and have clinical features of pneumonia on examination.[74,75] Predisposing factors to SAP include intravenous drug abuse and previous PCP, but underlying concomitant pulmonary disorders are commonly present in the patients.[74,75] The chest radiograph usually shows a lobar pneumonia/local infiltrates, especially in the lower lobes, but consolidation with cavitation, and interstitial-nodular infiltrates also occur.[74,75] Pleural effusions are quite common in patients with SAP.[75] Additionally, some of the earlier studies of HIV-infected patients with CAP documented parapneumonic effusions to be more common than in HIV-uninfected patients and noted *S. aureus* to be the most common cause,[76] although more recently pneumococcus may be more common. When SAP is suspected or documented, specific antibiotic therapy is clearly indicated. The mortality of SAP has been relatively high in the different studies (e.g., 21% in the study by Tumbarello and colleagues) and has been associated with advanced immunosuppression and recurrent pneumonia.[75] Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) pneumonia has been described more recently, which has been characterized by the presence of necrotizing features, and cases have been documented in HIV-infected patients.[77] In one series, the mortality was lower than previously described, which the authors attributed to the possible greater use of antibiotics (clindamycin or linezolid) that inhibited endotoxin production or the presence of nontoxigenic strains.[77] At least one case of Panton-Valentine leucocidin-producing SAP has been documented in an HIV-infected patient, associated with a poor outcome.[78]

Atypical Pathogens

Although studies have documented the presence of so-called atypical pathogens (*Legionella pneumophila*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*) as causes of pneumonia in HIV-infected persons, the true prevalence of these pathogens in this setting is uncertain.[79] Considering that basing the diagnosis of these infections on serological testing may not be accurate as antibody responses may be compromised in AIDS patients, Tarp and colleagues applied polymerase chain reaction (PCR) analyses for *Chlamydia* spp., *Legionella* spp., and *M. pneumoniae* to consecutively obtained BAL specimens obtained from HIV-infected patients with pneumonia. *L. pneumophila* was detected in 1% of BAL fluids, *M. pneumoniae* was documented as a coexisting pathogen in 2%, and *Chlamydia* spp., could not be detected.[79] The authors concluded that while these pathogens may be uncommon as causes of pneumonia in HIV-infected persons, they should be considered as possible causes in cases with treatment failure.

Several authors concur that Legionnaire's disease has been infrequently described in HIV-infected patients.[80] Part of the reason for this may be due to the use of cotrimoxazole prophylaxis against PCP, as this agent has good activity against *Legionella* and a similar case may be made in the case of the use of azithromycin prophylaxis for nontuberculous mycobacteria.[80] Another reason may be that *Legionella* infections may occur concurrently with other pneumonias, including PCP, and of these the former is the one that is difficult to document.[80] Other authors have documented the occasional occurrence of Legionnaire's disease in HIV-infected patients and suggested that it may be associated with a more severe presentation.[81] There does not appear to be an association between *Legionella* infection and any particular level of the CD4 cell count.[80,81] A case of *L. pneumophila* pneumonia in an HIV-seropositive patient with significant neurological manifestations, which are not uncommon in Legionellosis, has been reported more recently.[82]

C. pneumoniae pneumonia has been described not uncommonly in HIV-infected patients.[83,84] Infection appears to be associated with both a low CD4 cell count and high viral loads.[84] It also appears to be associated with hyperlipidemia and might represent an additional risk factor in HIV-infected patient.[84] While patients may develop focal pneumonia, others may develop diffuse interstitial pulmonary involvement and even respiratory failure.[83] *C. pneumoniae* may be the sole pathogen causing pneumonia in HIV-infected patients, but can also be found together with other pathogens.[83] It has been suggested that this pathogen should always be suspected as possible cause of pneumonia in HIV-infected patients with pneumonia who are not responding to standard β-lactam or PCP therapy.[83]

One study documented a relatively high prevalence of *M. pneumoniae* in HIV-infected patients with respiratory tract symptoms, higher than that occurring among HIV-uninfected cases and this pathogen should be considered as a possible cause of atypical respiratory infections.[85]

Pseudomonas aeruginosa

Several studies and reviews attest to the fact that HIV-infected patients are at increased risk of *P. aeruginosa* infections, especially pneumonia, including both community-acquired and nosocomial infections.[86–92] For example, one prospective, observational study designed to document the organisms causing bacterial pneumonia in hospitalized patients with HIV infection reported that *P. aeruginosa* was the most common cause, accounting for 32 of the recorded 111 admissions.[88] Community-acquired infections were much more common than nosocomial infections, as has also been documented in many of the other studies.[86,88,89] This study and others have documented that pseudomonal infections occur in cases with advanced HIV disease, in association with low CD4 cell counts.[86–89] In this study when compared with the cases with pneumococcal infection, the patients with pseudomonal pneumonia, in addition to having a lower CD4 cell count, also had a longer length of hospital stay, but a similar mortality.[88] While in some studies no additional risk factors other than HIV infection have been present, other studies have noted use of PCP prophylaxis, broad-spectrum antibiotics, and corticosteroids as additional risk factors for pseudomonal infections.[86–88] With regard to the clinical presentation of the respiratory infections, one study documented two patterns of disease, namely, a sepsis syndrome with a fulminant course, or an indolent course, with some of the latter cases relapsing after apparent successful treatment.[86] Some authors have documented resolution of these recurrent/persistent infections in patients initiated on antiretroviral therapy with immune reconstitution.[91] Varying radiological patterns were also noted in that study, including an interstitial pattern mimicking PCP, lobar pneumonia, and bronchial wall thickening.[86] Cavitating pneumonia may also occur. It appears that *P. aeruginosa* pneumonia is less common in the HAART era.[92]

Rhodococcus equi

Although an uncommon cause of human infection, quite a large number of cases of pneumonia caused by *R. equi* have been documented in HIV-infected patients.[93] Most patients have had more advanced immunosuppression.[93] While the lung is the most common site infected by this organism, other manifestations of infection can occur, including bacteremia and brain abscesses.[93] The most common presentation in the lung is that of focal cavitating pneumonia.[93] Bilateral pulmonary involvement and the occurrence of pleural effusions have been documented.[93] The isolated strains have varying antimicrobial susceptibility.[93] Although the optimal treatment of these infections is uncertain, combination of antibiotic therapy and early initiation of HAART appears to be associated with the best outcome.[93]

Moraxella catarrhalis

Moraxella catarrhalis has been described as a cause of pneumonia and bacteremia in HIV-infected patients.[94] Concomitant infections with other respiratory pathogens, including *S. pneumoniae* and *M. tuberculosis*, have also been noted.[94]

Laboratory Diagnosis

In the case of severe disease in both HIV-infected and -uninfected patients, traditional microbiological laboratory procedures for the detection of putative bacterial respiratory pathogens in body fluids are used to complement clinical and radiological investigations. Although useful, traditional microbiological procedures have significant limitations, particularly in the case of fastidious slow-growing organisms, resulting in prolonged time to both pathogen identification and antibiotic sensitivity. These limitations have resulted in the development of innovative, rapid, diagnostic tests based on the detection of bacterial antigens and/or nucleic acid in body fluids. In the case of the former, Binax NOW (ThermoFisher Scientific, Remel Microbiology Products, Lenexa, KS) immunochromatographic procedures are often used to detect the presence of the C-polysaccharide cell-wall component of the pneumococcus, which is common to all serotypes.[95] This type of procedure is also used to detect *L. pneumophila* serotype 1 antigen and has recently been adapted to enable simultaneous detection of both pathogens.[96] In the case of IPD, Binax NOW can be used in combination with, or may even eventually be replaced by, multiplex capsular polysaccharide antigen detection assays. This strategy enables rapid serotype identification, which is of importance not only in respect of epidemiology and surveillance but also in monitoring vaccine efficacy.[97–99] Additional antigen detection tests, of which several are available, include the Pneumotest-Latex procedure, also based on detection of pneumococcal capsular polysaccharides. Originally developed for improved serotyping/serogrouping,[100] this procedure has also been found to have diagnostic potential, demonstrating a level of 88.1% agreement with a molecular PCR-based diagnostic method.[101]

Quantitative RT-PCR-based detection of pneumococcal nucleic acid, in biological fluids, often combined with simultaneous detection of antibiotic resistance genes, is currently the method of choice for rapid diagnosis of pneumococcal infection. Of several genes investigated, including those encoding autolysin (*lytA*), pneumolysin, pneumococcal surface adhesin A, Spn9802, and capsular polysaccharides, detection of *lytA* appears to offer the highest specificity and sensitivity.[102–104] In this setting,

detection of *lytA* is not only diagnostic but also enables measurement of bacterial load, a determinant of disease severity and outcome.[103] More recently, several multiplex PCR procedures, both commercial and "in-house," have been developed which enable the simultaneous detection of a range of bacterial, as well as viral, respiratory pathogens.[105–107] However, application not only of these but also the other aforementioned laboratory diagnostic procedures should be tempered by an awareness of their limitations.[108]

Sputum smear microscopy for the detection of acid-fast bacilli (AFB) and culture are the traditional, cornerstone, microbiological procedures for the laboratory diagnosis of TB. Limitations of these procedures include a high frequency of smear negativity, particularly in the setting of advanced immunosuppression in HIV infection,[109–111] as well as the inability of microscopy to detect antibiotic resistance. Delayed acquisition of results is the major limitation of bacteriological culture procedures. The limitations of sputum smear microscopy, as well as those of radiographic confirmation, in patients coinfected with HIV and *M. tuberculosis* are underscored by the study of Chamie and colleagues.[109] These authors investigated the relationship between circulating $CD4^+$ T cell counts and the diagnostic accuracy of AFB sputum smear microscopy and chest radiographs in HIV-infected African patients ($n = 873$) with culture-proven pulmonary TB. The mean percentages of AFB sputum negativity were 23 and 1% in the subgroups of patients with circulating $CD4^+$ counts of $<50/\mu L$ and $>500/\mu L$, respectively, while the corresponding values for those with normal chest X-rays were 21 and 2%.[109]

The limitations of traditional microbiological procedures for the detection of *M. tuberculosis* have largely been overcome by the integration into routine diagnostic services of the Xpert MTB/RIF, a fully automated, rapid, molecular diagnostic procedure.[110,111] Apart from improved sensitivity relative to sputum smear microscopy, together with a level of accuracy comparable with that of bacteriological culture, the Xpert MTB/RIF also enables simultaneous detection of rifampicin resistance.[110,111] It is particularly useful in the clinical setting of HIV/*M. tuberculosis* coinfection, especially in patients with advanced immunosuppression, as well as in patients with multidrug-resistant TB.[110] The Xpert MTB/RIF can also measure sputum bacillary load at diagnosis, a determinant of infectiousness and transmissibility.[112]

In addition to detection of pathogen-specific antigens and/or nucleic acid, the adjunctive measurement of circulating host-derived biomarkers of inflammatory stress associated with microbial infection such as C-reactive protein, procalcitonin, and cortisol, together with stable biomarkers of cardiovascular stress such as midregional adrenomedullin and copeptin, may be predictive of disease severity, response to therapy, and outcome.[113,114]

Antibiotic Treatment

While several guidelines describing the appropriate management of patients with CAP exist, there have been no reports specifically addressing the issue in HIV-infected patients.[15] The IDSA/ATS CAP guideline (2007)[115] recommends that in outpatients with underlying comorbid conditions or risk factors for antibiotic-resistant pneumococcal infections, as well as for cases hospitalized, but not in the ICU, antibiotic treatment should include a β-lactam together with a macrolide or a respiratory fluoroquinolone only, and many experts believe that this would also be appropriate for HIV-infected patients.[15] While a small retrospective study appeared to show no benefit of the addition of a macrolide to a β-lactam agent above β-lactam monotherapy in HIV-infected patients with CAP,[116] a large multicenter prospective observational study of patients with pneumococcal bacteremia documented a better outcome in patients treated with combination antibiotic therapy (most commonly the β-lactam/macrolide combination) and this remained significant even when adjusted for HIV status.[117]

Severity of Illness and Outcome

Several studies determined whether various CAP severity of illness scores, or modifications of them, are able to accurately predict outcome in HIV-infected patients with CAP.[118–121] One study documented that the Pneumonia Severity Index (PSI) predicted 30-day mortality and need for ICU admission.[120] In that study, CD4 cell count did not predict patient outcome such that the authors concluded that the PSI could be used for mortality prediction at any level of immunosuppression. Another study, however, while documenting that a high PSI accurately predicted mortality, also noted that the mortality was significantly higher in patients with CD4 cell counts below 200 cells/μL.[118] These authors suggested that combining the CD4 cell count and PSI score may be a good strategy for deciding which HIV-infected patients with CAP needed hospital admission.[118]

There is still considerable debate as to whether the clinical, laboratory, and radiological features of CAP and the outcomes are different in HIV-infected and -uninfected cases. Studies have suggested that the clinical and radiological features of CAP are similar,[122] and that there are no differences in time to clinical stability, length of hospitalization, and mortality.[123,124] Furthermore, it has also been documented that CD4 cell counts and HIV-RNA levels do not predict the likely outcomes in HIV-infected patients hospitalized with CAP.[125] In the case of bacteremic pneumococcal pneumonia in HIV-infected patients, while an earlier study suggested that there were no differences in clinical presentation and outcomes when comparing HIV-infected with HIV-uninfected patients,[126] a more recent study reported not only that respiratory symptoms were more florid in HIV-infected patients but when the data were adjusted for age and severity of illness, the HIV-infected patients had a higher 14-day mortality, with a significant trend for an increasing mortality as the CD4 cell count decreased.[57] Because of this finding, and in consideration of the findings by Curran and colleagues, described earlier,[118] it has been suggested by some authors that a combined approach to severity assessment should be made and that all HIV-infected patients with CAP and a CD4 cell count below 200 cells/μL should be admitted to hospital

and in those with a CD4 cell count > 200 cells/μL, the PSI could be used to direct need for hospital admission.[15]

As in other medical conditions, it is not only HIV infection that impacts on the incidence, clinical features, and outcome of CAP, but the occurrence of an episode of CAP has permanent effects on the human host and on the course of HIV disease in the long term. Thus, one study showed that an episode of bacterial pneumonia (and also PCP) causes permanent decreases in lung function as measured by the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and diffusing capacity of carbon monoxide.[127] The authors suggest that while the clinical implications of this finding are unknown, they may be associated with prolonged respiratory symptoms after an episode of pneumonia. Furthermore, an additional study showed a significantly reduced median survival of HIV-infected patients following an episode of bacterial pneumonia (and also PCP) compared with median survival in control HIV-infected patients without an episode of bacterial pneumonia (24 vs. 37 months).[128] Both these study findings emphasize the need for prevention of respiratory infections in HIV-infected persons.

Immunization Strategies

Of the aforementioned bacterial pathogens, immunization strategies are available for the prevention of pneumococcal infections. Two types of vaccine, both of which target the polysaccharide capsule, are currently in use. These are the pneumococcal polysaccharide vaccine, PPV23, and several types of PCV.[129]

Pneumococcal Polysaccharide Vaccine

PPV23 is a cocktail consisting of capsular polysaccharides derived from 23 different serotypes of the pneumococcus which collectively account for 85 to 90% of cases of pneumococcal disease.[130] This vaccine elicits T-cell–independent antibody responses of the IgG/IgM isotypes which promote opsonophagocytosis, with antibodies of the IgG2 subclass dominating the IgG response.[131] The vaccine also induces serotype-specific anticapsular antibodies of the IgA class, promoting mucosal immunity.[131] Relative to PCVs, however, PPV23 exhibits poor immunogenicity in young children, does not affect nasopharyngeal colonization by pneumococcus, and induces only transient immunity in adults characterized by poor B-cell memory, necessitating revaccination at 5 to 6 yearly intervals for individuals at particularly high risk, including those infected with HIV. This vaccination schedule is based on minimizing the potential risk of hyporesponsiveness associated with shorter intervals between revaccinations.[130] For similar reasons, the Advisory Committee on Immunization Practices (ACIP) has recommended a maximum of two vaccinations with PPV23.

Current recommendations for immunization with PPV23 have been addressed in two recent, extensive reviews, both of which have highlighted the difficulties in establishing the efficacy of this vaccine, largely due to (1) poor immunogenicity and (2) conflicting clinical trial data.[129,130] While there is consensus in support of the efficacy of PPV23 in conferring partial protection against IPD in older, immunocompetent adults, as well as younger individuals with predisposing illnesses who are not severely immunosuppressed, the vaccine is of limited efficacy in those at highest risk for development of IPD.[129–131] The efficacy of PPV23 in preventing noninvasive pneumococcal pneumonia and all-cause pneumonia is also an issue of contention, and may be influenced by factors such as a more rapid decline in post-vaccination mucosal, as opposed to systemic, immunity, as well as timing of vaccination and gender.[129,130]

Two very recent studies confirm the utility of PPV23 in preventing IPD in older adults, as well as its lack of efficacy in preventing all-cause pneumonia. In the first of these, a retrospective case–control study nested in a population-based cohort aged ≥65 years ($n = 470{,}070$) covering a 4 year period, administration of PPV23 14 days to 5 years prior to the index date conferred significant protection against development of IPD (42% lower risk), but was ineffective in protecting against all-cause, hospital-treated pneumonia.[132] In the second study, a randomized, double-blind, placebo-controlled trial involving young military trainees ($n = 152{,}723$) followed up for up to 6.7 years postvaccination, administration of PPV23 had no protective effect on development of all-cause pneumonia.[133] Surprisingly, however, of the radiologically confirmed cases of pneumonia reported during the study period ($n = 371$), none was caused by the pneumococcus.[133]

Several retrospective studies have reported benefit of PPV23 in HIV-infected patients.[134–136] However, data from several other observational studies, as well as from a single randomized, double-blind trial conducted in Uganda, have failed to provide convincing evidence in support of a role for PPV23 in protecting against pneumococcal infections in HIV-infected patients with advanced immunosuppression.[129,130,137] Until fairly recently, however, the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention continued to recommend administration of PPV23 with revaccination after an interval of 5 years for the prevention of IPD in the setting of HIV infection.[138] However, as addressed in more detail later, this recommendation has been superseded by a prime-boost strategy involving sequential administration of PCV13 and PPV23.[139]

Pneumococcal Conjugate Vaccines

The second type of pneumococcal vaccine is the PCV in which capsular polysaccharides derived from the most common disease-causing serotypes are conjugated to a nontoxic, immunogenic, carrier protein, usually the diphtheria toxoid, CRM197.[129,130] These vaccines, of which PCV13 is the current front runner, having replaced its predecessors, PCV7 and PCV9, elicit a T-cell–dependent, anticapsular polysaccharide antibody response and have several major advantages over PPV23 including the following[129,130]:

- Immunogenicity in neonates and children <2 years of age
- Prevention of nasopharyngeal colonization due to more effective mucosal immunity

- Improved opsonophagocytic antibody responses, both qualitatively and quantitatively
- More durable antibody responses due to effective induction of memory B cells
- Induction of indirect protection (herd protection in adults, as well as nonvaccinated children)

Since its introduction in the United States in 2010 and integration into the national immunization programs of many other developed and developing countries thereafter, PPV13 has been reported to cause impressive decreases in the incidence of IPD caused by vaccine serotypes in children in the United States,[140] France,[141] England/Wales,[142] and Mexico,[143] as well as in adults due to indirect immunity.[140–142] With respect to immunization of adults, the U.S. Food and Drug Administration in late 2011 approved the use of PCV13 administered as a single dose to adults aged ≥50 years to protect against pneumonia and IPD. In 2012, the ACIP recommended routine use of PCV13 for adults aged ≥19 years with immunocompromising conditions, including HIV infection, functional or anatomic asplenia, cerebrospinal fluid leak, or cochlear implants using a prime-boost strategy.[139] This was based on primary immunization with PCV13 followed at least 8 weeks later by PPV23.[139] More recently, based on early analysis of the results of the CAPITA trial,[144] the ACIP recommended that PCV13 be used in combination with PPV23 in a similar prime-boost strategy with an interval of 6 to 12 months between immunizations in vaccine-naive subjects aged 65 years and older.[145] The CAPITA study demonstrated the efficacy of administration of a single dose of PCV13 to pneumococcal vaccine-naive adults aged ≥65 years ($n = 84{,}496$) in protecting against vaccine-type pneumococcal pneumonia (45.6%), vaccine-type nonbacteremic pneumococcal pneumonia (45%), and vaccine-type IPD (75%).[144]

With respect to the role of PCVs in preventing pneumococcal disease in those infected with HIV, immunization with PCV9 was found to decrease the incidence of a first episode of IPD due to vaccine serotypes in HIV-infected and -uninfected children by 65 and 83%, respectively.[146] In a second study, the protective efficacy of administration of two doses of PCV7 administered 7 weeks apart to HIV-infected Malawian adults was found to protect against recurrent infection caused by vaccine serotypes, as well as against the nonvaccine serotype, 6A.[147]

Although the efficacy of PCV13 in protecting HIV-infected persons remains to be established, the ACIP, as mentioned earlier, has recommended sequential administration of PCV13 and PPV23 in this setting.[139] This prime-boost strategy is based on the premise that "priming" (primary immunization) with a PCV, in this case PCV13, followed by secondary administration of PPV23 will significantly augment specific antibody responses to polysaccharide antigens common to both vaccines. Other advantages of the PCV13/PPV23 prime-boost strategy include expanded coverage of vaccine serotypes, as well as reduction in the cost of immunization in certain environments.

Prime-Boost Immunization for Prevention of Pneumococcal Disease

Evidence in support of this strategy is derived from two earlier studies, one undertaken in patients with treated Hodgkin's disease ($n = 57$) who received primary immunization with a variant of PCV7 known as 7-OMPC containing an outer membrane protein complex of *Neisseria meningitides* as carrier, followed by administration of PPV23 1 year later.[148] In the second study, HIV-infected patients ($n = 212$) were randomized to receive primary immunization with PCV7 followed 4 weeks later by PPV23 and antibody responses to capsular polysaccharides measured preimmunization and 8 weeks later relative to the responses of a control group immunized with a single dose of PPV23.[149] In both studies, the prime-boost strategy resulted in significant augmentation of the concentrations of circulating IgG antibodies to six of the seven capsular polysaccharides common to both vaccines.[148,149] However, similar prime-boost strategies undertaken in adult liver transplant patients (PCV7 followed 8 weeks later by PPV23) and Alaska Native adults aged 55 to 70 years (PCV7 followed 2–6 months later by PPV23) were found to be less effective.[150,151] In both studies, antibody responses to common serotypes induced by PCV7/PPV23 were comparable to those induced by PPV23 only.[150,151]

More recently, the efficacy of a revaccination strategy based on primary immunization with PCV13 or PPV23 followed by readministration of either of these vaccines was evaluated in older adults aged 50 to 64 years in two different studies.[152–154] In the first of these, two groups of adults aged 50 to 59 years ($n = 214$) and 60 to 64 years ($n = 407$) previously immunized with either PCV13 (both age groups) or PPV23 (60–64 years only, $n = 189$) when they were vaccine naive[152] were revaccinated 4 years later with PCV13 (younger group, PCV13/PCV13) or PPV (older group, PPV/PPV).[153] Those in the older group who had originally received PCV13 were revaccinated with either PCV13 ($n = 108$) or PPV23 (PCV13/PPV23, $n = 108$). Concentrations of circulating functional, opsonophagocytic, anticapsular antibodies were measured 4 weeks postimmunization. Relative to the responses following a first immunization with PPV23, postimmunization titers of opsonophagocytic antibodies in those who received PCV13/PPV23 were significantly higher for 10 of the serotypes common to both vaccines. Sequential immunization with PPV23, on the other hand, resulted in significantly decreased antibody titers to 9 of the common serotypes. Relative to the initial response to PCV13, sequential administration of PCV13 resulted in significantly improved antibody titers against 7 and 6 of the vaccine serotypes in the older and younger age groups, respectively, with responses to the remaining serotypes being largely noninferior.[153]

In the second study, the efficacy of primary immunization with PCV13 followed 1 year later by secondary administration of PPV23 was evaluated in vaccine-naive adults aged 60 to 64 years ($n = 720$).[154] Participants were randomized to receive PCV13/PPV23, PPV23/PCV13, or PCV13/PCV13 with measurement of circulating, functional, opsonophagocytic, anticapsular antibodies undertaken before and 4 weeks after

primary and secondary immunization. Initial immunization with PCV13 followed by PPV23 resulted in significant augmentation of opsonophagocytic antibody activities to 6 of the 12 common serotypes and noninferior responses to the others relative to the corresponding responses following sequential administration of PPV23.[154] When compared with the PPV23/PSV13 group, antibody responses were significantly higher to 11 of the 12 common serotypes. Sequential administration of PCV13 resulted in responses that were generally comparable to those following initial immunization, as well as being similar to, or somewhat lower, than those elicited following PCV13/PPV23.[154]

Pneumococcal Prime-Boost Immunization in HIV Infection

Although the efficacy of PCV13 in prevention of IPD in HIV-infected individuals has not been established, the ACIP, as mentioned earlier, currently recommends a routine prime-boost immunization strategy for immunocompromised adults aged ≥19 years, encompassing HIV-infected persons.[139] This strategy entails primary immunization with PCV13 followed 8 weeks later by a single dose of PPV23, and revaccination with PPV23 after 5 years,[138,139] a recommendation supported by the findings of a recent study.[155] It is currently recommended for all vaccine-naive HIV-infected persons. The possible exception is those subjects with circulating $CD4^+$ T-cell counts of <200/μL blood. In this setting, it has been proposed that PPV23 be withheld until the circulating $CD4^+$ T-cell count recovers to levels above the threshold of 200 cells/μL.[156] This latter proposal is not, however, supported by a recent study which reported that postimmunization opsonophagocytic and immunoreactive antibody titers did not differ between groups of newly diagnosed HIV-infected patients with CD4+ T-cell counts of <200/μL who were either immunized immediately with PPV23 or following 6 to 12 months of HAART.[157] Similar findings have been reported in HIV-infected patients with CD4+ counts of ≥200/μL.[158] Other aspects to be considered include the high percentage (~15%) of HIV-infected individuals who do not achieve circulating $CD4^+$ T-cell counts of >200/μL despite several years of virally suppressive HAART,[159,160] as well as the higher mortality rates within the first 3 to 12 months of treatment of HIV-positive patients living in low-income countries.[161,162]

A recent study has underscored the necessity for development of serotype-independent, protein-based vaccines in the prevention of IPD in those infected with HIV. In this study, concentrations of circulating specific IgG antibodies to 27 pneumococcal protein antigens and 30 serotype capsular polysaccharides were measured before and 87 ± 77.3 and 183 ± 97.5 days after IPD and compared with those of HIV-infected individuals without IPD.[163] In the IPD group, antibody responses to pneumococcal proteins were not only more frequent than those to capsular polysaccharides but also persisted for longer, with PcpA, PsaA, and PiaA, the first two of which are priority protein vaccine candidates,[129] being most immunogenic.[163] The IPD group also responded to a greater range of pneumococcal protein antigens than the control group. The finding that antibodies to pneumolysin were not detected is consistent with weak immunogenicity, underscoring the importance of development of vaccines which induce antibody responses to this major protein virulence factor of pneumococcus.[163]

Additional preventive measures include implementation of smoking screening and cessation strategies,[164] as well as influenza immunization to counter the threat of pneumococcal infection,[165–167] both of which should also be integrated into routine HIV care programs.

Conclusion

Despite all the advances there have been in the management of patients with HIV infection, it is clear when reviewing the literature that bacterial pneumonia, and in particular community-acquired pneumococcal pneumonia, remains globally a common problem among these patients, and is associated with considerable morbidity and mortality. Underlying HIV infection impacts on the frequency with which CAP occurs, even in the presence of HAART, its clinical manifestations and, at least in some cases, its outcome. Furthermore, an episode of CAP in HIV-infected persons is often followed by longer-term consequences, including a lower medium-term survival when compared with those who have not had an episode of pneumonia, as well as permanent declines in lung function parameters. It therefore remains important to prevent the occurrence of pneumonia in HIV-infected persons, which may be achieved through lifestyle changes and immunization strategies, with the PCV playing an important role in recommended vaccination practices.

Acknowledgment

Charles Feldman is supported by the National Research Foundation (SA).

References

1 Mayaud C, Parrot A, Cadranel J. Pyogenic bacterial lower respiratory tract infection in human immunodeficiency virus-infected patients. Eur Respir J Suppl 2002;36 (Suppl 36):28s–39s
2 Benito N, Moreno A, Miro JM, Torres A. Pulmonary infections in HIV-infected patients: an update in the 21st century. Eur Respir J 2012;39(3):730–745
3 Segal LN, Methé BA, Nolan A, et al. HIV-1 and bacterial pneumonia in the era of antiretroviral therapy. Proc Am Thorac Soc 2011; 8(3):282–287
4 Brown J, Lipman M. Community-acquired pneumonia in HIV-infected individuals. Curr Infect Dis Rep 2014;16(3):397
5 Feldman C, Anderson R. HIV-associated bacterial pneumonia. Clin Chest Med 2013;34(2):205–216
6 Feldman C, Anderson R. Respiratory infections in specific populations: HIV patients. In: Blasi F, Dimopoulos G eds. Textbook of Respiratory and Critical Care Infections. New Delhi, India: Jaypee Brothers Medical Publishers; 2015:139–158
7 Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. Lancet Infect Dis 2004;4(7):445–455

8 Boschini A, Smacchia C, Di Fine M, et al. Community-acquired pneumonia in a cohort of former injection drug users with and without human immunodeficiency virus infection: incidence, etiologies, and clinical aspects. Clin Infect Dis 1996;23(1):107–113
9 Kohli R, Lo Y, Homel P, et al; HER Study Group. 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
10 Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. Chest 2001; 120(6):1888–1893
11 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
12 Hirschtick RE, Glassroth J, Jordan MC, et al; Pulmonary Complications of HIV Infection Study Group. Bacterial pneumonia in persons infected with the human immunodeficiency virus. N Engl J Med 1995;333(13):845–851
13 Tumbarello M, Tacconelli E, de Gaetano K, et al. Bacterial pneumonia in HIV-infected patients: analysis of risk factors and prognostic indicators. J Acquir Immune Defic Syndr Hum Retrovirol 1998;18(1):39–45
14 Madeddu G, Porqueddu EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. Infection 2008;36(3):231–236
15 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
16 Mussini C, Galli L, Lepri AC, et al; ICONA Foundation Study Group. 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
17 Penner J, Meier AS, Mwachari C, et al. Risk factors for pneumonia in urban-dwelling HIV-infected women: a case-control study in Nairobi, Kenya. J Acquir Immune Defic Syndr 2003;32(2): 223–228
18 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
19 Bjerk SM, Baker JV, Emery S, et al; INSIGHT SMART Study Group. Biomarkers and bacterial pneumonia risk in patients with treated HIV infection: a case-control study. PLoS ONE 2013;8(2):e56249
20 Twigg HL III, Knox KS. Impact of antiretroviral therapy on lung immunology and inflammation. Clin Chest Med 2013;34(2): 155–164
21 Huson MA, Grobusch MP, van der Poll T. The effect of HIV infection on the host response to bacterial sepsis. Lancet Infect Dis 2015;15(1):95–108
22 Rossouw TM, Anderson R, Feldman C. Impact of HIV infection and smoking on lung immunity and related disorders. Eur Respir J 2015;46(6):1781–1795
23 Perreau M, Savoye AL, De Crignis E, et al. Follicular helper T cells serve as the major CD4 T cell compartment for HIV-1 infection, replication, and production. J Exp Med 2013;210(1):143–156
24 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
25 Gordon SB, Jagoe RT, Jarman ER, et al. The alveolar microenvironment of patients infected with human immunodeficiency virus does not modify alveolar macrophage interactions with *Streptococcus pneumoniae*. Clin Vaccine Immunol 2013;20(6): 882–891
26 Malley R. Antibody and cell-mediated immunity to *Streptococcus pneumoniae*: implications for vaccine development. J Mol Med (Berl) 2010;88(2):135–142
27 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
28 Feldman JG, Minkoff H, Schneider MF, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. Am J Public Health 2006;96(6):1060–1065
29 Gordin FM, Roediger MP, Girard P-M, 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
30 Petrosillo N, Cicalini S. Smoking and HIV: time for a change? BMC Med 2013;11:16
31 Helleberg M, Afzal S, Kronborg G, et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. Clin Infect Dis 2013;56(5):727–734
32 Feldman C, Anderson R. Cigarette smoking and mechanisms of susceptibility to infections of the respiratory tract and other organ systems. J Infect 2013;67(3):169–184
33 Sapkota AR, Berger S, Vogel TM. Human pathogens abundant in the bacterial metagenome of cigarettes. Environ Health Perspect 2010;118(3):351–356
34 Brook I, Gober AE. Recovery of potential pathogens and interfering bacteria in the nasopharynx of smokers and nonsmokers. Chest 2005;127(6):2072–2075
35 Voss M, Wonnenberg B, Honecker A, et al. Cigarette smoke-promoted acquisition of bacterial pathogens in the upper respiratory tract leads to enhanced inflammation in mice. Respir Res 2015;16(1):41
36 Kulkarni R, Antala S, Wang A, et al. Cigarette smoke increases *Staphylococcus aureus* biofilm formation via oxidative stress. Infect Immun 2012;80(11):3804–3811
37 Mutepe ND, Cockeran R, Steel HC, et al. Effects of cigarette smoke condensate on pneumococcal biofilm formation and pneumolysin. Eur Respir J 2013;41(2):392–395
38 Hutcherson JA, Scott DA, Bagaitkar J. Scratching the surface - tobacco-induced bacterial biofilms. Tob Induc Dis 2015;13(1):1
39 Kearley J, Silver JS, Sanden C, et al. Cigarette smoke silences innate lymphoid cell function and facilitates an exacerbated type I interleukin-33-dependent response to infection. Immunity 2015;42(3):566–579
40 Bourdonnay E, Zasłona Z, Penke LR, et al. Transcellular delivery of vesicular SOCS proteins from macrophages to epithelial cells blunts inflammatory signaling. J Exp Med 2015;212(5):729–742
41 Grigg J, Walters H, Sohal SS, et al. Cigarette smoke and platelet-activating factor receptor dependent adhesion of *Streptococcus pneumoniae* to lower airway cells. Thorax 2012;67(10):908–913
42 Schamberger AC, Mise N, Jia J, et al. Cigarette smoke-induced disruption of bronchial epithelial tight junctions is prevented by transforming growth factor-β. Am J Respir Cell Mol Biol 2014; 50(6):1040–1052
43 Lozupone C, Cota-Gomez A, Palmer BE, et al; Lung HIV Microbiome Project. Widespread colonization of the lung by *Tropheryma whipplei* in HIV infection. Am J Respir Crit Care Med 2013; 187(10):1110–1117
44 Cui L, Lucht L, Tipton L, et al. Topographic diversity of the respiratory tract mycobiome and alteration in HIV and lung disease. Am J Respir Crit Care Med 2015;191(8):932–942
45 Morris A, Beck JM, Schloss PD, et al; Lung HIV Microbiome Project. Comparison of the respiratory microbiome in healthy nonsmokers and smokers. Am J Respir Crit Care Med 2013; 187(10):1067–1075
46 Sopena N, Pedro-Botet ML, Sabrià M, García-Parés D, Reynaga E, García-Nuñez M. Comparative study of community-acquired pneumonia caused by *Streptococcus pneumoniae*, *Legionella pneumophila* or *Chlamydia pneumoniae*. Scand J Infect Dis 2004;36(5):330–334

47 Chidiac C. Pneumococcal infections and adult with risk factors. Med Mal Infect 2012;42(10):517–524

48 Kyaw MH, Rose CE Jr, Fry AM, et al; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis 2005;192(3): 377–386

49 Lynch JP III, Zhanel GG. *Streptococcus pneumoniae*: epidemiology, risk factors, and strategies for prevention. Semin Respir Crit Care Med 2009;30(2):189–209

50 Mufson MA, Hao JB, Stanek RJ, Norton NB. Clinical features of patients with recurrent invasive *Streptococcus pneumoniae* disease. Am J Med Sci 2012;343(4):303–309

51 Dworkin MS, Ward JW, Hanson DL, Jones JL, Kaplan JE; Adult and Adolescent Spectrum of HIV Disease Project. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. Clin Infect Dis 2001;32(5):794–800

52 Perelló R, Miró O, Marcos MA, et al. Predicting bacteremic pneumonia in HIV-1-infected patients consulting the ED. Am J Emerg Med 2010;28(4):454–459

53 Munier AL, de Lastours V, Porcher R, Donay JL, Pons JL, Molina JM. Risk factors for invasive pneumococcal disease in HIV-infected adults in France in the highly active antiretroviral therapy era. Int J STD AIDS 2014;25(14):1022–1028

54 Jover F, Cuadrado JM, Andreu L, et al. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. Eur J Intern Med 2008;19(1):15–21

55 Yin Z, Rice BD, Waight P, et al. Invasive pneumococcal disease among HIV-positive individuals, 2000-2009. AIDS 2012;26(1):87–94

56 Madeddu G, Fois AG, Pirina P, Mura MS. Pneumococcal pneumonia: clinical features, diagnosis and management in HIV-infected and HIV noninfected patients. Curr Opin Pulm Med 2009;15(3): 236–242

57 Feldman C, Klugman KP, Yu VL, et al; International Pneumococcal Study Group. Bacteraemic pneumococcal pneumonia: impact of HIV on clinical presentation and outcome. J Infect 2007;55(2): 125–135

58 Schleicher GK, Feldman C. Dual infection with *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* in HIV-seropositive patients with community acquired pneumonia. Int J Tuberc Lung Dis 2003;7(12):1207–1208

59 Sanz JC, Cercenado E, Marín M, et al. Multidrug-resistant pneumococci (serotype 8) causing invasive disease in HIV+ patients. Clin Microbiol Infect 2011;17(7):1094–1098

60 Isea-Peña MC, Sanz-Moreno JC, Esteban J, Fernández-Roblas R, Fernández-Guerrero ML. Risk factors and clinical significance of invasive infections caused by levofloxacin-resistant *Streptococcus pneumoniae*. Infection 2013;41(5):935–939

61 Allen SH, Brennan-Benson P, Nelson M, et al. Pneumonia due to antibiotic resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* in the HAART era. Postgrad Med J 2003;79(938): 691–694

62 Jordano Q, Falcó 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

63 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

64 Saindou M, Chidiac C, Miailhes P, et al. Pneumococcal pneumonia in HIV-infected patients by antiretroviral therapy periods. HIV Med 2008;9(4):203–207

65 Siemieniuk RAC, Gregson DB, Gill MJ. The persisting burden of invasive pneumococcal disease in HIV patients: an observational cohort study. BMC Infect Dis 2011;11:314

66 Nunes MC, von Gottberg A, de Gouveia L, et al. Persistent high burden of invasive pneumococcal disease in South African HIV-infected adults in the era of an antiretroviral treatment program. PLoS ONE 2011;6(11):e27929

67 Falcó V, Burgos J, Pahissa A. The spectrum of invasive pneumococcal disease in adults in the XXI century. Clin Pulm Med 2013; 20(5):214–220

68 Schlamm HT, Yancovitz SR. *Haemophilus influenzae* pneumonia in young adults with AIDS, ARC, or risk of AIDS. Am J Med 1989; 86(1):11–14

69 Moreno S, Martinez R, Barros C, Gonzalez-Lahoz J, Garcia-Delgado E, Bouza E. Latent *Haemophilus influenzae* pneumonia in patients infected with HIV. AIDS 1991;5(8):967–970

70 Casadevall A, Dobroszycki J, Small C, Pirofski LA. *Haemophilus influenzae* type b bacteremia in adults with AIDS and at risk for AIDS. Am J Med 1992;92(6):587–590

71 Rich JD, Sax PE, Kazanjian PH. Bacteremic *H. influenzae* type b infections and HIV. Am J Med 1993;95(1):118–119

72 Muñoz P, Miranda ME, Llancaqueo A, Peláez T, Rodríguez-Créixems M, Bouza E. Haemophilus species bacteremia in adults. The importance of the human immunodeficiency virus epidemic. Arch Intern Med 1997;157(16):1869–1873

73 Cordero E, Pachón J, Rivero A, et al. *Haemophilus influenzae* pneumonia in human immunodeficiency virus-infected patients. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. Clin Infect Dis 2000;30(3):461–465

74 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

75 Tumbarello M, Tacconelli E, Lucia MB, Cauda R, Ortona L. Predictors of *Staphylococcus aureus* pneumonia associated with human immunodeficiency virus infection. Respir Med 1996; 90(9):531–537

76 Gil Suay V, Cordero PJ, Martínez E, et al. Parapneumonic effusions secondary to community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients. Eur Respir J 1995;8(11):1934–1939

77 Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. Chest 2010;138(1):130–136

78 Daneshvar C, Smith NC, Waghorn DJ, Luzzi GA, Wathen CG. Community-acquired pneumonia due to Panton-Valentine leukocidin-producing *Staphylococcus aureus* in an HIV-2-infected patient. Int J STD AIDS 2011;22(10):610–612

79 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

80 Sandkovsky U, Sandkovsky G, Suh J, Smith B, Sharp V, Polsky B. Legionella pneumonia and HIV: case reports and review of the literature. AIDS Patient Care STDS 2008;22(6):473–481

81 Pedro-Botet ML, Sabrià M, Sopena N, et al. Legionnaires disease and HIV infection. Chest 2003;124(2):543–547

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

83 Comandini UV, Maggi P, Santopadre P, Monno R, Angarano G, Vullo V. *Chlamydia pneumoniae* respiratory infections among patients infected with the human immunodeficiency virus. Eur J Clin Microbiol Infect Dis 1997;16(10):720–726

84 Tositti G, Rassu M, Fabris P, et al. *Chlamydia pneumoniae* infection in HIV-positive patients: prevalence and relationship with lipid profile. HIV Med 2005;6(1):27–32

85 Shankar EM, Kumarasamy N, Vignesh R, et al. Epidemiological studies on pulmonary pathogens in HIV-positive and -negative subjects with or without community-acquired pneumonia with

special emphasis on *Mycoplasma pneumoniae*. Jpn J Infect Dis 2007;60(6):337–341
86 Ali NJ, Kessel D, Miller RF. Bronchopulmonary infection with *Pseudomonas aeruginosa* in patients infected with human immunodeficiency virus. Genitourin Med 1995;71(2):73–77
87 Meynard JL, Barbut F, Guiguet M, et al. *Pseudomonas aeruginosa* infection in human immunodeficiency virus infected patients. J Infect 1999;38(3):176–181
88 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
89 Manfredi R, Nanetti A, Ferri M, Chiodo F. *Pseudomonas* spp. complications in patients with HIV disease: an eight-year clinical and microbiological survey. Eur J Epidemiol 2000;16(2):111–118
90 Sadikot RT, Blackwell TS, Christman JW, Prince AS. Pathogen-host interactions in *Pseudomonas aeruginosa* pneumonia. Am J Respir Crit Care Med 2005;171(11):1209–1223
91 Williams BJ, Dehnbostel J, Blackwell TS. *Pseudomonas aeruginosa*: host defence in lung diseases. Respirology 2010;15(7): 1037–1056
92 Fujitani S, Sun HY, Yu VL, Weingarten JA. Pneumonia due to *Pseudomonas aeruginosa*: part I: epidemiology, clinical diagnosis, and source. Chest 2011;139(4):909–919
93 Topino S, Galati V, Grilli E, Petrosillo N. *Rhodococcus equi* infection in HIV-infected individuals: case reports and review of the literature. AIDS Patient Care STDS 2010;24(4):211–222
94 Manfredi R, Nanetti A, Valentini R, Chiodo F. *Moraxella catarrhalis* pneumonia during HIV disease. J Chemother 2000;12(5): 406–411
95 Smith MD, Derrington P, Evans R, et al. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW *Streptococcus pneumoniae* urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol 2003;41(7): 2810–2813
96 Jørgensen CS, Uldum SA, Sørensen JF, Skovsted IC, Otte S, Elverdal PL. Evaluation of a new lateral flow test for detection of *Streptococcus pneumoniae* and *Legionella pneumophila* urinary antigen. J Microbiol Methods 2015;116:33–36
97 Sheppard CL, Harrison TG, Smith MD, George RC. Development of a sensitive, multiplexed immunoassay using xMAP beads for detection of serotype-specific *streptococcus pneumoniae* antigen in urine samples. J Med Microbiol 2011;60(Pt 1):49–55
98 Pride MW, Huijts SM, Wu K, et al. Validation of an immunodiagnostic assay for detection of 13 *Streptococcus pneumoniae* serotype-specific polysaccharides in human urine. Clin Vaccine Immunol 2012;19(8):1131–1141
99 Elberse K, van Mens S, Cremers AJ, et al. Detection and serotyping of pneumococci in community acquired pneumonia patients without culture using blood and urine samples. BMC Infect Dis 2015;15:56
100 Slotved HC, Kaltoft M, Skovsted IC, Kerrn MB, Espersen F. Simple, rapid latex agglutination test for serotyping of pneumococci (Pneumotest-Latex). J Clin Microbiol 2004;42(6):2518–2522
101 Kuch A, Gołębiewska A, Waśko I, et al. Usefulness of Pneumotest-latex for direct serotyping of *Streptococcus pneumoniae* isolates in clinical samples. J Clin Microbiol 2014;52(7):2647–2649
102 Carvalho MdaG, Tondella ML, McCaustland K, et al. Evaluation and improvement of real-time PCR assays targeting lytA, ply, and psaA genes for detection of pneumococcal DNA. J Clin Microbiol 2007;45(8):2460–2466
103 Werno AM, Anderson TP, Murdoch DR. Association between pneumococcal load and disease severity in adults with pneumonia. J Med Microbiol 2012;61(Pt 8):1129–1135
104 Strålin K, Herrmann B, Abdeldaim G, Olcén P, Holmberg H, Mölling P. Comparison of sputum and nasopharyngeal aspirate samples and of the PCR gene targets lytA and Spn9802 for quantitative PCR for rapid detection of pneumococcal pneumonia. J Clin Microbiol 2014;52(1):83–89
105 Bogaerts P, Hamels S, de Mendonca R, et al. Analytical validation of a novel high multiplexing real-time PCR array for the identification of key pathogens causative of bacterial ventilator-associated pneumonia and their associated resistance genes. J Antimicrob Chemother 2013;68(2):340–347
106 Jamal W, Al Roomi E, AbdulAziz LR, Rotimi VO. Evaluation of Curetis Unyvero, a multiplex PCR-based testing system, for rapid detection of bacteria and antibiotic resistance and impact of the assay on management of severe nosocomial pneumonia. J Clin Microbiol 2014;52(7):2487–2492
107 Gadsby NJ, McHugh MP, Russell CD, et al. Development of two real-time multiplex PCR assays for the detection and quantification of eight key bacterial pathogens in lower respiratory tract infections. Clin Microbiol Infect 2015;21(8):788.e1–788.e13
108 Jain S, Self WH, Wunderink RG, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373(5):415–427
109 Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. Int J Tuberc Lung Dis 2010;14(10): 1295–1302
110 Piatek AS, Van Cleeff M, Alexander H, et al. GeneXpert for TB diagnosis: planned and purposeful implementation. Glob Health Sci Pract 2013;1(1):18–23
111 Theron G, Peter J, van Zyl-Smit R, et al. Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in a high HIV prevalence setting. Am J Respir Crit Care Med 2011; 184(1):132–140
112 Hanrahan CF, Theron G, Bassett J, et al. Xpert MTB/RIF as a measure of sputum bacillary burden. Variation by HIV status and immunosuppression. Am J Respir Crit Care Med 2014;189(11):1426–1434
113 Florin TA, Ambroggio L. Biomarkers for community-acquired pneumonia in the emergency department. Curr Infect Dis Rep 2014;16(12):451
114 Kolditz M, Ewig S, Höffken G. Management-based risk prediction in community-acquired pneumonia by scores and biomarkers. Eur Respir J 2013;41(4):974–984
115 Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. 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–S72
116 Mello CF, Negra MD. Impact of macrolide therapy on mortality of HIV-infected patients with community-acquired pneumonia in a tertiary teaching hospital. Braz J Infect Dis 2011;15(3):262–267
117 Baddour LM, Yu VL, Klugman KP, et al; International Pneumococcal Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170(4):440–444
118 Curran A, Falcó 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
119 Cordero E, Pachón 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
120 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
121 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

122 Yone EW, Balkissou AD, Kengne AP, Kuaban C. Influence of HIV infection on the clinical presentation and outcome of adults with acute community-acquired pneumonia in Yaounde, Cameroon: a retrospective hospital-based study. BMC Pulm Med 2012;12:46
123 Christensen D, Feldman C, Rossi P, et al; Community-Acquired Pneumonia Organization Investigators. 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
124 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–e27
125 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–e827
126 Feldman C, Glatthaar M, Morar R, et al. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. Chest 1999;116(1):107–114
127 Morris AM, Huang L, Bacchetti P, et al; The Pulmonary Complications of HIV Infection Study Group. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. Am J Respir Crit Care Med 2000;162(2, Pt 1):612–616
128 Osmond DH, Chin DP, Glassroth J, et al; Pulmonary Complications of HIV Study Group. Impact of bacterial pneumonia and *Pneumocystis carinii* pneumonia on human immunodeficiency virus disease progression. Clin Infect Dis 1999;29(3):536–543
129 Feldman C, Anderson R. Review: current and new generation pneumococcal vaccines. J Infect 2014;69(4):309–325
130 Musher DM. Pneumococcal vaccination in adults. UpToDate; April 2015, Available at: www.uptodate.com
131 WHO. . Pneumococcal polysaccharide vaccine. WHO position paper; March 2008, Available at: http://www.who.int/immunization/sage/1_PPV23_draft_March_3_clean.pdf
132 Leventer-Roberts M, Feldman BS, Brufman I, Cohen-Stavi CJ, Hoshen M, Balicer RD. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged ≥65 years: a retrospective case-control study. Clin Infect Dis 2015;60(10):1472–1480
133 Russell KL, Baker CI, Hansen C, et al. Lack of effectiveness of the 23-valent polysaccharide pneumococcal vaccine in reducing all-cause pneumonias among healthy young military recruits: a randomized, double-blind, placebo-controlled trial. Vaccine 2015;33(9):1182–1187
134 Peñaranda 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–e87
135 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
136 Imaz A, Falcó V, Peñaranda M, et al. Impact of prior pneumococcal vaccination on clinical outcomes in HIV-infected adult patients hospitalized with invasive pneumococcal disease. HIV Med 2009; 10(6):356–363
137 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
138 Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb Mortal Wkly Rep 2010;59(34): 1102–1106
139 Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61(40):816–819
140 Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis 2015;15(3):301–309
141 Lepoutre A, Varon E, Georges S, et al; Microbiologists of Epibac; ORP Networks. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001-2012. Vaccine 2015;33(2):359–366
142 Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MP, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis 2015;15(5):535–543
143 Chacon-Cruz E, Rivas-Landeros RM, Volker-Soberanes ML. Early trends in invasive pneumococcal disease in children following the introduction of 13-valent pneumococcal conjugate vaccine: results from eight years of active surveillance in a Mexican hospital. Ther Adv Vaccines 2014;2(6):155–158
144 Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015;372(12):1114–1125
145 Tomczyk S, Bennett NM, Stoecker C, et al; Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2014;63(37):822–825
146 Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003;349(14):1341–1348
147 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
148 Chan CY, Molrine DC, George S, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. J Infect Dis 1996;173(1):256–258
149 Lesprit P, Pédrono G, Molina JM, et al; ANRS 114-Pneumovac Study Group. Immunological efficacy of a prime-boost pneumococcal vaccination in HIV-infected adults. AIDS 2007;21(18): 2425–2434
150 Kumar D, Chen MH, Wong G, et al. A randomized, double-blind, placebo-controlled trial to evaluate the prime-boost strategy for pneumococcal vaccination in adult liver transplant recipients. Clin Infect Dis 2008;47(7):885–892
151 Miernyk KM, Butler JC, Bulkow LR, et al. Immunogenicity and reactogenicity of pneumococcal polysaccharide and conjugate vaccines in Alaska native adults 55-70 years of age. Clin Infect Dis 2009;49(2):241–248
152 Jackson LA, Gurtman A, van Cleeff M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine 2013;31(35): 3577–3584
153 Jackson LA, Gurtman A, van Cleeff M, et al. Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older. Vaccine 2013;31(35): 3594–3602
154 Greenberg RN, Gurtman A, Frenck RW, et al. Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-

valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adults 60-64 years of age. Vaccine 2014;32(20): 2364–2374

155 Iyer AS, Leggat DJ, Ohtola JA, et al. Response to pneumococcal polysaccharide vaccination in HIV-positive individuals on long term highly active antiretroviral therapy. J AIDS Clin Res 2015; 6(2):421

156 Hibberd PL. Immunizations in HIV-infected patients. UpToDate; May 2015; Available at: www.uptodate.com

157 Leggat DJ, Iyer AS, Ohtola JA, et al. Response to pneumococcal polysaccharide vaccination in newly diagnosed HIV-positive individuals. J AIDS Clin Res 2015;6(2):419

158 Rodriguez-Barradas MC, Serpa JA, Munjal I, et al. Quantitative and qualitative antibody responses to immunization with the pneumococcal polysaccharide vaccine in HIV-infected patients after initiation of antiretroviral treatment: results from a randomized clinical trial. J Infect Dis 2015;211(11):1703–1711

159 Engsig FN, Zangerle R, Katsarou O, et al; Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery. Clin Infect Dis 2014;58(9):1312–1321

160 Zoufaly A, Cozzi-Lepri A, Reekie J, et al; EuroSIDA in EuroCoord. Immuno-virological discordance and the risk of non-AIDS and AIDS events in a large observational cohort of HIV-patients in Europe. PLoS ONE 2014;9(1):e87160

161 Braitstein P, Brinkhof MW, Dabis F, et al; Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration; ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006; 367(9513):817–824

162 Keiser O, Orrell C, Egger M, et al; Swiss HIV Cohort Study (SHCS) and the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA). Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. PLoS Med 2008; 5(7):e148

163 Kantsø B, Green N, Goldblatt D, Benfield T. Antibody response is more likely to pneumococcal proteins than to polysaccharide after HIV-associated invasive pneumococcal disease. J Infect Dis 2015;212(7):1093–1099

164 Mdodo R, Frazier EL, Dube SR, et al. Cigarette smoking prevalence among adults with HIV compared with the general population in the United States. Ann Intern Med 2015; 162(5):335–344

165 McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev 2006;19(3): 571–582

166 Remschmidt C, Wichmann O, Harder T. Influenza vaccination in HIV-infected individuals: systematic review and assessment of quality of evidence related to vaccine efficacy, effectiveness and safety. Vaccine 2014;32(43):5585–5592

167 Cohen C, Moyes J, Tempia S, et al. Mortality amongst patients with influenza-associated severe acute respiratory illness, South Africa, 2009-2013. PLoS ONE 2015;10(3): e0118884