ORIGINAL ARTICLE

Pneumonia due to antibiotic resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* in the HAART era

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Antibiotic resistance profiles are useful in directing therapeutic strategies during bacterial infections. Patterns of antimicrobial resistance in *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* associated pneumonia were investigated in an HIV-1 infected cohort during the era of highly active antiretroviral therapy. The median CD4 count at presentation was significantly lower for cases of *P aeruginosa* than for *S pneumoniae*. However, the number of antibiotic resistant cases of *P aeruginosa* decreased throughout the study period, while the incidence of *S pneumoniae* remained unchanged. In contrast to pneumococcal pneumonia, we show that antiretrovirals have protected from pneumonia due to antibiotic resistant *P aeruginosa*. These findings have implications for the treatment of individuals presenting with serious infections in which antibiotic therapy needs to be instituted before identification and sensitivities are known.

Highly active antiretroviral therapy (HAART) has revolutionised the treatment and prognosis of patients with HIV, resulting in large decreases in their rates of hospitalisation.[1] Studies assessing the impact of HAART on the incidence of pneumonia differ however in their conclusions. Some demonstrate an overall decrease in the rates of pneumonia,[1 2] some an increase,[3] and others have found a decrease in pneumonia caused by *Pseudomonas aeruginosa* with an increase in cases caused by *Streptococcus pneumoniae*.[4] Despite the widespread availability of HAART and of antibiotics in the United Kingdom, pneumonia caused by these organisms remains a common cause of morbidity and mortality in HIV-1 infected individuals.[5] Such individuals also have an increased risk of recurrent infections[6] often resulting from relapse with the same bacterial strain or from reinfection with a different strain of the same species.[7] It is also known that the incidence and severity of pneumonia may increase with more advanced immunosuppression.[8] With the emergence of antibiotic resistance among pulmonary pathogens, the effective treatment of individuals with pneumonia and rational prescribing policy is aided by knowledge of antimicrobial susceptibility patterns from isolates obtained.[9]

We therefore determined the incidence of antimicrobial resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginsoa* associated pneumonia in an HIV infected cohort attending an HIV centre in London from the time that HAART was introduced, on 1 January 1996.

PATIENTS AND METHODS

The Chelsea and Westminster Hospital cohort of HIV positive individuals is one of the largest in Europe and we prospectively collect data on those patients who attend. The inclusion criteria for this study were those HIV positive patients who had symptoms and clinical and/or radiological signs of pneumonia between January 1996 and May 2002 and from whom at least one positive isolate of *S pneumoniae* or of *P aeruginosa* was obtained. Isolates were obtained from either blood culture, sputum, or bronchoalveolar lavage specimen for each hospital episode. Patients presenting with recurrent episodes of pneumonia were reincluded if they presented with a separate hospital episode after a previous test of cure as defined by clearance of the causative pathogen on repeat testing coupled with disease resolution.

Data were analysed by AIDS defining diagnosis, CD4 count, HIV-1 viral load, antiretroviral therapy, and mode of acquisition of HIV. Antibiotic susceptibility testing for all isolates was performed as part of the routine microbiological protocol using standard disc diffusion assays (Oxoid, Basingstoke, Hampshire, UK). Cut off values for antibiotic resistance to *S pneumoniae* and *P aeruginosa* isolates were determined using the British Standard for Antimicrobial Chemotherapy criteria and further validated by E-test minimal inhibitory concentrations in accordance with Cambridge Diagnostic Services protocol.

CD4 subset analysis in these individuals was performed using whole blood stained with murine antihuman monoclonal antibodies to CD4 (TetraOne, Beckman Coulter, High Wycombe, UK) that was then evaluated on an Epics XL-MCL (Beckman Coulter) flow cytometer. HIV viral loads in patient's plasma were measured using the Quantiplex HIV-RNA 3.0 (Chiron Diagnostics bDNA, Halsted, UK) assay with a lower limit of detection of 50 HIV-1 copies/ml (Chiron). Statistical analysis was performed using SPSS version 8.0.

RESULTS

Between January 1996 and May 2002, over 4000 HIV-1 positive individuals have been seen at the Chelsea and Westminster Hospital. In excess of two thirds of this cohort are men who have sex with men. During this time, we have observed 110 cases of pneumonia attributable to *S pneumoniae* and 64 attributable to *P aeruginosa*.

Streptococcus pneumoniae associated pneumonia

Throughout the study period, the CD4 count and HIV viral load at the time of diagnosis of a *S pneumoniae* associated chest infection remained unchanged (fig 1). There were no significant differences in either the CD4 count or the HIV viral load between patients with fully sensitive isolates of *S pneumoniae* compared with resistant isolates.

The median CD4 count at presentation measured 257 cells/mm^3 (range 1–792) and the median viral load was 47 722 copies/ml (range <50–500 000 copies/ml). The antibiotic resistance profile over time is shown in table 1. The highest
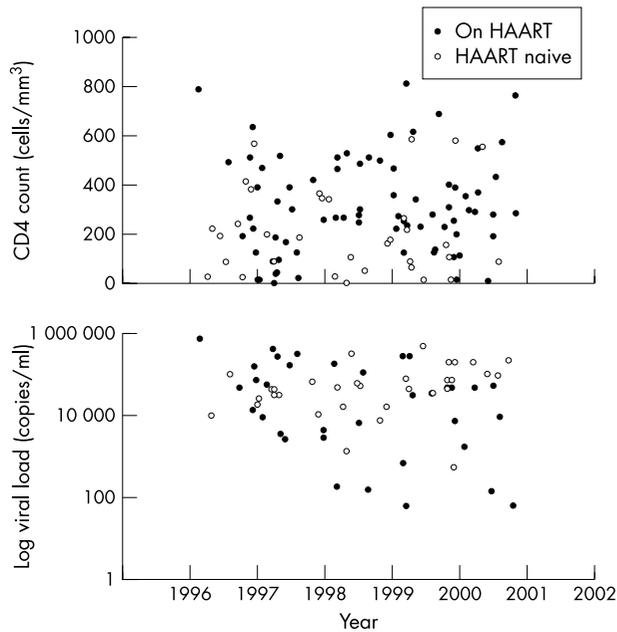
Figure 1 CD4 count and viral load for all HIV positive patients presenting with fully sensitive and with antibiotic resistant *S pneumoniae* pneumonia between May 1996 and May 2002.
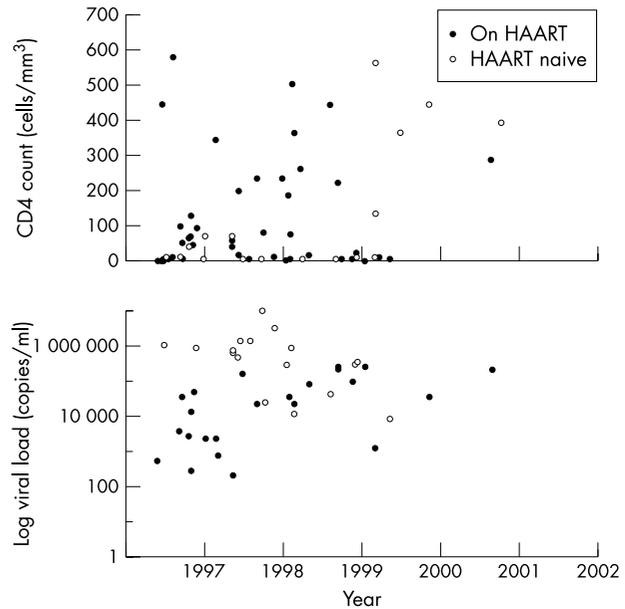

Figure 2 CD4 count and viral load for all HIV positive patients presenting with fully sensitive and with antibiotic resistant *Pseudomonas aeruginosa* pneumonia between May 1996 and May 2002.

incidence of resistant cases was observed in 1997, approximately two years after the introduction of HAART. At this time, multiple resistance profiles were not uncommon and resistance to penicillins, trimethoprim, and erythromycin was evenly distributed.

For HAART naive patients (n = 36) who acquired *S pneumoniae* chest infections, the median CD4 count was 290 cells/mm^3 (range 1–618) and the median viral load 45 784 copies/ml and we observed no significant differences between the HAART naive and experienced patients. Nine of the HAART naive patients (25%) had acquired a resistant isolate of *S pneumoniae* with the median CD4 count of these measuring 190 cells/mm^3 (range 12–512) and the median viral load 43 769 copies/ml (range <50–198 367). Once again, the difference in CD4 count and viral load between those who acquired fully sensitive and resistant strains of *S pneumoniae* was not statistically significant. In addition, we observed no significant differences in the incidence of antibiotic susceptible versus antibiotic resistant *S pneumoniae* between those individuals receiving HAART and those who were HAART naive.

Pseudomonas aeruginosa associated pneumonia

P aeruginosa was identified in 64 patients presenting with pneumonia (fig 2). The median CD4 count at presentation in this group measured 42 cells/mm^3 (range 1–560) which was

significantly lower than the CD4 count in the pneumococcal pneumonia group (p<0.01, Mann-Whitney U test). The median viral load measured 68 976 copies/ml (range 20 287–1 000 000) which showed no differences in statistical significance.

The antibiotic resistance profile in these patients over time is shown in table 2. During the HAART era, we observed a decrease in the number of cases of antibiotic resistant *P aeruginosa* from 19 patients in 1996 to two individuals in 2001. Unlike the situation with pneumococcal pneumonia, there were no cases of *P aeruginosa* resistant to more than two antibiotics.

Seventeen patients from whom isolates of *P aeruginosa* were obtained were HAART naive. For these, the median CD4 count measured 17 cells/mm^3 (range 3–503), significantly lower than in the HAART naive patients with pneumococcal pneumonia (p<0.01, Mann-Whitney U test) and median viral load was 230 433 copies/ml (range 20 287–1 000 000). Only four of these patients acquired antibiotic resistant strains of *P aeruginosa* and interestingly, these individuals had a median CD4 count of 227 cells/mm^3 (range 12–441) and a median viral load of greater than 500 000 copies/ml (range 34 331–>500 000).

DISCUSSION

Illness associated with pneumonia ranges from a self limiting infection to life threatening sepsis that requires rapid and

Table 1 Antibiotic resistance profiles in *Streptococcus pneumoniae* isolates collected from HIV infected patients between January 1996 and May 2002

Year	No of individuals	Penicillin resistant	Tetracycline resistant	Trimethoprim resistant	Erythromycin resistant	Resistant to 2 antibiotics	Resistant to 3 antibiotics	Resistant to 4 antibiotics
1996	10	1	1	1	1	1	1	0
1997	26	8	7	2	8	1	4	2
1998	13	0	0	0	0	0	0	0
1999	15	1	2	0	0	0	0	0
2000	20	4	5	0	5	1	2	0
2001	21	2	6	0	6	3	0	0
2002	6	1	0	1	0	0	0	0

Table 2 Antibiotic resistance in *Pseudomonas aeruginosa* isolates collected from HIV infected patients between January 1996 and May 2002

Year	No of individuals	Ciprofloxacin resistant	Imipenem resistant	Other resistance	Resistant to ≥2 or more antibiotics
1996	19	3	1	0	0
1997	13	1	0	0	0
1998	13	1	1	0	0
1999	14	1	0	0	0
2000	7	2	1	0	0
2001	1	0	1	0	0
2002	2	0	0	1 (pen)	0

aggressive antimicrobial treatment, a situation complicated by the increasing antibiotic resistance worldwide. Information on trends and antibiotic resistance in bacteraemia is needed to inform prescribing and infection control policy and to guide development of new antibiotics and vaccines.

In this study using data from the largest single centre HIV cohort in Europe, we observed that (i) pneumonia due to *S pneumoniae* was more common than pneumonia due to *P aeruginosa*, (ii) the CD4 count at presentation of pneumococcal pneumonia was significantly lower than the CD4 count at presentation of pseudomonal pneumonia, (iii) multidrug resistance profiles remain common in pneumococcal pneumonia, and (iv) the incidence of drug resistant isolates has decreased only for *P aeruginosa* and not for *S pneumoniae*.

The London region has the highest rates of penicillin and erythromycin resistance reported for pneumonia in the United Kingdom,[10] and the dense population here may well be a contributing factor. *S pneumoniae*, the commonest pathogen causing community acquired pneumonia, has over time developed resistance to most antibiotics used in its treatment and we show that the number of individuals presenting with resistant cases in the HAART era remains constant. Here, resistance exists most frequently to the β-lactam antibiotics but we also found resistance to macrolides (erythromycin), trimethoprim, and the tetracyclines. In contrast to this situation, we found that the number of cases presenting with antibiotic resistant *P aeuruginosa* decreased. While we found several cases of multiresistant *S pneumoniae*, we did not find that this was the case for *P aeuruginosa*. Co-trimoxazole is routinely used in our cohort as both primary (for patients with CD4 cell counts below 200/mm³) and secondary prophylaxis against *Pneumocystis carinii* pneumonia. We suggest that this may reduce the acquisition of antibiotic resistance. Patients with *P aeuruginosa* had lower CD4 cell counts and were therefore more likely to be receiving co-trimoxazole prophylaxis than patients who developed *S pneumoniae*. This may account for the falling incidence of antibiotic resistance in the former organism. This is also supported by the finding that antibiotic resistant *S pneumoniae* occurred in patients with a lower CD4 cell count and therefore more likely to be receiving co-trimoxazole prophylaxis than those who developed antibiotic sensitive *S pneumoniae*.

The consequences of resistance development are different depending on the class of antibiotic. For β-lactam penicillin antibiotics, the increase in the minimal inhibitory concentration is usually moderate, thus the high concentrations of antibiotic that can be achieved with this class does not inevitably lead to treatment failure. In contrast, resistance to other classes of antibiotics must be assumed to render these drugs ineffective.

In comparing HAART naive patients with HAART experienced patients we found that HAART naive patients who acquired resistant pneumococcal pneumonia had a lower CD4 count than those with fully sensitive cases. The data for the *P aeruginosa* group is confounded by a small sample size and lack of data concerning different HAART regimens and adherence to them. We found no differences between either pneumonia in age, sex, or of original mode of acquisition of HIV (data not shown).

In our HIV infected population we found an incidence of approximately 675/100 000 for *S pneumoniae* pneumonia and of these, one quarter had resistant isolates. The incidence for *P aeruginosa* was 350/100 000 of whom one fifth had resistant isolates. These findings are consistent with earlier findings among an HIV infected population in the pre-HAART era,[11] although the incidence is considerably higher than in the HIV negative population.

Specific immunisation against *S pneumoniae* is currently recommended for all HIV infected persons.[12] This 23 valent polysaccharide vaccine has a projected coverage of greater than 95% of all invasive disease due to *S pneumoniae*. However, the debate about whether revaccination of HIV infected persons, who are unable to mount a sustainable antibody response continues.[13 14] *P aeruginosa* associated chest infections are increasingly being recognised as an important cause of morbidity and mortality in HIV infected individuals,[15] and previous exposure of HIV positive patients to hospital environs is associated with increased incidence of pseudomonal infection.[16] This is accompanied by increased hospital stay, secondary bacteraemia, and higher mortality especially when the CD4 count is low.[15 17]

The newer quinolones, for example moxifloxacin, represent valuable alternatives for the treatment of pneumonia in HIV infected persons. They cover the three most common pulmonary pathogens in our HIV infected population (the third being *Haemophilus influenzae*) as well as atypical pathogens and, their efficacy is not affected by resistance to other classes of antibiotics. However, they should be used with caution in order to preserve this valuable class of drugs.

AUTHORSHIP
SHA and PBB are joint first authors, BG and JS joint last.

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Fetus by Chris Pye

Chris Pye began carving in 1975 with the late master carver Gino Masero. He had previously spent four years as a medical student in Cardiff but left to pursue a more creative career. Apart from woodcarving Chris writes books, draws, paints, models in clay, and teaches. He is also on the faculty at the Center for Furniture Craftsmanship in Rockport, Maine and has taught woodcarving in Finland.

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