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Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study

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***Objectives*: First-line therapy for *Pneumocystis jirovecii* pneumonia (PCP) is trimethoprim/sulfamethoxazole. Few data exist to guide the choice of second-line therapy for patients failing or developing toxicity to first-line therapy.**

***Methods*: A case note review of 1122 patients with 1188 episodes of HIV-associated PCP from three observational cohorts in Copenhagen, London and Milan, between 1989 and 2004, was conducted.**

***Results*: Trimethoprim/sulfamethoxazole (962 PCP episodes, 81%) was the most frequently used first-line therapy, followed by intravenous pentamidine (87 episodes, 7%), clindamycin/primaquine (72 episodes, 6%) and 'other' (atovaquone, dapsone/pyrimethamine, trimetrexate or inhaled pentamidine; 67 episodes, 6%). Rates of unchanged therapy were trimethoprim/sulfamethoxazole = 79%, clindamycin/primaquine = 65% and pentamidine = 60% ($P<0.001$). First-line therapy was changed because of failure in 82 (7%) episodes and because of toxicity in 198 (17%) episodes. Three month survival rates were trimethoprim/sulfamethoxazole = 85%, clindamycin/primaquine = 81% and pentamidine = 76% ($P=0.09$). After adjustment for possible confounders, pentamidine was associated with a significantly greater risk of death at 3 months [hazard ratio (HR) = 2.0, 95% confidence interval (CI) = 1.2–3.4]. Second-line therapy survival rates differed: trimethoprim/sulfamethoxazole = 85%; clindamycin/primaquine = 87%; and pentamidine = 60% ($P=0.01$). Multivariable time-updated Cox regression analysis showed a greater risk of death associated with pentamidine (HR = 3.3, 95% CI = 2.2–5.0), but not for clindamycin/primaquine, when both were compared with trimethoprim/sulfamethoxazole.**

***Conclusions*: Pentamidine was associated with a greater risk of death when used as first- and second-line therapy for HIV-associated PCP, and was associated with more treatment changes. Clindamycin/primaquine appeared superior to pentamidine as second-line therapy for PCP in patients failing or developing toxicity with trimethoprim/sulfamethoxazole. In patients failing first-line treatment with non-trimethoprim/sulfamethoxazole regimens, second-line therapy should be trimethoprim/sulfamethoxazole.**

Keywords: PCP, pneumocystis, therapy, adverse drug reactions, HIV-1

Introduction

Pneumocystis jirovecii is the cause of *P. jirovecii* pneumonia (PCP). Early in the AIDS pandemic, PCP was a major cause of morbidity and mortality. The use of PCP prophylaxis and combination antiretroviral therapy has dramatically reduced the risk of PCP, but it remains a significant problem among individuals without access to these therapies, among individuals who are intolerant or non-adherent and among individuals unaware of their HIV infection.[1]

The recommended treatment of PCP has remained unchanged for many years. Several options, but few data, exist to guide

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first- and second-line treatment for PCP. In two randomized clinical trials (RCTs) of HIV-associated PCP, trimethoprim/sulfamethoxazole and pentamidine were equally effective.[2,3] However, interpretation of these trials remains limited by a high rate of treatment switches due to toxicity or treatment failure and a limited sample size. In a small non-crossover RCT, treatment with trimethoprim/sulfamethoxazole was associated with fewer adverse events and improved survival.[4] Subsequent trials have demonstrated comparable efficacy of oral trimethoprim/sulfamethoxazole, clindamycin/primaquine and trimethoprim/dapsone, but patients with severe PCP were excluded.[5,6] Use of primaquine, dapsone and trimethoprim may be restricted, because they can only be administered orally. Thus, intravenous pentamidine has been recommended as the main alternative to trimethoprim/sulfamethoxazole for moderate to severe PCP in spite of its toxicity.[7] RCTs of second-line treatment of PCP have not been performed. A meta-analysis suggested that second-line treatment with clindamycin/primaquine is associated with a more favourable outcome compared with pentamidine.[8] In an updated systematic review, which included data from patients in the present study who switched treatment due to failure, this finding was confirmed.[9] In the present study, we provide a more detailed analysis of the efficacy and toxicity of first- and second-line PCP treatment, based on 1188 episodes of HIV-associated PCP between 1989 and 2004.

Methods

Patients

Data were collected from three cohorts of HIV-associated PCP in Copenhagen (Denmark), London (UK) and Milan (Italy). In Copenhagen, all cases of HIV-associated PCP admitted to the Department of Infectious Diseases or to the Intensive Care Unit (ICU) of Hvidovre University Hospital or Copenhagen University Hospital, from January 1989 through June 2004, were included. Patients were identified from a prospective study of HIV-associated PCP and a manual search of the case records of all HIV-infected patients during the study period.[10] In London, all cases of HIV-associated PCP admitted to the specialist HIV/AIDS inpatient facility and to the ICU of University College London Hospitals, from January 1989 through June 2004, were included. Patients were identified from a prospective study of HIV-associated PCP, and from a manual and electronic search of the case records of all HIV-infected patients receiving care at these centres during the study period. In Milan, all cases of HIV-associated PCP admitted to the II Department of Infectious Diseases and to the ICU of Luigi Sacco Hospital from January 1994 through June 2004 were included. All patients had PCP diagnosed by analysis of bronchoscopic alveolar lavage (BAL) fluid, induced sputum, sputum/oral rinse or at autopsy.

Data collection

Treatment data were collected through chart review. Patient demographics, laboratory data, mode of diagnosis of PCP, presence of pulmonary co-pathology, prescription of PCP prophylaxis, dates of treatment start and cessation, treatment switches and reasons for treatment changes were recorded. Additionally, development of pneumothorax, need for ICU and mechanical ventilation (MV), and outcome were recorded for each patient.

Treatment

During the study period, choice of PCP treatment was consistent across all three centres, using similar protocols for drug dosage and administration as recommended in international guidelines:[11] a 21 day course of treatment was standard. Additionally, nebulized pentamidine (8 mg/kg/day once daily) was used in a few patients at the beginning of the study period. From 1990 onwards, adjuvant glucocorticoids (methylprednisolone or prednisone in dosages as recommended[12]) were used for patients with moderate to severe PCP (based on a PaO_2 of <9.3 kPa, breathing room air at admission) at all sites. Use of PCP prophylaxis was defined as a patient's receipt of specific PCP prophylaxis during the 3 months prior to admission.

Definitions of endpoints

The reason for a switch of drug treatment was classified as either caused by toxicity or caused by suspected failure of treatment.

Toxicity was determined by the attending physician and frequently was a composite of the following criteria: *dermatological*—severe rash not present prior to starting PCP therapy; *haematological*—fall in neutrophil count, methaemoglobinaemia $>5\%$, anaemia (fall in haemoglobin by >3 g/dL) or fall in platelet count (if normal at baseline, fall to $<100\times10^9$/L, or if low at baseline, fall by $>25\times10^9$/L); *renal*—rise in serum creatinine to $>2\times$ the upper limit of normal; *gastrointestinal*—severe nausea with or without vomiting on ≥2 days, diarrhoea, or a rise in alanine or aspartate aminotransferase or alkaline phosphatase enzyme levels by $>2\times$ the upper limit of normal; *drug fever*—onset of fever to $>38^\circ$C, after the patient had been afebrile on therapy for >48 h; or *other*—hypotension, hypoglycaemia, symptomatic hypocalcaemia or elevated amylase level by $>5\times$ the upper limit of normal.

Treatment failure was defined as persistent fever and worsening hypoxia, and/or radiographic deterioration, occurring after ≥4 full days of first-line or second-line therapy. *Survival* was defined as being alive 3 months after therapy was initiated. Treatment response was defined as survival or definitive clinical improvement (defervescence, improvements in dyspnoea and chest radiographs, and hospital discharge).

Statistical analysis

Data were analysed using Stata, version 9.1 (StataCorp). The main endpoint was 3 month mortality after the start of initial PCP treatment. Patients were left-truncated with regard to episode of PCP (i.e. only the last episode was included in analyses). Time to mortality was analysed with multivariable Cox regression models. In all analyses, PCP treatment, arterial PaO_2 on admission, age, latest CD4 count, year of diagnosis and country were placed into the model. Additional predictors assessed were use of PCP prophylaxis, sex, HIV risk transmission group and detection of bacterial co-infection or cytomegalovirus (CMV) in BAL fluid. From these predictor variables, a final parsimonious model was defined by backward selection using minimization of the Aikaike Information Criterion, which has been shown to be an appropriate method for selecting the degree to which a model should be simplified.[13,14] The proportionality of hazards assumptions was tested using the Schoenfeld residual test and overall model fit by Cox–Snell residuals. Detection of CMV was dropped from the final model, because of many missing variables. In all analyses, robust (Huber–White) variance estimates were used.

Hazard ratios (HRs) are presented with robust 95% confidence intervals (CIs). Since changes of treatment were frequent, many

patients died while receiving second- or third-line drugs. In an attempt to analyse the risk of death according to the drug received, time-updated Cox regression analysis was done by splitting exposure time according to each treatment received, which allowed a time-dependent analysis of exposure to each drug. Prognostic variables included were PaO_2 at admission, age, CD4 cell count, year of diagnosis, bacterial co-infections, use of previous PCP prophylaxis and country. Optimally, time-updated regression analysis would have included PaO_2 at each treatment change; however, since PaO_2 measurements during the course of treatment were either unavailable or unreliable, admission PaO_2 was used as a fixed value for each patient in the analysis.

Results

In total, 1188 episodes of HIV-associated PCP in 1122 patients from January 1989 through June 2004 were analysed. There were 555 episodes of PCP from Copenhagen, 418 episodes from London and 215 episodes from Milan. Key data for each centre are shown in Table 1.

Following treatment of PCP, 17 (1.5%) patients were lost to follow-up before 3 months.

Throughout the study period, the age of patients and the severity of PCP, as judged by the median PaO_2 or the need for admission to the ICU, remained unchanged. Only minor variation in age or severity of disease, as measured by PaO_2 at admission, was observed between the three countries, but patients from Milan were more often female (21%) and more often had a history of intravenous drug use (44%) compared with patients from Copenhagen (8% female, 2% intravenous drug users) and London (8% female, 6% intravenous drug users). During the study period, an increasing number of patients presented with PCP as their first AIDS-defining event (in London and Copenhagen, data unavailable for Milan: 1989–92, 87%; 1993–96, 85%; 1997–2000, 93%; and 2001–04, 95%; χ^2 for trend $P=0.03$) and had never received PCP prophylaxis (1989–92, 88%; 1993–96, 86%; 1997–2000, 93%; and 2001–04, 96%; χ^2 for trend $P=0.0072$).

Treatment

First-line treatment regimens, reasons for switch and outcome are shown in Tables 2 and 3.

Trimethoprim/sulfamethoxazole was used as the first-line treatment regimen in 81% of episodes ($n=962$). Intravenous pentamidine ($n=87$, 7%) and clindamycin/primaquine ($n=72$, 6%) were the most frequently used alternative drugs. In London prior to 1992, 49 patients (4%) were treated with nebulized pentamidine. Overall, 18 patients (2%) received dapsone/trimethoprim, atovaquone or trimetrexate as their first-line treatment regimen (Table 1).

In 311 (26%) of episodes, first-line treatment was changed to another drug; in 207 because of toxicity and in 104 because of treatment failure. Among patients in who first-line treatment changed due to suspected failure, 22 patients were changed before 4 full days of therapy and so were excluded from analysis. The majority of such early 'failure' changes occurred before 1992. The median time to change was 10 days, regardless of reason. In 65 (6%) of episodes, a third-line regimen was chosen because of toxicity ($n=48$) or failure ($n=17$). Commonly observed adverse effects leading to a change of treatment were dermatological and haematological toxicity (trimethoprim/sulfamethoxazole), renal toxicity (intravenous pentamidine) and haematological toxicity (clindamycin/primaquine).

Change in first-line treatment occurred more frequently in London (41%) compared with Milan (23%) and Copenhagen (16%). The higher rate of treatment change in London was only partly explained by the use of nebulized pentamidine; 22 patients were changed from nebulized pentamidine (19 failure and 3 toxicity). Excluding these cases, the rate of treatment change in London was 36%. In all three cohorts, there was overall similar availability and access to alternative PCP treatments during the study period. The observed difference was largely explained by less frequent switching due to toxicity; only 9% of patients were switched due to toxicity in Copenhagen compared with 29% in London and 17% in Milan. However, across the study period, only relatively minor changes in the rate and the reasons for change of treatment were observed (23% of patients had their first-line treatment changed in 1989–92 compared with 18% in 2001–04, $P=0.23$).

Response to first-line treatment regimen

Overall response rates were initially analysed as a function of first-line treatment without adjustment for change of treatment (intention-to-treat) (Table 3 and Figure 1). Three month mortality rates according to first-line treatment were trimethoprim/sulfamethoxazole = 15%, clindamycin/primaquine = 19% and pentamidine = 24%. Mortality was significantly lower (3%) for the few patients who received first-line treatment with 'other' treatment (nebulized pentamidine, atovaquone, dapsone/trimethoprim or trimetrexate); however, the majority had mild disease at admission (median $PaO_2 = 10.7$ kPa, compared with $PaO_2 = 8.6$ kPa for patients receiving trimethoprim/sulfamethoxazole, $P=0.0001$). In contrast, use of pentamidine was associated with a significantly increased risk of death at 3 months in multivariable analysis, after adjustment for possible confounders [HR = 2.0 (95% CI = 1.2–3.4)]. There was no indication that the efficacy of trimethoprim/sulfamethoxazole declined over the study period. In intention-to-treat analysis of trimethoprim/sulfamethoxazole as first treatment, 3 month mortality fell from 15% in 1989–92 and 18% in 1993–96 to 12% in 1997–2000 and 10% in 2001–04.

Response to second-line therapy

Outcome, defined as survival 3 months after admission, was analysed according to choice of second-line therapy, in which treatment was changed due to toxicity or because of failure (Figure 2). In patients switched because of toxicity, 3 month survival rates were numerically, but non-significantly, lower than for patients switched due to treatment failure: trimethoprim/sulfamethoxazole, 0/9 versus 4/24; pentamidine, 18/63 versus 17/32; clindamycin/primaquine, 7/101 versus 7/20; and 'other', 2/33 versus 1/6. The 3 month mortality was significantly higher for patients receiving pentamidine (53%) compared with trimethoprim/sulfamethoxazole (17%) and clindamycin/primaquine (29%) when used because of treatment failure [odds ratio = 3.5 (95% CI = 2.4–4.9)]. In time-updated Cox regression analysis, in which exposure time to individual drugs was taken into account, use of pentamidine conferred an adjusted HR of

Table 1. Clinical characteristics of study subjects by country

Variable	Copenhagen, Denmark	London, UK	Milan, Italy	Total
No. of PCP episodes/patients	555/531	418/376	215/215	1188/1122
Period, *n* (%)				
1989–92	264 (48%)	156 (37%)	NA	420 (35%)
1993–96	179 (32%)	172 (41%)	54 (25%)	405 (34%)
1997–2000	63 (11%)	57 (14%)	67 (31%)	187 (16%)
2001–04	49 (9%)	33 (8%)	94 (44%)	176 (15%)
Male sex, *n* (%)	485 (91%)	346 (92%)	170 (79%)	1001 (89%)
Median age, years	39 (17–76)	37 (21–72)	37 (20–75)	39 (17–76)
Method of diagnosis, *n* (%)				
bronchoalveolar lavage	354 (63%)	385 (92%)	196 (91%)	935 (79%)
induced sputum	181 (33%)	20 (5%)	15 (7%)	216 (18%)
sputum/oral wash	18 (4%)	11 (3%)	4 (2%)	33 (3%)
autopsy	2 (0.4%)	2 (0.5%)		4 (0.3%)
CD4 T cell count	6 (0–349)	40 (0–400)	30 (0–378)	21 (0–400)
HIV transmission group, *n* (%)				
homosexual	334 (63%)	309 (82%)	42 (20%)	685 (61%)
heterosexual	107 (20%)	46 (12%)	79 (37%)	233 (21%)
IDU	30 (6%)	8 (2%)	94 (44%)	132 (13%)
transfusion	9 (2%)			9 (1%)
unknown	50 (9%)	13 (3%)		63 (6%)
PaO_2 at admission, kPa	8.6 (4.1–13.9)	9.4 (3.9–13.6)	8.4 (3.5–14.0)	8.8 (2.9–14.0)
Adjunctive steroid, *n* (%)	338 (61%)	193 (46%)	118 (55%)	649 (55%)
PCP as first AIDS diagnosis, *n* (%)	486 (88%)	368 (88%)	NA	854 (88%)
First-line treatment regimen, *n* (%)				
SXT	507 (91%)	263 (63%)	192 (89%)	962 (81%)
pentamidine	40 (7%)	44 (11%)	3 (1%)	87 (7%)
clindamycin/primaquine	4 (1%)	53 (13%)	15 (7%)	72 (6%)
other[a]	4 (1%)	58 (14%)[b]	5 (2%)	67 (6%)
Switch of first-line treatment, *n* (%)				
no switch	466 (84%)	245 (59%)	166 (77%)	877 (74%)
toxicity switch	50 (9%)	120 (29%)	37 (17%)	207 (17%)
failure switch, >4 days of treatment	31 (6%)	43 (10%)	8 (4%)	82 (7%)
failure switch, <5 days of treatment	8 (1%)	10 (2%)	4 (2%)	22 (2%)
Second-line treatment regimen, *n* (%)				
SXT	8 (9%)	26 (15%)	7 (14%)	41 (13%)
pentamidine	62 (70%)	32 (18%)	9 (18%)	103 (33%)
clindamycin/primaquine	16 (18%)	83 (48%)	27 (55%)	126 (41%)
other[a]	3 (3%)	32 (18%)	6 (12%)	41 (13%)
Switch to third-line regimen, *n* (%)	7 (1%)	43 (10%)	15 (7%)	65 (5%)
ICU admission, *n* (%)	66 (12%)	46 (11%)	11 (6%)	123 (10%)
MV, *n* (%)	57 (10%)	28 (7%)	10 (5%)	95 (8%)
3 month mortality, %	18.2%	13.1%	7.9%	14.5%

IDU, intravenous drug use; NA, not available; SXT, trimethoprim/sulfamethoxazole.
All values are medians and ranges unless otherwise stated.
[a]Other treatment: atovaquone; dapsone/trimethoprim; or inhaled pentamidine.
[b]Forty-nine patients received inhaled pentamidine.

Table 2. First-line treatment for PCP and reasons for switching treatment

First-line treatment regimen	Toxicity switch, *n* (%)	Failure switch, *n* (%)
SXT, $n=962$	159 (17)	46 (5)
Pentamidine, $n=87$	22 (25)	13 (15)
Clindamycin/primaquine, $n=72$	18 (25)	7 (10)
Other treatment,[a] $n=67$	8 (12)	16 (24)
Total	207 (17)	82 (7)

SXT, trimethoprim/sulfamethoxazole.
Data from all episodes of PCP.
Failure switch: switch after >4 full days of treatment because of treatment failure.
Episodes in which treatment was changed before 5 days ($n=22$), because of suspected toxicity, are not listed.
Part of these data was published previously.[9]
[a]Other treatment: inhaled pentamidine ($n=49$); dapsone ($n=8$); atovaquone ($n=7$); and trimetrexate ($n=3$).

3.3 (95% CI=2.2–5.0) of risk of death before 3 months compared with trimethoprim/sulfamethoxazole (Table 4).

The majority of patients initiated treatment with trimethoprim/sulfamethoxazole ($n=962$). Overall, a proportionally higher rate of patients who experienced trimethoprim/sulfamethoxazole toxicity were switched to clindamycin/primaquine ($n=88$, 56%) rather than pentamidine ($n=54$, 34%), whereas more patients received pentamidine ($n=27$, 59%) compared with clindamycin/primaquine ($n=16$, 35%) for treatment failure. Restricting the analysis to patients initiating treatment with trimethoprim/sulfamethoxazole and who switched therapy due to toxicity ($n=159$), 3 month mortality rates were pentamidine=33% and clindamycin/primaquine=7% ($P=0.0001$). Among patients who failed a first-line regimen of trimethoprim/sulfamethoxazole ($n=46$), the 3 month mortality rate for pentamidine was 60% ($n=27$) compared with 38% for clindamycin/primaquine ($n=16$) ($P=0.17$).

Rates of ICU admission and MV were similar among patients failing first-line treatment who were switched to pentamidine (ICU=50%, MV=43%) and to clindamycin/primaquine (ICU=45%, MV=30%) ($P=0.32$ and 0.73, respectively). Among patients who were switched because of toxicity, 14% of patients who received pentamidine as second-line treatment were already in the ICU at the time of the switch, compared with 6% of patients receiving clindamycin/primaquine and none receiving trimethoprim/sulfamethoxazole ($P=0.112$). After switch of treatment to pentamidine (regardless of reason), 9% of patients had progressive disease necessitating subsequent ICU admission, compared with 5% of patients switched to clindamycin/primaquine and 5% of trimethoprim/sulfamethoxazole-switched patients ($P=0.156$).

Bacterial co-infection

The impact of concomitant infection on outcome of drug treatment was assessed. According to first-line PCP therapy, rates of concomitant bacterial lower respiratory tract infection were pentamidine=15%, trimethoprim/sulfamethoxazole=10% and clindamycin/primaquine=5% ($P=0.031$). Among patients switching due to toxicity, a higher rate of concomitant bacterial co-infection was seen in patients switching to pentamidine=13% compared with other second-line treatment=3% ($P=0.025$).

Discussion

A recent systematic review of second-line therapy for HIV-related PCP, which included some second-line treatment outcome data from the current cohort study, examined the efficacy of different second-line treatments for HIV-associated PCP.[9] Analysis was limited to patients failing first-line treatment; adjustments for potential confounding by baseline factors or toxicity were not possible due to the study design (a pooled analysis with an average odds ratio of survival). In this study, we have expanded our analysis, and describe in detail the outcome and toxicity for use of both first- and second-line treatment of PCP.

Our data show that both first- and second-line treatment with intravenous pentamidine was associated with a significantly worse outcome compared with other drug regimens. The increased risk of death associated with pentamidine was primarily related to inferior efficacy when used as second-line treatment. Importantly, the greater risk of death was observed for patients switched to pentamidine because of suspected treatment failure as well as patients who changed to pentamidine because of toxicity. Overall, we observed a better outcome from PCP treated with trimethoprim/sulfamethoxazole compared with other treatment options, for both first- and second-line treatment.

Several explanations may be offered for the apparent inferiority of intravenous pentamidine. First, toxicity caused by pentamidine may have contributed. Several studies have described serious and fatal adverse effects from pentamidine.[15,16] Second, the inferior efficacy of pentamidine could result from the absence of an antibacterial effect (in contrast to trimethoprim/sulfamethoxazole or clindamycin/primaquine). This latter hypothesis is difficult to test, but is in part supported by the significantly higher rate of concomitant bacterial co-infection among patients treated with pentamidine, when compared with other agents. Finally, the lower response rate for patients who were switched to pentamidine because of toxicity could be explained by more severe disease rather than lower efficacy, as patients failing their first-line treatment regimen preferentially were switched to pentamidine. However, disease severity, as assessed by need for ICU admission and MV at the time of switch, was similar among patients switched to pentamidine and to clindamycin/primaquine as a result of treatment failure. Additionally, the increased risk of death associated with pentamidine as second-line treatment remained statistically significant in the time-updated model that accounted for individual drug exposure throughout the episode of PCP; albeit, the HR fell from 12- to 3-fold.

The finding of an apparent excess mortality associated with intravenous pentamidine must be interpreted with caution. Since our study was retrospective and observational, inferences about causation are speculative. Our study includes patients from four hospitals in three countries and spans a considerable time period during which several changes in the management of HIV-related PCP were introduced, including adjunctive corticosteroids in 1990 and improved ICU management of all-cause acute respiratory failure from 1996 onwards.[12,17] During the study period, the incidence of and mortality from PCP declined. The introduction of combination antiretroviral therapy (cART) after 1996 has led

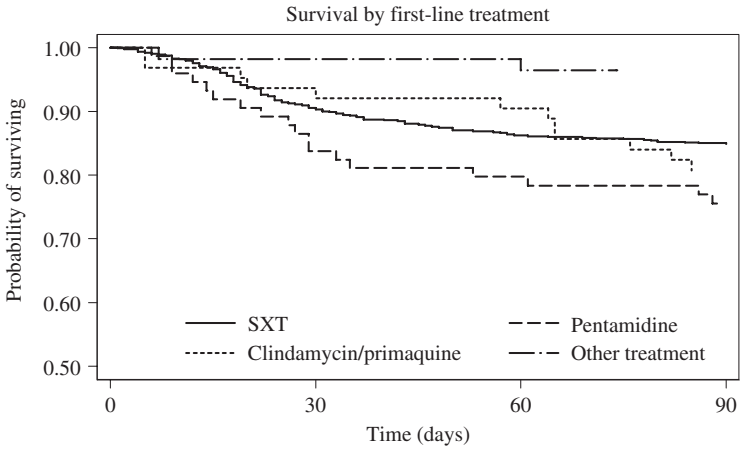
Table 3. Univariate and multivariable analysis of 3 month survival from PCP according to first-line treatment regimen

Characteristics	Subjects, *n* (%)	Univariate analysis, HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
First-line treatment					
SXT	929 (83%)	1.0 (reference group)			
pentamidine	74 (7%)	1.70 (1.04–2.77)	0.035	2.0 (1.2–3.4)	0.013
clindamycin/primaquine	63 (6%)	1.25 (0.70–2.20)	0.465	1.6 (0.8–3.2)	0.145
other treatment	56 (5%)	0.22 (0.05–0.90)	0.035	0.7 (0.1–3.5)	0.682
PaO_2 at diagnosis (kPa)					
>10.2	274 (24%)	1.0 (reference group)			
8.8–10.2	247 (22%)	1.40 (0.83–2.37)	<0.001[a]	1.2 (0.7–2.1)	0.45
7.3–8.7	276 (25%)	1.47 (0.88–2.45)		1.3 (0.8–2.3)	0.281
<7.3	266 (24%)	3.12 (1.97–4.93)		3.2 (1.9–5.4)	<0.001
missing data	59 (5%)				
Age (years)					
17–29	167 (15%)	1.0 (reference group)			
30–39	502 (45%)	0.93 (0.56–1.55)	<0.001[a]	0.7 (0.4–1.3)	0.29
40–49	293 (27%)	1.39 (0.83–2.35)		1.3 (0.7–2.2)	0.411
≥50	160 (14%)	2.75 (1.63–4.63)		2.5 (1.4–4.3)	0.001
CD4 cell count (cells/mm^3)					
>100	158 (14%)	1.0 (reference group)			
50–99	168 (15%)	0.87 (0.42–1.80)	0.002[a]	0.7 (0.3–1.6)	0.406
25–49	155 (14%)	1.28 (0.65–2.52)		1.4 (0.7–2.9)	0.338
<25	537 (48%)	2.24 (1.31–3.85)		1.9 (1.1–3.5)	0.027
missing data	104 (9%)				
Year of diagnosis					
1989–92	389 (35%)	1.0 (reference group)			
1993–96	376 (34%)	1.36 (0.97–1.91)	0.014[a]	1.3 (0.9–1.9)	0.22
1997–2000	185 (16%)	0.81 (0.50–1.31)		0.7 (0.4–1.3)	0.321
2001–04	172 (15%)	0.56 (0.32–0.99)		0.6 (0.3–1.2)	0.211
Bacterial co-infection detected at admission					
no	1014 (90%)	1.0 (reference group)			
yes	108 (10%)	1.89 (1.25–2.85)	0.002	1.48 (0.9–2.4)	0.119
Prescribed PCP prophylaxis					
no	929 (83%)	1.0			
yes	193 (17%)	1.53 (1.07–2.18)	0.017	1.7 (1.1–2.6)	0.106
Country					
Denmark	531 (47%)	1.0 (reference group)			
UK	376 (34%)	0.7 (0.5–1.1)	0.07	1.2 (0.8–1.9)	0.368
Italy	215 (19%)	0.4 (0.2–0.7)	<0.001	0.6 (0.3–1.1)	0.119

SXT, trimethoprim/sulfamethoxazole.
Analysis of last episode of PCP.
Multivariable analysis adjusted for PaO_2 at admission, age, year of admission, CD4 cell count, PCP prophylaxis, bacterial co-infection and country.
Goodness of fit: log likelihood = −944.8, $\chi^2 = 102.8$, $P < 0.00001$.
[a]χ^2 for trend.

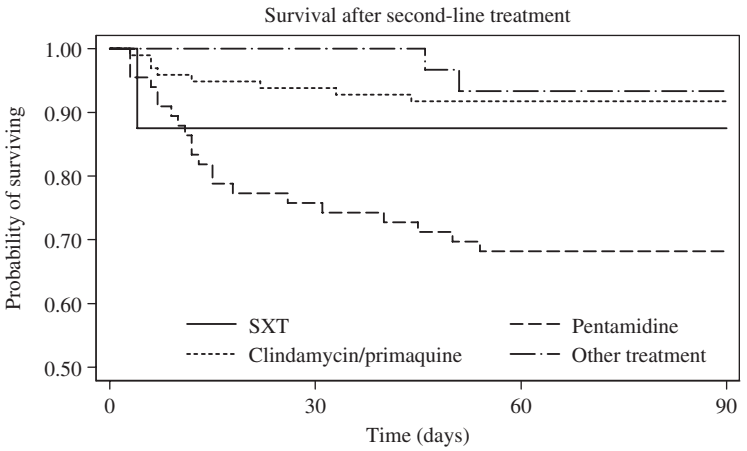
to markedly improved immune function and, thus, explains the decreased incidence of PCP.[18] In our study, very few patients were receiving cART at the time of PCP diagnosis, which for the majority was the manifestation of HIV. Until recently, there had not been randomized controlled trials to support or discourage early initiation of cART in the setting of an acute opportunistic infection.[19] In our hands, we have deferred cART until the completion of antimicrobial treatment in order to minimize drug toxicity and interactions. A recent study from the AIDS Clinical Trials Group, however, indicates that the early use of cART resulted in less AIDS progression and death.[20] Thus, it is likely that the use of cART after diagnosis of PCP may have contributed to improvements in outcome over time.

In clinical practice it may be difficult to distinguish between progressive PCP, drug toxicity or concomitant infection as the cause of clinical deterioration. Previously reported failure rates with trimethoprim/sulfamethoxazole as first-line treatment in HIV-associated PCP have varied considerably, ranging from



Number at risk				
SXT	929	837	789	776
Pentamidine	74	62	58	53
Clindamycin/primaquine	63	59	57	49
Other treatments	56	55	55	53

Figure 1. Kaplan–Meier plot of 3 month mortality according to first-line treatment by intention-to-treat. SXT, trimethoprim/sulfamethoxazole.



Number at risk				
SXT	16	14	14	14
Pentamidine	66	50	45	45
Clindamycin/primaquine	97	91	87	85
Other treatments	30	30	28	28

Figure 2. Kaplan–Meier survival plot of time to death according to second-line treatment after switch of treatment. Only patients in which secondary treatment due to toxicity or suspected treatment failure after 4 days of primary treatment are shown. SXT, trimethoprim/sulfamethoxazole.

10% to 40%.[21–23] We observed pronounced differences between the three centres in frequency of treatment changes. More patients were switched due to toxicity in London compared with Copenhagen. It is likely that the observed difference between centres in management of toxicity are explained by different treatment practices. In Denmark, patients experiencing minor toxicity from trimethoprim/sulfamethoxazole are managed by dose reduction. In contrast, in London and Milan toxicity is usually managed by switching treatment to a different drug regimen. Overall, a proportionally higher rate of patients who experienced toxicity from trimethoprim/sulfamethoxazole was switched to clindamycin/primaquine rather than pentamidine compared with those switched because of failure. Although we aimed to correct for this differential choice of second-line agents, residual confounding may be present.

The implications of our study help inform the choice of second-line treatment in patients intolerant of or unresponsive to first-line regimens. Based on our findings, we suggest that clindamycin/primaquine should be preferred to pentamidine for patients who develop treatment-limiting toxicity from trimethoprim/sulfamethoxazole. Although, in theory, recently described sulpha resistance in *P. jirovecii* may limit the efficacy of trimethoprim/sulfamethoxazole, we observed consistent efficacy of first-line treatment with trimethoprim/sulfamethoxazole over time.[24,25] We found equivalent efficacy from trimethoprim/sulfamethoxazole and clindamycin/primaquine when used for

Table 4. Risk of mortality at 3 months according to treatment by time-updated Cox regression analysis

Treatment	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
SXT (reference group)	1	1
Pentamidine	3.5 (2.4–4.9)	3.3 (2.2–5.0)
Clindamycin/primaquine	1.2 (0.8–2.0)	1.6 (0.9–2.8)
Other drugs	0.7 (0.3–1.5)	1.4 (0.6–3.6)

SXT, trimethoprim/sulfamethoxazole.
Analysis of last episode of PCP.
Goodness of fit: log likelihood = −932.8, $\chi^2 = 133.3$, $P < 0.00001$.
[a]Adjusted for PaO_2 at admission, age, CD4 cell count, year of diagnosis, bacterial co-infection, previous PCP prophylaxis and country.

patients failing first-line therapy with non-trimethoprim/sulfamethoxazole treatment first-line regimens. Our results suggest that trimethoprim/sulfamethoxazole should remain the second-line treatment of choice, based on greater clinical data and experience with trimethoprim/sulfamethoxazole. For patients failing trimethoprim/sulfamethoxazole therapy as first-line therapy, our findings suggest that clindamycin/primaquine should be used in preference to intravenous pentamidine. However, this recommendation is based on observational data with a high risk of confounding by indication.

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Transparency declarations

None to declare.

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