



Original article

Ceftriaxone versus ceftriaxone plus a macrolide for community-acquired pneumonia in hospitalized patients with HIV/AIDS: a randomized controlled trial

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ABSTRACT

Objectives: To evaluate if treatment with ceftriaxone and a macrolide, improved patient outcome when compared with monotherapy with ceftriaxone, in hospitalized patients with human immunodeficiency virus/acquired immunodeficient syndrome (HIV/AIDS) with community-acquired pneumonia (CAP).

Methods: Adult patients with HIV hospitalized due to suspected CAP were randomized to receive one of two regimens, ceftriaxone plus macrolide or ceftriaxone plus placebo, at a 1:1 proportion (Brazilian Clinical Trials Registry: RBR-8wtq2b). The primary outcome was in-hospital mortality and the secondary outcomes were mortality within 14 days, need for vasoactive drugs, need for mechanical ventilation, time to clinical stability and length of hospitalization.

Results: A total of 227 patients were randomized, two were excluded after randomization; 225 patients were analysed (112 receiving ceftriaxone plus placebo and 113 receiving ceftriaxone plus macrolide). The frequency of the primary outcome, in-hospital mortality, was not statistically different between the regimens: 12/112 (11%) patients who received ceftriaxone plus placebo and 17/113 (15%) who received ceftriaxone plus macrolide died during hospitalization (hazard ratio 1.22, 95% CI 0.57–2.59). We did not find differences between the regimens for any of the secondary outcomes, including mortality within 14 days, which occurred in 5/112 (4%) patients with ceftriaxone plus placebo and in 12/113 (11%) patients with ceftriaxone plus macrolide (relative risk 2.38, 95% CI 0.87–6.53).

Conclusions: Among hospitalized patients with HIV/AIDS with CAP, treatment with ceftriaxone and a macrolide did not improve patient outcomes, when compared with ceftriaxone monotherapy.

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Introduction

The treatment of community-acquired pneumonia (CAP) is often empirical and different approaches have been studied and compared across the literature. The use of a macrolide in addition to a β -lactam in hospitalized patients is a major part of this debate [1].

There are three main explanations why macrolide added to a β -lactam treatment may have an effect on the outcome in patients with CAP: coverage against atypical bacteria; synergistic activity with β -lactams and immunomodulatory properties [2].

Even though some of the current evidence suggests a benefit in mortality from macrolide-based antibiotic therapy [3–8], different conclusions about the impact of macrolides on mortality can be drawn from recently published meta-analyses and, apparently, this effect is more pronounced in severely ill patients [9–11].

Two recently published clinical trials showed somewhat conflicting results for moderately severe CAP. One is a pragmatic,

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cluster-randomized, crossover trial that found that β -lactam monotherapy was not inferior to β -lactam–macrolide combination or fluoroquinolone monotherapy concerning 90-day mortality [12].

The other one was an open-label, multicentre, randomized trial that was unable to demonstrate no inferiority of clinical stability at day 7 comparing empirical treatment with a β -lactam alone relative to a β -lactam–macrolide combination. Patients infected with atypical pathogens or category IV pneumonia severity index were less likely to reach clinical stability if they received monotherapy. In this study, severely immunosuppressed patients were excluded [13].

Current studies have heterogeneous target populations, treatment regimens and evaluated outcomes. The majority excluded patients with human immunodeficiency virus (HIV) or severely immunosuppressed patients. Although patients with HIV/acquired immunodeficient syndrome (AIDS) are at increased risk of acquiring pneumonia when compared with the general population and have higher mortality rates [14], there is a lack of studies in this population.

To the best of our knowledge, the only study that compared different treatments of CAP in patients with HIV/AIDS is a retrospective study that showed similar mortality rates between patients who received ceftriaxone and those with ceftriaxone plus clarithromycin, and there are no clinical trials of antibiotic treatment for CAP in patients with HIV/AIDS [15].

The aim of this study was to evaluate if treatment with ceftriaxone and a macrolide improved patient outcome when compared with monotherapy with ceftriaxone, in hospitalized patients with HIV/AIDS with CAP.

Materials and methods

Trial design and participants

This is a randomized controlled trial of parallel groups (1: 1), conducted at the Instituto de Infectologia Emílio Ribas, a tertiary teaching infectious disease hospital in São Paulo, Brazil (Brazilian Clinical Trials Registry: RBR-8wtq2b).

The eligibility criteria for participants were: patients 18 years of age or older, who refer with HIV infection at admission, with clinically and radiologically suspected CAP who required antibiotic treatment and hospitalization. Patients were eligible irrespective of CAP severity and requirement of intensive care unit admission.

Suspected CAP was defined by the three following criteria: 1, cough; 2, dyspnoea, or chest pain or sputum production; 3, lung opacity detected by a radiological method. These criteria are derived from previously suggested diagnostics approaches [16,17].

The exclusion criteria were: empirical antibiotic treatment directed for CAP other than ceftriaxone, risk factors for healthcare-associated pneumonia (hospitalization for 2 days or more in the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy, chronic dialysis within 30 days or home wound care) [18], presence of an aetiology established before admission that explained all the symptoms, previous inclusion in the trial and pregnancy or breastfeeding.

The attending physicians identified patients who met the inclusion criteria and did not meet any exclusion criteria. The investigators obtained informed consent.

All patients provided written informed consent and the study was approved by the Institutional Committee of Ethics in Research (number 17/11).

Interventions

Physicians prescribed intravenous ceftriaxone 1 g, at 12-hour intervals and, after informed consent, the intravenous ‘study

medication’. The pharmacy prepared its content according to the allocation: regimen 1—NaCl 0.9% 500 mL (placebo) or regimen 2—macrolide diluted in NaCl 0.9% 500 mL. Irrespective of the content, the containers were indistinguishable and were labelled as ‘17/11 study medication’.

The preferred macrolide was azithromycin 500 mg, once a day. When unavailable, clarithromycin 500 mg every 12 h was dispensed. During the period in which only clarithromycin was available, two containers were dispensed per day, ensuring the masking.

The first dose of the assigned regimen was administered within the first 48 h of hospitalization and was given in hospital for at least 7 days.

Outcomes

The primary outcome was in-hospital mortality and the secondary outcomes were mortality within 14 days, need for vasoactive drugs, need for mechanical ventilation, time to clinical stability and length of hospitalization.

Patients discharged before day 14 were considered alive for the analyses of the mortality within 14 days if confirmed by review of health records (Brazilian CD4⁺ T-cell count/HIV viral load database and medical records from Instituto de Infectologia Emílio Ribas, Instituto Adolfo Lutz and Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) of consultations, diagnostic procedures or antiretroviral therapy (ART) administration after the discharge.

Patients who left the hospital against medical recommendation where excluded from the analysis of clinical stability and length of hospitalization. Patients who died were counted as maximum value +1.

The first day of admission was considered day 1 and the time to clinical stability was considered as the first day on which all the vital signs were stable or the discharge day. The stability cut points for vital signs were: heart rate ≤ 100 beats/min; systolic blood pressure > 90 mmHg; respiratory rate ≤ 24 breaths/min [19]; and axillary temperature $\leq 37.8^\circ\text{C}$.

Sample size

Based on a mortality rate of 29% with regimen 1 and 11% with regimen 2 [7], and assuming a two-sided 5% significance level, a power of 80% and a dropout rate of 30%, the calculated sample size was 228 patients (114 per regimen).

Randomization and masking

A collaborator generated a simple randomized sequence using MICROSOFT EXCEL version 2013 (Microsoft Corporation, Redmond, WA) in which participants were assigned to receive one of two regimens, at a 1: 1 proportion. This list was delivered to the pharmacy. Allocation to the study was done in the pharmacy. As a result, patients, caregivers and those who evaluated outcomes were blinded to the antibiotic treatment regimen.

Unmasking the regimen was only possible in two situations: identification of a serious adverse event at the discretion of the attending physician in agreement with the principal investigator, and microbiological findings that required an appropriate antibiotic.

Statistical methods

The primary outcome, in-hospital mortality, was compared between regimens using Cox regression. Mortality within 14 days

was compared using log-binomial regression and the other dichotomous secondary outcomes were compared with logistic regression. Continuous secondary outcomes, time to clinical stability and length of hospitalization, were compared between regimens using Mann–Whitney *U*-test.

Analyses were performed in accordance with the intention-to-treat principle.

We did four *post hoc* subgroup analyses: severely ill patients (CURB-65 score [20] >2 or pneumonia severity index [21] >III), patients with an identified bacterial pathogen, patients with identified atypical bacteria, and patients with CD4⁺ T-cell count >200 cells/mm³.

A sensitivity analysis was performed to take into account competing events: we constructed a competing-risks model for in-hospital mortality, treating discharge as a competing event.

The level of significance was set at 0.05 (two-tailed). Analyses were performed using STATA 14.0 (StataCorp. 2007. Stata Statistical Software: Release 14; College Station, TX, USA).

Follow up

The following data were recorded on admission: sociodemographic characteristics, time since HIV diagnosis, use of ART, comorbidities, drug use, antibiotic use within the last 30 days and pneumococcal vaccination status.

CD4⁺ T-cell counts and HIV viral load were recorded if collected within the last 3 months or during hospitalization.

Subjects of this study were submitted to an extensive microbiological investigation, with details and results described elsewhere [22]. CAP caused by atypical organisms was defined by *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* or *Legionella pneumophila* infection. The results of serology and PCR for atypical organisms were not accessible for the clinicians, as they were performed posteriorly for analysis purposes only.

Administration of a macrolide or a fluoroquinolone in therapeutic or prophylactic doses was not allowed while the patient was

receiving the study regimens. As indicated by the attending physician, other antimicrobial agents could be associated with the study regimen to ensure proper treatment of other microorganisms, such as fungi or mycobacteria.

The patients were followed until hospital discharge, and the following data were registered: use of other antimicrobial drugs, use of antiretroviral treatment and causes of change or interruption of the initial antibiotic regimen.

Results

Baseline characteristics and clinical data

Patients were assessed for eligibility between September 2012 and July 2014 and 227 were randomized. We had two exclusions after randomization, one patient who withdrew consent for data inclusion and use and one that had previously been included (Fig. 1), leaving a total of 225 patients to analyse (112 received ceftriaxone plus placebo and 113 received ceftriaxone plus macrolide).

The baseline characteristics of the patients are shown in Table 1. Patients had prolonged HIV infection, the median period was 12 years, and most of them did not make regular use of ART. Only 32/202 patients (16%) had viral load <50 copies/mL and 146/202 (72%) had a CD4⁺ T-cell count <200 cells/mm³.

Regarding the severity of the pneumonia, 16/225 (7%) had a CURB-65 score >2 and 39/225 (17%) had a pneumonia severity index >3.

Microbiological findings and antimicrobial treatment

A microbiological agent was determined in 144/225 (64%) patients. No important differences were observed between the regimens (Table 2).

Mixed aetiology was found in a large proportion of cases 48/225 (21%), with multiple combinations detailed elsewhere [22].

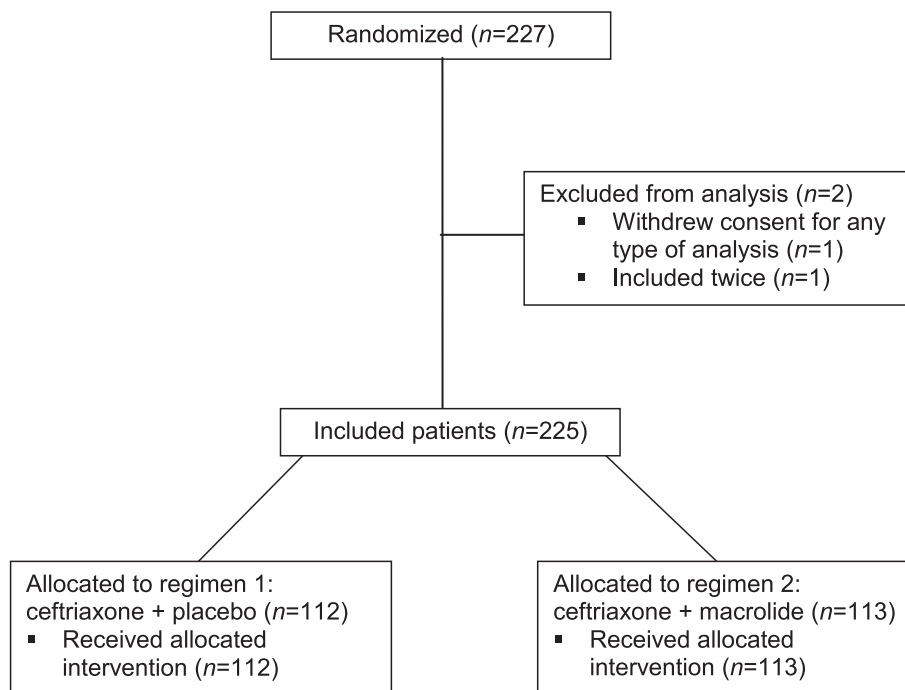


Fig. 1. Inclusion of patients, randomization and analysis of a controlled trial of hospitalized patients infected with HIV/AIDS treated for community-acquired pneumonia.

Table 1
Baseline characteristics of the patients allocated to the treatment regimens

Characteristics	Ceftriaxone + Placebo (n = 112)	Ceftriaxone + Macrolide (n = 113)
Age (years), mean (SD)	40.0 (12.5)	40.7 (10.6)
Male sex	75 (67%)	80 (71%)
Years of HIV infection, median (range) (n = 188 ^a)	12 (1–30)	11.5 (1–27)
Regular usage of antiretroviral therapy	22 (20%)	20 (18%)
Viral load <50 copies/mL (n = 202 ^a)	19 (19%)	13 (13%)
CD4 T-cell count (/mm ³), median (range) (n = 202 ^a)	100.5 (1–1108)	36.5 (1–920)
1–49	40 (39%)	58 (58%)
50–199	30 (30%)	18 (18%)
200–349	10 (10%)	10 (10%)
350–499	10 (10%)	7 (7%)
>499	12 (12%)	7 (7%)
Co-morbidities	35 (31%)	33 (29%)
Hypertension	11 (10%)	15 (13%)
Liver disease	11 (10%)	11 (10%)
Neoplastic disease	6 (5%)	4 (3%)
Diabetes mellitus	4 (4%)	5 (4%)
Cardiac insufficiency	4 (4%)	5 (4%)
Renal disease	3 (3%)	2 (2%)
Chronic obstructive pulmonary disease dependent on oxygen	0	3 (3%)
Cerebrovascular disease	1 (1%)	2 (2%)
Drug use (n = 224 ^a)	63 (57%)	69 (61%)
Tobacco (n = 223 ^a)	45 (41%)	47 (42%)
Alcoholism (n = 221 ^a)	36 (33%)	48 (42%)
Inhaled drug (n = 224 ^a)	32 (29%)	36 (32%)
Intravenous drug (n = 224 ^a)	1 (<1%)	1 (<1%)
Antibiotic use in the last 30 days (n = 219 ^a)	56 (50%)	54 (50%)
Prophylactic (n = 216 ^a)	20 (18%)	17 (16%)
Therapeutic (n = 215 ^a)	44 (41%)	43 (40%)
Pneumococcal vaccination (n = 162 ^a)	26 (30%)	24 (32%)
CURB-65 score		
0–1	82 (73%)	80 (71%)
2	20 (18%)	27 (24%)
3–5	10 (9%)	6 (5%)
Pneumonia Severity Index		
I–II	69 (61%)	68 (60%)
III	21 (19%)	28 (25%)
IV–V	22 (20%)	17 (15%)

Data are shown as frequency (%) unless otherwise indicated.

^a Number of patients for whom data was available.

Among patients who received macrolide treatment as part of the study regimen, 97/113 (86%) patients received azithromycin and 16/113 (14%) patients received clarithromycin. Clarithromycin was given for a 2-month period when azithromycin was unavailable.

Initial antibiotic regimen was interrupted or changed in 35/112 (31%) patients who received the ceftriaxone plus placebo regimen and in 52/113 (46%) patients who received the ceftriaxone plus macrolide regimen, the detailed reasons are listed in the [Supplementary material \(Table S1\)](#).

The use of additional antimicrobials administered outside the study regimens was similar for both regimens ([Table 2](#)). ART was prescribed during hospitalization for 63/112 (56%) patients who received ceftriaxone plus placebo and 68/113 (60%) patients who received ceftriaxone plus macrolide. No serious adverse events were observed during the study.

Outcomes

The frequency of the primary outcome, in-hospital mortality, was not statistically different between the studied regimens:

Table 2
Microbiological findings and antimicrobial treatments administered outside the study regimens

	Ceftriaxone + Placebo (n = 112)	Ceftriaxone + Macrolide (n = 113)
Seven most frequent pathogens:		
Fungi	23 (20)	33 (29)
<i>Pneumocystis jirovecii</i>	23 (20)	29 (26)
Bacteria	21 (19)	21 (19)
<i>Streptococcus pneumoniae</i>	11 (10)	11 (10)
<i>Mycoplasma pneumoniae</i>	8 (7)	4 (3)
<i>Chlamydia pneumoniae</i>	2 (2)	5 (4)
Virus	22 (20)	22 (19)
Rhinovirus	10 (9)	12 (11)
Influenza virus	7 (6)	8 (7)
Mycobacteria	21 (19)	14 (12)
<i>Mycobacterium tuberculosis</i>	15 (13)	14 (12)
Seven most frequent additional antimicrobials		
Trimethoprim-Sulfamethoxazole	50 (45)	62 (55)
Fluconazole	38 (34)	48 (43)
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol	21 (19)	21 (19)
Acyclovir	15 (13)	16 (14)
Vancomycin	11 (10)	19 (17)
Clindamycin	10 (9)	11 (10)
Piperacillin-Tazobactam	10 (9)	11 (10)

Data are shown as frequency (%).

12/112 (11%) patients who received ceftriaxone plus placebo and 17/113 (15%) who received ceftriaxone plus macrolide died during hospitalization (HR 1.22, 95% CI 0.57–2.59) ([Table 3](#)).

We did not find differences between the regimens for the secondary outcomes: mortality within 14 days (relative risk 2.38, 95% CI 0.87–6.53), need for vasoactive drug (OR 1.18, 95% CI 0.60–2.29) or mechanical ventilation (OR 1.24, 95% CI 0.64–2.40) ([Table 3](#)).

The median time until clinical stability was 5 days for those who received ceftriaxone monotherapy and 6 days for those who received ceftriaxone plus macrolide, and the median length of hospitalization was 15 days for those who received ceftriaxone monotherapy and 18 days for those who received ceftriaxone plus macrolide ([Table 3](#)).

In the sensitivity analysis, a competing-risk model for in-hospital mortality, treating discharge as a competing event, there was no significant difference in the cumulative incidence function curves between groups (see [Supplementary material, Fig. S1](#), sub-hazard ratio 1.49, 95% CI 0.71–3.10, p 0.29).

There was no statistically significant difference for in-hospital mortality between the regimens in all four subgroup *post hoc* analyses: severely ill patients, patients with an identified bacterial pathogen, patients with identified atypical bacteria, and patients with CD4⁺ T-cell count >200 cells/mm³ (see [Supplementary material, Table S2](#)).

Discussion

Patients with HIV/AIDS treated with ceftriaxone and a macrolide did not have better outcomes than patients treated with ceftriaxone alone. Double therapy, with ceftriaxone and a macrolide did not improve the outcomes in any of the studied subgroups: patients with an identified bacterial pathogen, patients with identified atypical bacteria, and patients with CD4⁺ T-cell count >200 cells/mm³.

The sensitivity analysis, treating discharge as an in-hospital mortality competing event, strengthened our confidence in the

Table 3
Primary and secondary outcomes according to treatment regimen

Outcome	Ceftriaxone + Placebo (n = 112)	Ceftriaxone + Macrolide (n = 113)	Relative risk (95% CI)	p-value
Primary outcome				
In-hospital mortality	12 (11)	17 (15)	1.22 (0.57–2.59) ^a	0.61
Secondary outcomes				
Mortality within 14 days	5 (4)	12 (11)	2.38 (0.87–6.53) ^b	0.09
Use of vasoactive drug	20 (18)	23 (20)	1.18 (0.60–2.29) ^c	0.63
Use of mechanical ventilation	20 (18)	24 (21)	1.24 (0.64–2.40) ^c	0.52
Days to reach clinical stability, median (range)	5 (1–44)	6 (1–44)	N/A	0.80 ^d
≤7 days	64 (57.1)	63 (55.8)	0.98 (0.76–1.23)	0.83
Days of hospitalization, median, (range)	15 (2–114)	18 (2–114)	N/A	0.31 ^d
≤10 days	32 (28.6)	29 (25.7)	0.90 (0.58–1.38) ^b	0.62
≤20 days	68 (60.7)	68 (53.1)	0.87 (0.70–1.10) ^b	0.25

N/A not applicable.

Data are shown as frequency (%) unless otherwise indicated.

^a Hazard ratio calculated with Cox regression.

^b Risk ratio calculated with log-binomial regression.

^c Odds ratio calculated with logistic regression.

^d Mann–Whitney *U*-test.

conclusion that the frequency of the primary outcome, in-hospital mortality, was not statistically different between the regimens.

The low CD4⁺ T-cell counts of our cohort reflected their impaired immunological status. Although patients in the combination arm tended to have lower CD4⁺ T-cell counts, the randomization ensures that allocation of patients to treatments is left purely to chance [23]. Moreover, the proportion of patients with CD4⁺ T-cell counts < 200/mm³ is similar between the groups and this is the threshold considered as a prognostic factor for HIV-infected patients with CAP [14].

The immunomodulatory effects of macrolides remain incompletely understood [24] and could influence both the pathogen and the host [2], it being postulated that the systemic inflammatory response syndrome generated by CAP could be modulated through macrolide effects [2,25]. Notwithstanding, not all patients suffer from an excessive inflammatory response during pneumonia and we speculate that for our group of patients, the immunomodulatory effects of macrolides are unpredictable and may range from reducing inflammation to worsening the inflammation due to immune reconstitution.

Atypical bacteria occurred in a substantial proportion of our population (19/225, 8%). This finding would suggest that coverage against atypical agents could be beneficial. However, we failed to demonstrate a clinical benefit considering the entire cohort and in the subgroup of patients with proven atypical infection, although the sub-analyses were underpowered (Table 3, and see Supplementary material, Table S2).

The ability to detect differences between the regimens may have been reduced due to the small number of observations and due to the low proportion of severe outcomes expected for *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* infections. CAP caused by atypical organisms tends to present mild-to-moderate severity, with low in-hospital mortality (around 5%) and leads to very low rates of use of mechanical ventilation and septic shock (<1%). Furthermore, the length of hospitalization is usually short (median of 3 days) [26]. *Legionella pneumophila*, which is most frequently responsible for severe cases [27], was investigated in the majority of patients and all were negative. This pathogen seems to have a lower incidence in South America than globally [28].

In our study, we resorted to an extended microbiological investigation and found a high frequency of non-bacterial (111/225, 49%) and mixed (48/225, 21%) diagnoses [22]. However, there is no accurate method to differentiate between bacterial CAP and other

causative agents (for example, virus or *Pneumocystis jirovecii*) in patients with HIV/AIDS and studies of empiric CAP treatment have to deal with this difficulty [29].

We performed a subgroup analysis of patients with an identified bacterial pathogen that did not indicate a benefit of combination therapy, even though the sample size was limited (see Supplementary material, Table S2).

This is a single centre study, conducted in the Instituto de Infectologia Emílio Ribas, in the metropolitan region of São Paulo (approximately 20 million inhabitants). Not all patients who met the criteria for inclusion were enrolled in the trial because we used convenience sampling and data on number of screened patients or number of patients excluded by each criteria were not recorded. Although this could limit the external validity of our results, this is attenuated by the fact that it was performed in a hospital that is a reference for the entire state and we have no reason to believe that the group of patients who were not included would have been substantially different from the studied patients.

Some severe cases could have been excluded (neutropenic patients, for example) if this was the reason why the attending physician decided to start empirical antibiotic treatment with something different from ceftriaxone, but the low CD4⁺ T-cell counts of our cohort indicate that severely immunosuppressed patients were not likely to be excluded.

The overall mortality rate of our study (13%) was lower than the study used for sample size calculation (24%) and hence we could not rule out a type II error. On the other hand, we found a slightly higher mortality with the ceftriaxone plus macrolide regimen.

Finally, the macrolide or placebo was initiated within 48 h of admission and this could have influenced the lack of an effect found in this study. It is possible that a more prompt start of macrolide therapy could have improved efficacy. The initial antibiotic regimen was discontinued or changed in 39% of the participants, which reflects real-life challenges when dealing with a CAP episode in patients with HIV/AIDS.

In conclusion, among hospitalized HIV/AIDS patients with CAP, treatment with ceftriaxone plus macrolide was not superior to ceftriaxone monotherapy in spite of a non-negligible prevalence of atypical bacteria.

Transparency declaration

All authors declare no competing interest.

Authors' contributions

CF-M was the main conductor of the work and main writer of this manuscript, she had full access to the data and is the guarantor for the data. PN contributed to the analysis and interpretation of data and helped with data presentation in the manuscript. MDN contributed to the conception of the work and acquisition of data and added important intellectual content to the manuscript. ASL was the main advisor of the work and guided all stages of the process, from conception of the study to revision of this manuscript.

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Previous abstract presentation

Some of the results were presented orally at the 26th European Congress of Clinical Microbiology and Infectious Diseases (Amsterdam, the Netherlands, 2016), the abstract is appended to the online submission (see [Supplementary material, Appendix S1](#)).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cmi.2017.06.013>.

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