plasma HIV RNA load below the detection threshold. At this point, the median (Q1–Q3) change in the CD4+ cell count was 44 (–47 to 139) cells/mm³. Other relevant characteristics of the population studied are shown in Table 1.

Three patients (3%) had suffered a severe liver event: one individual (1%) developed grade 3 HT and two (2%) suffered from liver decompensation. The density of incidence of grade 3–4 HT was 1.1 per 100 person-years (95% CI = 0.06–6.9) and that of any severe liver event was 3.3 per 100 person-years (95% CI = 0.9–10). Among HCV- or HBV-coinfected patients, one (2.4%) presented with grade 3 HT and two (4.9%) developed hepatic decompensation. Thus, the density of incidence of grade 3–4 HT among coinfected individuals was 2.5 per 100 person-years (95% CI = 0.1–15.1) and that of any severe liver event was 7.6 per 100 person-years (95% CI = 2.01–21.9) in this population.

Ten individuals (10%) had a grade 4 increase in the plasma level of total bilirubin (TB), i.e. a plasma TB value ≥5 mg/dL. A grade 4 increase in TB was observed in five patients (12.2%) coinfected with HBV or HCV. Atazanavir was stopped in one patient (1%) due to hyperbilirubinaemia.

HCV seropositivity and a low baseline CD4+ cell count were associated with the development of severe liver events (Table 1). There was no significant difference in the CD4+ cell gain at month 6 between patients who developed grade 3–4 HT or hepatic decompensation and those who did not [median (Q1–Q3) = 60 (37–146) cells/mm³ versus 41 (–48 to 136) (P = 0.6), respectively]. The relationship between other parameters and the emergence of these events is shown in Table 1.

The above results show that severe adverse liver events are uncommon in patients receiving antiretroviral combinations including atazanavir. In particular, grade 3–4 HT is seen less frequently than has been reported in patients taking other PIs and non-nucleoside reverse transcriptase inhibitors in both cohort studies and clinical trials.1,2 In this regard, in our study most patients were treatment-experienced, showed undetectable HIV viral load and had high CD4+ cell counts. Perhaps, if a higher number of naive patients, with more severe immunosuppression, had been included, more increases in aminotransferases due to immune reconstitution would have been observed. Thus, the rate of HT would have been higher. In agreement with that, the emergence of HT or hepatic decompensation was associated with low CD4+ counts. In any case, the frequency of HT found in this study is similar to that observed in patients on atazanavir in clinical trials.4–7

In the present study a high number of participants were coinfected with HCV and/or HBV, a circumstance that may complicate antiretroviral therapy. HCV coinfection was associated with the emergence of HT or hepatic decompensation, as has been found in patients on therapy with other antiretroviral drugs.1,9 However, the incidence of these events was low in patients coinfected with hepatitis viruses, which suggests that atazanavir is safe in this setting.

As previously reported, hyperbilirubinaemia may emerge in patients taking atazanavir. This event is much more common than HT. However, in the patients included in this study atazanavir was well tolerated and led to therapy removal in only one case.

In summary, the frequency of liver toxicity associated with atazanavir therapy is low, even in patients with HCV or HBV coinfection. This indicates that antiretroviral combinations including atazanavir can be safely used in patients with chronic viral hepatitis.
Sir,
A combination therapy with aminoglycoside and an anti-pseudomonal β-lactam agent is the recommended treatment for acute pulmonary exacerbations caused by <i>Pseudomonas aeruginosa</i> in cystic fibrosis (CF) patients. The activity of β-lactams depends on the duration that the drug concentrations exceed the MIC for the organism. Rapid regrowth of the organisms is seen once the drug concentration falls below the MIC. Importantly, all patients receiving CI maintained drug concentrations that exceeded the MIC for 70% of the dosing interval; thus, outcome differences between the cefepime II regimen may not be feasible against <i>P. aeruginosa</i> with reduced susceptibility to multiple antibiotics, thereby allowing efficient choice of antibiotics as a result of antibiotic therapy have been reported previously which are probably related to the ongoing chronic inflammation present within the airways of patients with CF. The pharmacokinetics of cefepime did not differ when given as an II or CI (Table 1) and was well described by a two-compartment model. Significant differences between the two groups were noted in C<sub>max</sub>, C<sub>min</sub> and C<sub>ss</sub> values as expected. Importantly, all patients receiving CI maintained drug concentrations above the MIC (range 4–12 mg/L) throughout the dosing period. In contrast, in patients receiving II, the serum concentrations dropped below the MIC for 25% of the dosing interval. Notably, the dose of cefepime administered by CI was also 20% lower than in the II regimen (5 versus 6 g).

Response to cefepime therapy was assessed based on changes in bacterial density, inflammatory mediators and improvement in pulmonary function (Table 1). <i>P. aeruginosa</i> density declined from baseline at the end of the antibiotic therapy as expected, but it returned to baseline concentrations by 2 weeks post-therapy. The changes in bacterial density between follow-up and baseline were similar between the two groups. Changes in IL-8 concentrations and ESR between the groups were not significantly different during the treatment phase or at follow-up. Inconsistent results on changes in levels of inflammatory mediators as a result of antibiotic therapy have been reported previously which are probably related to the ongoing chronic inflammation present within the airways of patients with CF. Pulmonary function (FEV<sub>1</sub>) improved in both groups during the treatment period. The improvement appeared slightly greater in the CI group; however, the difference was not statistically significant. At follow-up, values for bacterial density, IL-8, ESR and FEV<sub>1</sub> did not differ significantly from the baseline values in both groups (data not shown).

Maximal activity of β-lactams is observed when serum concentrations remain above the MIC for 70% of the dosing interval; however, this may not be feasible against <i>P. aeruginosa</i> or other Gram-negative organisms with increasing resistance. We have demonstrated that CI provides a more efficient means of attaining the pharmacodynamic target (concentrations 4–5 times the MIC), resulting in an overall reduction in the daily dosage.

The limitation of our study is that it was a pilot study with a small sample size. Thus, outcome differences between the cefepime II group and the cefepime CI group did not reach statistical significance. Larger studies are needed to confirm the positive

**Table 1. Pharmacokinetics of and clinical response<sup>a</sup> to intermittent infusion (II) and continuous infusion (CI) of cefepime**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>II (n = 5)</th>
<th>CI (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>130 (119, 165)</td>
<td>–</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (mg/L)</td>
<td>8.01 (4.29, 18.6)</td>
<td>–</td>
</tr>
<tr>
<td>C&lt;sub&gt;ss&lt;/sub&gt; (mg/L)</td>
<td>–</td>
<td>28.4 (23.4, 34.8)</td>
</tr>
<tr>
<td>% t &gt; MIC</td>
<td>76.5 (36.0, 83.0)</td>
<td>100 (100, 100)</td>
</tr>
</tbody>
</table>

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<sup>a</sup>Change between end of therapy and baseline.
trends in clinical outcomes with CI cefepime in CF patients noted in this pilot study.

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Transparency declarations

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Non-adherence to infectious disease consultations: are surgeons to blame?

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Sir,

Pulcini et al.1 reported the compliance with recommendations from infectious disease consultations in a university hospital in France. Despite the fact that the consultations were not specifically requested or initiated by the primary teams, the compliance was as high (>80%) as that reported for specifically requested consultations in a university and public hospitals in the United States.2 Another similar finding in both studies was the fact that compliance was diminished in surgical services. In fact, in Pulcini et al.’s study,3 after multivariate analysis was performed the odds ratio of compliance was 4.9 [95% confidence interval 2.0–12.1, \( P = 0.001 \)] in ward A (mainly a medical ward) as compared with ward B (a ward managed by the trauma team). In the study that I co-authored,4 the difference was not that pronounced but was still significant. In a logistic regression mixed model we found that the adjusted probability of adherence to recommendations was 79% for medicine and 68% for surgery (odds ratio 1.9, 95% confidence interval 1.2–2.9, \( P = 0.006 \)). Another study reported from a university hospital in Korea5 regarding compliance with targeted antibiotic (glycopeptides, carbapenems, antipseudomonal cephalosporins and aminoglycosides) advisory consultations described the compliance as being higher in medical services than in surgical services (64.2 versus 43.1%; \( P = 0.005 \)).

The issue of antibiotic use in surgical wards has caused heated debate. Some surgical units are closed to infectious disease advice and only surgical housestaff have prescribing authority for them.4 In other institutions, surgeons believe that antibiotic drug restriction policies are monopolized by infectious disease physicians, preventing surgical practitioners from taking direct control of important issues related to their own patients.5 Furthermore, at least one study has drastically concluded that ‘medical infectious disease specialists may overtreat common surgical infections with antibiotics’ and that ‘surgical infections should be treated by surgeons’6.

I believe with Tenenbaum7 that the importance of an infectious disease consultation goes beyond the proper use of antibiotics and has an ‘aggregated’ value of the clinical expertise of the infectious disease practitioner.

The issue, however, is not who better prescribes antibiotics but how patients will benefit more. At the personal level, physician–physician communication alone may not be sufficient to improve compliance with recommendations;2 a deeper level of trust, cooperation and understanding between infectious diseases specialists and surgeons may be required. At the institutional level, several measures may improve understanding of infectious disease endeavours: participation of surgeons in infection control committees, collaborative efforts by professional societies in the elaboration of guidelines (an excellent example of this are the Guidelines for the Selection of Anti-infective Agents for Complicated Intra-abdominal Infections, conjointly formulated by the Infectious Disease Society of America and the Surgical Infection Society)7 and the active participation of surgeons in infectious disease mini-fellowships or rotations, particularly at the assistant professor level, when surgeons believe they acquire their greatest expertise.8

Transparency declarations

None to declare.

References