several antibiotics including temocillin (MIC 16 mg/L) and showed intermediate susceptibility to piperacillin/tazobactam (MIC 64/4 mg/L) (Table 1). She was treated with temocillin (1 g iv once daily), a lower dose regimen being applied due to renal impairment [estimated glomerular filtration rate (eGFR) 27 mL/min]. The patient rapidly improved over the next 48 h (temperature 37.2 °C and C-reactive protein 75 mg/L compared with 38.7 °C and 145 mg/L, respectively, on admission). During this time, her renal function improved (eGFR 103 mL/min) and her temocillin dose was increased to 1 g twice daily accordingly. On the fourth day of temocillin treatment she deteriorated and repeat blood cultures again grew an ESBL-producing K. pneumoniae. In contrast to the initial isolate, this breakthrough isolate was of only intermediate susceptibility to temocillin (MIC 32 mg/L) and resistant to mecillinam and piperacillin/tazobactam (MIC > 64/4 mg/L). The patient was changed from temocillin to etapenem (1 g iv once daily), and made a good recovery.

To our knowledge, this is the first reported case of breakthrough bacteraemia on temocillin treatment. One factor that may have predisposed to the loss of susceptibility in this patient was her renal function, which, having initially been sufficiently impaired to merit once daily dosing, rapidly improved and could therefore have resulted in temocillin levels falling and remaining below the MIC for protracted periods. In addition, biliary concentrations of temocillin would have been particularly compromised because the biliary tree was severely damaged due to primary biliary cirrhosis. The simultaneous acquisition of resistance to mecillinam and piperacillin/tazobactam is particularly worrying, and might reflect mediation by a common mechanism or genetic element.

Two other patients were treated with temocillin for infections caused by E. coli not producing ESBLs or AmpC. The first patient was a 78-year-old lady who was admitted to the Intensive Therapy Unit with severe urosepsis complicated by acute renal failure. She responded very well to a single dose of temocillin (1 g iv) and a 2 day course of gentamicin (2 mg/kg iv once daily). A fully susceptible E. coli was cultured from urine and treatment was de-escalated to co-amoxiclav (1.2 g iv thrice daily) for a further 4 days. The second patient was a 67-year-old lady with an intra-abdominal collection following biliary reconstruction, who was treated with temocillin (1 g iv twice daily) and metronidazole (500 mg iv thrice daily). She developed VAP with Pseudomonas aeruginosa on the fourth day of treatment; amikacin (15 mg/kg iv once daily) was added and temocillin switched to meropenem (1 g iv thrice daily). The patient subsequently deteriorated and died.

No side effects attributable to temocillin and no cases of Clostridium difficile infection were reported in this series of patients. These data illustrate the potential clinical usefulness of temocillin, particularly as a directed-spectrum alternative to the carbapenems in infection due to ESBL/AmpC-positive Enterobacteriaceae. Comparative clinical trials are now needed.

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Rapid selection and archiving of mutation E157Q in HIV-1 DNA during short-term low-level replication on a raltegravir-containing regimen

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Sir,

Raltegravir is the first antiretroviral agent from the integrase inhibitor class that has demonstrated virological efficacy in heavily pre-treated HIV-1-infected patients harbouring multi-resistant strains.1,2 Viral replication of >400 copies/mL upon raltegravir selective pressure has been associated with the selection of mutations associated with raltegravir resistance in the vast majority of cases, particularly when the genotypic sensitivity score (GSS) is close to zero.3 Little is known, however, regarding the impact of short-term low-level viraemia on the development of resistance to raltegravir.

A man infected with HIV-1 subtype B, diagnosed since 1995, with a history of AIDS-defining events and with prior failure to four antiretroviral classes [nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), protease inhibitors (PIs) including tipranavir and darunavir, and fusion inhibitors (FIs)], was started on a raltegravir-containing regimen in March 2006. At that time, plasma HIV-1 RNA was 66 200 copies/mL with 92 CD4 cells/mm3. A genotypic resistance test showed 9 NRTI-associated resistance mutations, 2
NNRTI-associated resistance mutations, 12 PI-associated resistance mutations [including 3 major PI resistance mutations according to the 2008 International AIDS Society (IAS) list] and 1 FI-associated resistance mutation. Raltegravir was associated with abacavir, lamivudine, tenofovir, low-dose ritonavir, atazanavir and darunavir at standard doses, and the GS5 of the optimized regimen was 0.5 excluding raltegravir [according to the 2008 Agence Nationale de Recherche sur le SIDA (ANRS) French resistance algorithm interpretation]. Of note, no new antiretroviral agent (such as etravirine or maraviroc) was available at that time except raltegravir. Plasma HIV-1 RNA reduced to undetectable levels. Plasma HIV-1 RNA was rechecked every 8 weeks thereafter and undetectability was subsequently sustained up to W84, but plasma HIV-RNA reached 82 copies/mL at W92. This low-level replication was confirmed at W94, with a plasma HIV-RNA of 66 copies/mL. In addition, a genotypic resistance test and phenotypic determination of HIV co-receptor tropism were performed and trough plasma concentrations measured. Amplification of the integrase gene from plasma HIV-RNA and HIV co-receptor tropism determination were not successful due to the very low-level replication. We then performed a genotypic resistance test on intracellular HIV-DNA extracted from peripheral blood mononuclear cells sampled at W94 as previously described,4,5 with successful amplification of the integrase gene, and mutation E157Q was evident. Mutation E157Q confers resistance to raltegravir according to the 2008 resistance algorithm interpretation of the French National Agency for Research on AIDS (http://www.hivfrenchresistance.org). Interestingly, this mutation at position 157 of the HIV integrase gene was not evident in a pre-salvage treatment plasma HIV-RNA sample obtained in March 2006. The patient reported excellent adherence to his antiretroviral treatment combination and trough plasma concentrations at W94 were adequate: abacavir, <10 ng/mL; lamivudine, 96 ng/mL; tenofovir, 46 ng/mL; darunavir, 3965 ng/mL; atazanavir, 760 ng/mL; ritonavir, 379 ng/mL; and raltegravir, 638 ng/mL. Intensified treatment with etravirine durably resuppressed plasma HIV-RNA to <50 copies/mL.

As the lower detection limit of HIV-RNA decreases with improvements in quantification techniques, low-level viraemia is a growing issue for physicians managing HIV-infected patients. In some cases, this low-level viraemia does not allow amplification of plasma HIV-RNA in order to perform genotypic resistance tests, making the selection of an optimized subsequent regimen difficult. Thus, amplification of intracellular HIV-DNA might then prove useful. To the best of our knowledge, this is the first report of detection of a raltegravir resistance mutation in intracellular HIV-DNA. Unlike Katlama et al.,6 who recently reported that the presence of raltegravir resistance mutations was only associated with high-level viral replication, we show that raltegravir-associated mutation E157Q was rapidly selected and archived in the presence of short-term low-level viral replication. Indeed, mutation at position 157 of the integrase gene was not present in baseline plasma HIV-RNA. In addition, unlike for subtypes A, CRF-01, CRF-03 and CRF-04, this mutation has not been reported to be a natural polymorphism in HIV-1 subtype B strains.7 Thus, given that plasma HIV-RNA was permanently <50 copies/mL up to W84 and that the first HIV-RNA value above this threshold was measured at W92, and given that mutation E157Q was evident at W94, we show that mutation E157Q was rapidly selected and archived in intracellular HIV-DNA within a short term of 8 weeks of low-level replication (assuming that HIV replication started at a midpoint between W84 and W92). Of note, emergence of mutation E157Q in plasma HIV-RNA has already been reported after 8 weeks on a failing raltegravir-containing regimen, but with a much higher level of HIV-RNA (>5 log$_{10}$ copies/mL).8 More data are needed to better define guidelines for patients with low-level replication upon raltegravir drug-selective pressure, in order to minimize the risk of selection and addition of resistance mutations to avoid jeopardizing future therapeutic options with next-generation integrase inhibitors.

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A multicentre cohort experience with double-boosted protease inhibitors

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