HIV-1 integrase variability and relationship with drug resistance in antiretroviral-naive and -experienced patients with different HIV-1 subtypes

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last accessed). This isolate (submitted in 2010) originated from Poland and is described as methicillin susceptible. Multilocus sequence typing showed that the isolate belonged to the novel sequence type ST2497, a single-locus variant of ST1943 with one nucleotide difference in the glpF gene.

The isolate described in this study represents the first detection of an mecC-containing MRSA from an animal host in Norway. The mecC gene has been detected recently in a total of eight MRSA isolates from humans in Norway and K. W. Larssen, unpublished data). All eight mecC MRSA, isolated during 2006–12, belonged to CC130. The genotype of the feline isolate represents a new mecC-positive genotype identified in our country; however, isolates within this clonal lineage with mecC have been described from other countries.1,4 The detection of mecC in an MRSA from a clinical sample from a cat submitted to our diagnostic bacteriological service unit demonstrates the importance of taking mecC into consideration in diagnostic units that examine samples from companion animals. Our finding extends our knowledge of MRSA carrying mecC from animals and demonstrates that detection of mecC is not only a rare event when screening historical isolate collections.

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References


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Sir,

The prevalence of natural polymorphisms and mutations associated with integrase (IN) inhibitor (INI) resistance in the HIV-1 IN has already been analysed.\textsuperscript{1–5} The aim of the study was to characterize the HIV-1 IN variability in antiretroviral (ARV)-naive and -experienced patients, never treated with INIs, in a panel of different HIV-1 subtypes, and the relationship with drug resistance. This multicentre study included 590 HIV-1-infected individuals never treated with INIs (308 drug-naive and 282 ARV-experienced patients) who were enrolled in seven clinical centres in France and one centre in Switzerland. Nucleotide and amino acid sequences were compared with the HxB2 HIV-1 clade B consensus sequence (GenBank accession number K03455.1) using the Bioedit software program. The sequences of the samples have been submitted to GenBank and assigned accession numbers JX425421 to JX425885 and JX451875 to JX451963. Thirty-seven of the 590 sequences are not available in the NCBI database because we have only the description of the polymorphism for these sequences and not the nucleotide sequence. The median CD4+ T cell count at the time the samples were drawn was 280 CD4+ T cells/mm\textsuperscript3 (range 2–1692) and the median log\textsubscript{10} viral load was 4.43 log\textsubscript{10} copies/mL (1.92–6.94). Drug-treated patients were exposed to an average of 1.96 ± 2.65 nucleotide reverse transcriptase inhibitors (n = 526), 0.18 ± 0.41 non-nucleoside reverse transcriptase inhibitors (n = 473) and 0.86 ± 1.59 protease inhibitors (n = 481). The entire IN protein sequences (288 amino acids) derived from 308 drug-naive and 282 experienced patients infected with HIV-1 B or non-B subtype, all INI-naive, were analysed (Figure 1). All important residues involved in catalytic activity or in binding to the human cellular cofactor LEDGF/p75 were conserved in both drug-naive and ARV-treated patients (variability < 0.5%). The presence of polymorphic substitutions at codon 124 was significantly associated with previous ARV exposure (P = 0.03). Limited data are available on the prevalence of specific polymorphisms in the IN gene of HIV-1 non-B subtypes. We investigated the diversity of the IN region of different HIV-1 subtypes in INI-naive patients. Among the 590 samples, 252 corresponded to non-B subtypes. No difference in reverse transcriptase and IN sequences was observed between subtypes. Twenty-six changes were found with significantly different prevalence between B isolates and at least one non-B group (prevalence of polymorphism >50%; P < 0.05). Polymorphisms at codons D10, K14, S17, A21, S24, D25, V31, V32, S39, V72, L101, T112, T125, G134, I135, K136, D167, V201, T206, I208, K215, T218, L234, D256, D278 and S283 could be related to specific non-B subtypes. Among the 26 analysed codons, we analysed the T125A mutations. T125A (specific GCA codon) was significantly more prevalent in non-B samples (P < 0.0001). A similar result was found in a recent study on the analysis of polymorphisms in the IN gene of ART-naive patients infected with HIV-1 non-B subtypes.\textsuperscript{6}

Twenty-two out of 36 HIV-1 IN resistance mutations (H51Y, L68I/V, V72I, L74M, Q95K, T97A, S119G/R, A128T, T125K, V151I, M151I, K156N, E157Q, K160N, G163K/R, V165I, V201I, I203M, T206S, S230N, D232N and V249I) already associated with INI resistance were detected. Polymorphic changes included some known residues associated with INI resistance, such as V72I, L74M, T97A, V151I, E157Q and I203M, but were not statistically different between ARV-naive and -experienced patients not including INIs. In contrast, the frequency of L101I and T124A mutations, but not the M154I mutation, selected in vitro by dolutegravir was higher in naive patients. Regarding viral subtypes, mutations L101I and T124A, either alone or in combination, were significantly more prevalent in non-B than B subtypes in ARV-naive patients (65.5% versus 34.6% for L101I, 74.4% versus 25.6% for T124A and 85.7% versus 14.3% for L101I+T124A; P < 0.0001 in all cases), as recently described by Garrido et al.\textsuperscript{7} Except at position 157 (E157Q), none of the primary mutations detected in patients failing on raltegravir-containing regimens (Y143R/C, Q148H/K/R and N155H) or on elvitegravir-containing regimens (T66L, E92Q, E138K, S147G, Q148H/K/R and N155H) was detected. The E157Q mutation was observed among 2.9% (n = 17) of patient samples, including four of subtype B, one of subtype H, seven of subtype CRF02_AG, one of subtype A, two of subtype D, one of subtype CRF11_cpx and one of subtype G, without a significant difference in polymorphism between ARV-naive and -experienced patients. The primary mutations detected in patients failing on dolutegravir-containing regimens (V151I, S153Y, T66K/L74M, E92Q/N155H, E138A/K/Q148H/K/R, G140C/S/Q148H/K/R and Q148R/N155H) were completely absent.

In our study, dolutegravir resistance-associated mutations, in particular R263K, were not found to be polymorphic. Only the mutations L101I and T124A, which were previously shown to be selected in vitro in the presence of dolutegravir,\textsuperscript{4,9} either alone or in combination, were common in both naïve and experienced patients. However, these mutations have shown little impact on virological response to dolutegravir.\textsuperscript{8} Recently, the HIV-1 CRF01_AE IN coding region of the pol gene was evaluated for the prevalence of natural polymorphisms in 87 ARV-naive individuals from Cambodia, Thailand and Vietnam.\textsuperscript{10} Amino acid substitutions occurred in 60% of the subjects and none of these substitutions have been reported to be associated with resistance to INIs. Many polymorphisms in non-B viruses are considered to be secondary resistance mutations since they emerge in B subtype viruses after drug exposure.\textsuperscript{11} Nevertheless, the selection of resistance mutations could be influenced by the naturally occurring variations between the different non-B subtypes.

In conclusion, all patients in our study lacked previously described major resistance mutations to raltegravir, elvitegravir and dolutegravir. However, we found evidence of important variations regarding the IN polymorphisms according to the different HIV-1 subtypes. Further studies of INI-treated patients will be needed to fully elucidate the role of polymorphic IN mutations in the context of HIV-1 variability.

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Catalytic core domains I–VI and the Q sequence, are indicated by boxes.

Figure 1. Distribution of variants among group M HIV-1 IN sequences. Amino acid polymorphism in HIV-1 IN from 308 plasma samples from drug-naive patients and 282 samples from experienced patients are reported. The consensus subtype B sequence is shown in bold at the top of each 30 amino acid section. Numbers given as superscripts below each position are the numbers of isolates with that specific polymorphism. Grey boxes signify positions associated with in vivo resistance defined according to the algorithms from the ANRS (update October 2012, v.22, http://www.hivfrenchresistance.org/2012/Algo-sep-2012.pdf). Highly conserved motifs, the HHCC motif (coordinates zinc binding), the DDE motif, catalytic core domains I–VI and the Q sequence, are indicated by boxes.
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**Transparency declarations**

None to declare.

**References**


**Pharmacokinetic interaction of maraviroc with tacrolimus in a patient coinfeated with HIV and hepatitis B virus following hepatic transplant due to hepatocellular carcinoma**

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Sir,

Limited data are available regarding interactions between tacrolimus and commonly used highly active antiretroviral therapies, such as first-line nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and some protease inhibitors (PIs). When first-line combinations are contraindicated and newer antiretroviral agents are required, there are even less data on the interactions between newer agents such as maraviroc (a CCR5 inhibitor) with immunosuppressants such as tacrolimus (a calcineurin inhibitor). There are some animal model data of the beneficial effects on cardiac allograft survival when using maraviroc alongside immunosuppressants, with the potential that CCR5 inhibition could improve long-term outcomes after transplantation.1,2 In our patient undergoing hepatic transplant, with limited antiretroviral therapy options available and the necessity to be started on a newer agent, we set out to observe concentrations of the immunosuppressant tacrolimus before and after administration of maraviroc to ensure that effective and non-toxic concentrations of both drugs were achieved.

We describe a 49-year-old man from Sierra Leone, recently diagnosed with fully sensitive HIV clade C and chronic hepatitis B virus (HBV). After routine blood tests revealed abnormal liver...