transporter CorC in numerous *P. multocida* sequences deposited in GenBank. The sequence of Tn*7407*, including the alternative integration site, matched closely the sequence of a bovine *P. multocida* isolated in 2013 in the USA (GenBank accession no. CP015567) (Figure 1b). This finding underlined the wide distribution of highly similar ICEs with variable resistance regions among epidemiologically unrelated *P. multocida* from cattle.

The results of the study showed the occurrence of MDR *P. multocida* and *M. haemolytica* isolates carrying unusual resistance genes within multiresistance-mediating ICEs, which have so far not been described in Europe. These elements might enhance the spread of resistance genes among the respective pathogens and diminish treatment options for BRD in the future.

Acknowledgements

We thank Petra Krienke for technical support generating the MiSeq reads.

Funding

This study was supported by internal funding. T.S. was funded by the German Federal Ministry of Health (BMG) within the ZooSeq MinION-Zoo project, grant number ZMVI1-2519NIK704. A.B., A.L.-B. and S.S. were financially supported by the German Federal Ministry of Education and Research (BMBF) as part of the Research Network Zoonotic Diseases, project number 01KI2009D. A.B. and A.L.-B. were also funded by the German Federal Ministry of Food and Agriculture (BMEL) based on a decision of the Parliament of the Federal Republic of Germany, granted by the Federal Office for Agriculture and Food (BLE; grant number 2820HS002).

Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online.

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J Antimicrob Chemother 2022; **77**: 2035–2037
https://doi.org/10.1093/jac/dkac134
Advance Access publication 27 April 2022

HIV-1 non-B resistance mutations and natural polymorphisms to integrase strand transfer inhibitors in recently diagnosed patients in Gabon, Central Africa

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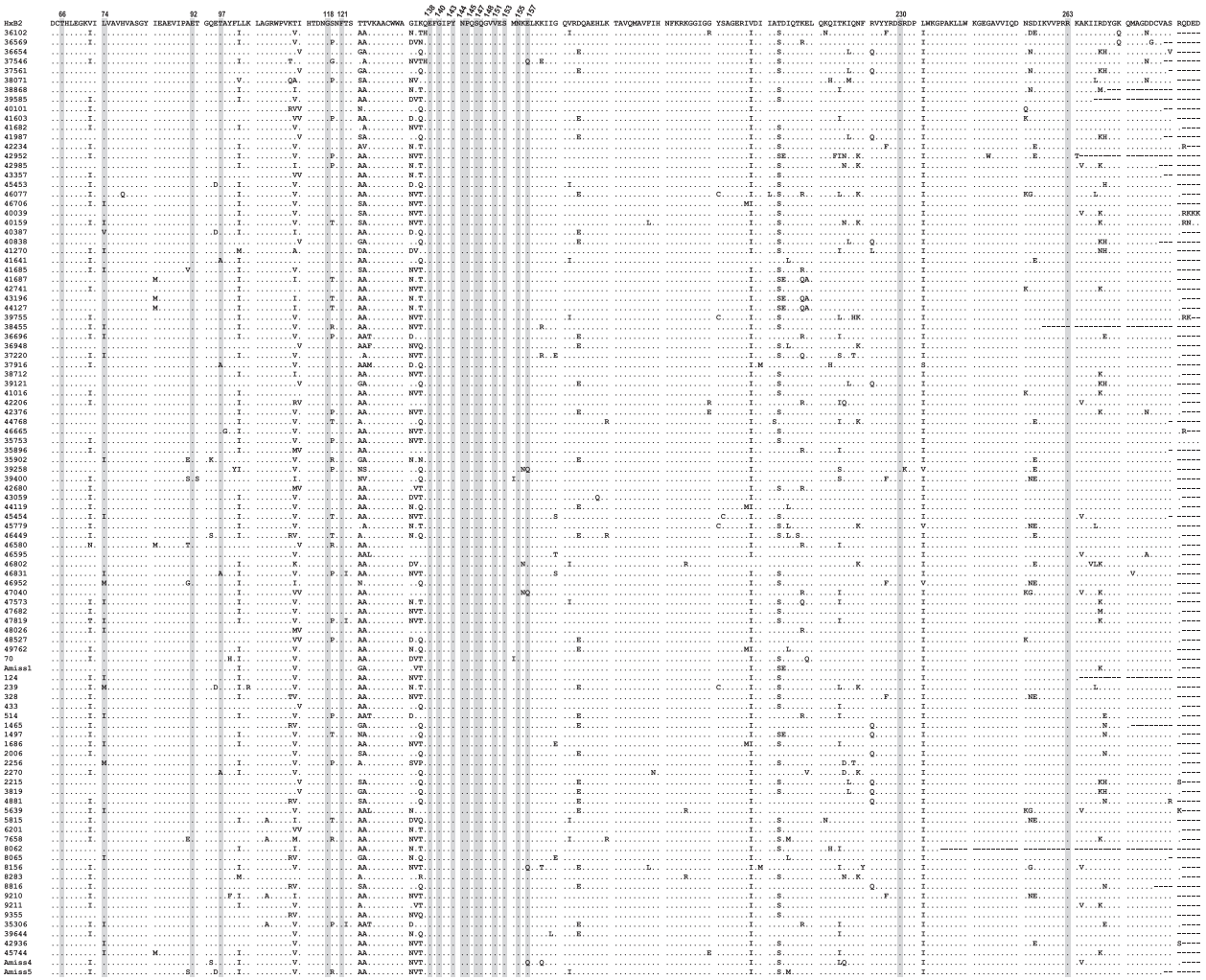

Figure 1. Amino acid sequence alignment of the newly generated HIV-1 integrase region against the reference subtype B HxB2 sequence (K03455.1). Dots indicate conserved amino acid positions when compared with the reference subtype B sequence. Dashes represent gaps. Numbers on top of the figure represent positions associated with resistance to INSTIs.

Integrase strand transfer inhibitors (INSTIs) are drugs used to combat HIV infection and have been approved by the US FDA since 2007. This drug class includes raltegravir and elvitegravir for the first generation, and dolutegravir, cabotegravir and bictegravir for the second generation. They target the strand transfer reaction of the HIV proviral DNA 3′ ends to the cellular DNA and thus inhibit viral replication.[1] Due to the increasing levels of HIV drug resistance to NNRTIs in resource-limited countries (RLCs), the WHO has recently recommended INSTIs in combination with NRTIs as the preferred first-line regimen for people living with HIV and initiating or failing ART in RLCs.[2]

The high efficacy of INSTIs for HIV treatment, especially the second generation that includes dolutegravir, has been documented, even in heavily treated individuals infected with viruses carrying important resistance mutations background.[3] However, these evidences have been mostly generated from populations in developed countries, and there are major knowledge gaps on INSTIs efficacy and resistance pathways across diverse populations and contexts, including the sub-Saharan Africa. In this study, we investigated the role of existing viral mutations among INSTI-naive HIV-1 non-B-infected individuals in Gabon and their potential impact on the efficacy of this drug class. The study was implemented in the southern region of the country in the Haut-Ogooué Province that includes Franceville and the neighbouring sub-districts.

Overall, we recruited 103 individuals tested positive for the first-time for HIV-1 infection. Women represented 58.2% of this population ($n=60$) and the median age was 37 years (IQR 28–44). All participants were treatment naive and reported no history of ARV exposure. Drug resistance genotyping was successfully carried out for all and three participants were excluded because of epidemiological relationship indicated by the obtained phylogeny. For the remaining 100 sequences representing our final study population, the HIV-1 subtype distribution was as follows:

CRF02_AG (46%), A1 (17%), D (7%), CRF45_cpx (5%), G (7%), CRF37_cpx (7%), H (4%), CRF11_cpx (4%), F2 (2%), CRF06_cpx (1%), CRF09_cpx (1%), and Unknown (6%). These 100 sequences, that cover at least amino acid positions 66 to 263 of the HIV integrase gene (Figure 1), were interpreted using the HIV French Resistance algorithm (http://www.hivfrenchresistance.org). Two primary drug resistance mutations, T97A and E157Q, were found in 4 (4%) and 5 (5%) of the sequences, respectively, resulting in an overall drug resistance prevalence of 9%. T97A is a polymorphic accessory mutation reported in up to 4% of viruses from untreated persons. This mutation reduces elvitegravir susceptibility by about 3-fold and can markedly reduce raltegravir and dolutegravir susceptibility when combined with other INSTI resistance mutations.[4,5] E157Q is frequently reported at low frequencies (<5%) in INSTI-naive persons, and confers potential resistance to raltegravir and elvitegravir, but minimal or no resistance to second generation of INSTIs.[6,7] Recent phenotypic assessments of this mutation in context of CRF02_AG viruses showed a fold change in EC_{50} of 1.1, 1.9 and 2.4 for raltegravir, dolutegravir and elvitegravir, respectively,[6] stressing the need for more surveillances of this mutation in a HIV-1 non-B context, especially in settings where CRF02_AG viruses predominate as in Gabon and in other African countries.

Two additional mutations, L74M and L74I, considered as potentially associated with resistance to INSTIs were identified at rates of 3% and 21%, respectively, 24% overall, and in almost all HIV-1 subtypes of our study panel, with CRF02_AG viruses predominantly represented. These mutations are known as polymorphic and have been reported in HIV-1 non-B viruses, with higher frequencies (>10%) reported in CRF02_AG strains.[8] By themself, L74I and L74M have minimal, if any, effect on INSTI susceptibility.[9] However, they can affect INSTI susceptibility if present with other mutations such as T66K, V75I and E92Q.[10]

In summary, we report here an overall high frequency of INSTI resistance mutations in ART-naive populations. Most of these mutations are known as associated with resistance to the first generation of INSTIs, including raltegravir and elvitegravir; drugs that are still recommended for neonates' treatment in RLCs by the WHO. The impact of these mutations on second generation INSTIs such as dolutegravir, cabotegravir and bictegravir is limited, but their contribution to resistance can significantly increase if they are associated with other INSTI resistance mutations. The recent introduction of dolutegravir-based first-line regimens in RLCs will rapidly result in millions of patients receiving INSTI-based treatments in contexts where routine treatment monitoring is still one of the major challenges and acquisition of resistant viruses a major threat. Our results stress the need for continuous surveillance of drug resistance in naive and ART-experienced populations in these settings.

Sequence accession number

The newly reported integrase sequences have been submitted to GenBank under accession numbers OM877162–OM877261.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Gabon National Ethics Committee for Research (0011/2013/SG/CNE).

Acknowledgements

We thank all patients who participated in this study, the medical staff and the Gabonese national health authorities for providing the research authorizations.

Funding

This work was supported by the Centre International de Recherches Médicales de Franceville (CIRMF), Gabon, and the Institut de Recherche pour le Développement (IRD), France.

Transparency declarations

None to declare.

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