BREACH
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Transmission of primary resistance mutation K103N in a cluster of Belgian young patients from different risk groups.

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SUMMARY

We identified a transmission cluster of drug resistant HIV-1variants mainly including homo- and heterosexual young adults. Most individuals are of Belgian origin and are living around the city of Namur. The K103N mutation found in those variants had no apparent impact on transmission fitness as its spread raised during the last years. Those observations may impact on local prevention, ARV prophylaxis strategies, and on first-line drug regimen options.

BACKGROUND

In 2009, 11% of the new HIV-1 diagnosis in Belgium were related to strains with drug resistance mutations. In 2011, several cases with evidence of recent seroconversion seemed to be linked to a same subtype B strain with typical signatures in the RT (A98S and K103N mutations) and in the PR (C67S and V77I mutations). The RT K103N mutation is a primary resistance mutations to EFV and NVP, two drugs that are widely used in first-line therapies.

OBJECTIVES AND METHODS

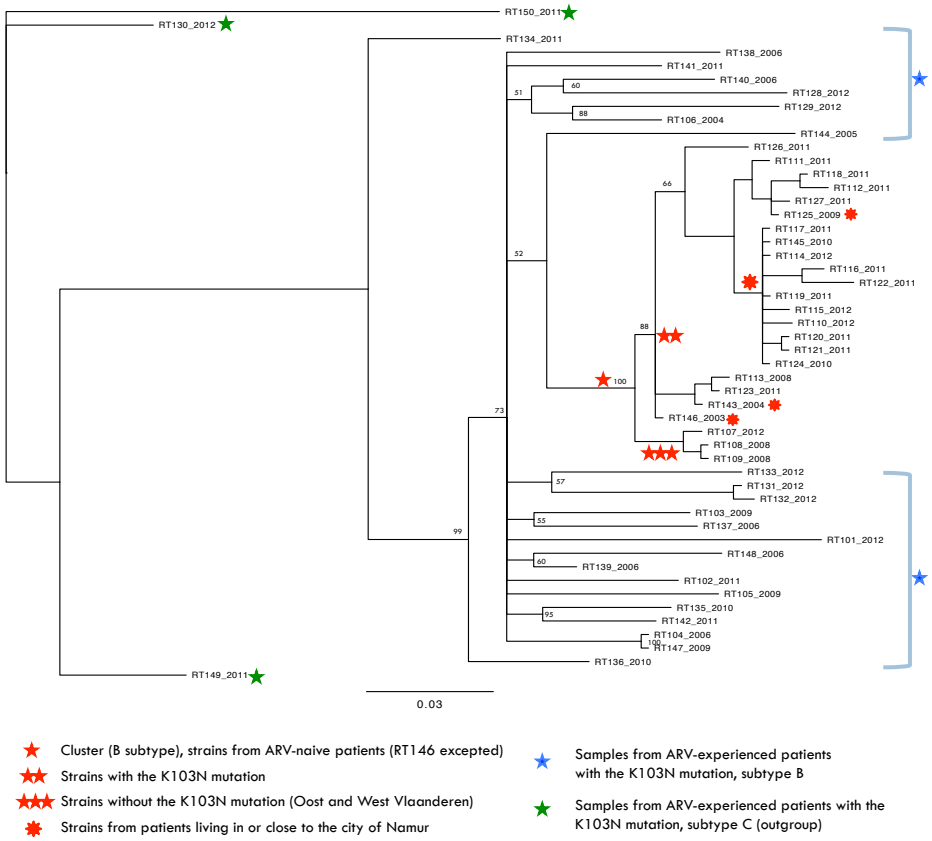
The aim was to demonstrate the presence of a cluster of drug resistant strains, and investigate its importance in incident cases. The Belgian AIDS reference laboratories searched their databases for HIV-1 subtype B sequences harbouring the K103N mutation in the reverse transcriptase (RT) or the C67S and V77I mutations in the protease (PR). We included the earliest RT sequence available of drug-naïve patients as well as sequences related to treatment failure. Epidemiological data were collected through the Institute of Public Health national database. In addition, three sequences from the cluster were analysed by deep sequencing using the Roche GS Junior platform.

RESULTS

Fifty sequences were aligned omitting the codon 103 and submitted to phylogenetic analysis. Maximum likelyhood and neighbour joining trees obtained from the PR and RT sequences all revealed the presence of a 24 virus sequences cluster. The figure presented here was obtained by Bayesian inference using the GTR model. The sample code ends by the year of collection.

All except one of those sequences (RT146_2003, possible index case whose virus selected for K103N during therapy) resulted from patients who were ARV-naïve at the time of sampling, and 21 had the K103N mutation. Two thirds of the clustered patients were infected through homosexual or bisexual contacts while the others were heterosexuals. No case was related to migrants contaminated abroad. Fifteen of the clustered patients were diagnosed between January 2011 and June 2012; 87% of them were aged between 20 and 29 at the time of diagnosis.
Interestingly, 60% of them reside in or close to the city of Namur although the province of Namur was up to now associated with low HIV incidence compared to other Belgian provinces. One subcluster from 11 strains is related to hetero- or bisexual patients, all living in the province of Namur (except RT110).

Deep sequencing analysis of 3 individuals sampled near seroconversion revealed no other resistance mutations at a frequency > 1% than those already picked up by Sanger sequencing (RT A98S, K103N; PR V77I), except the RT V90I.



★ Cluster (B subtype), strains from ARV-naive patients (RT146 excepted)
★★ Strains with the K103N mutation
★★★ Strains without the K103N mutation (Oost and West Vlaanderen)
✸ Strains from patients living in or close to the city of Namur
★ Samples from ARV-experienced patients with the K103N mutation, subtype B
★ Samples from ARV-experienced patients with the K103N mutation, subtype C (outgroup)

CONCLUSIONS AND PERSPECTIVES

- We observed a transmission cluster of HIV-1variants resistant to nevirapine and efavirenz, drugs recommended as part of first-line therapies.
- New cases are continuing to be diagnosed, the incidence of the strain studied here compared to the local HIV incidence is under investigation.
- The K103N can persist several years without drug pressure and doesn't affect the transmission fitness.
- Prevention efforts are needed among young adults living in Belgium, whatever the risk category.
- The study of transmission clusters may impact on local prevention strategies, and provide tools to investigate the virological determinants of transmission fitness.

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