Letters to the Editor

Transparency declarations

None to declare.

References


Comment on: High sensitivity of specific genotypic tools for detection of X4 variants in antiretroviral-experienced patients suitable to be treated with CCR5 antagonists

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Sir,

We read with interest the article by Seclén et al.,1 on the reliability of genotypic tools for detecting CCR4- and CCR5-using variants in patients at different stages of HIV-1 infection. Seclén et al.1 reported that the concordance between the Phenoscript® tropism assay and genotypic methods based on plasma virus RNA ranged from 63% to 85%. The best predictors for detecting X4 variants were WebPSSM_{X4/R5} (sensitivity 77%, specificity 87%) and Geno2pheno_{PR=5%} (sensitivity 80%, specificity 77%). Seclén et al.1 also used two simple rules combining the ‘11/25’ and ‘net charge’ rules and termed Garrido’s rule and Delobel’s rule. Delobel’s rule was first derived from clonal analyses of genotypic–phenotype correlations.2 We validated this rule using a large set of clinical data.3 According to Delobel’s rule, one of the following criteria is required for predicting CXCR4 co-receptor usage: (i) 11 R/K and/or 25K; (ii) 25R and a net charge of ≥ +5; or (iii) a net charge of ≥ +6. In the article by Seclén et al.,1 Delobel’s rule was ‘a sample is labelled as X4 if a basic amino acid (R or K) is recognized at positions 11/25 within the V3 region AND if the global net charge of the V3 sequence is ≥ 5, otherwise it is R5’. Thus, Delobel’s rule was not applied adequately. This mistake probably had a great impact on the prediction of co-receptor usage and on the concordance between genotype and phenotype. In fact, Delobel’s rule is closer, although not identical, to Garrido’s rule giving 80% sensitivity and 79% specificity in this study for the global population.

Our previous study on antiretroviral-experienced patients showed that Delobel’s rule was 77% sensitive and 96% specific.5 We also genotyped naive patients, for whom Delobel’s rule was 63% sensitive and 97% specific. This is very different from the performance reported in the Seclén et al.1 study (sensitivity 20%). These differences in algorithm performance, whatever the stage of the HIV-1 infection, can be explained by the incorrect use of Delobel’s rule.

Seclén et al.1 found that the algorithms were poorly sensitive for detecting CXCR4-using variants in non-B subtypes. Unfortunately, this analysis was global due to the small number of each subtype. In contrast, we used a panel of CRF-02 strains to demonstrate the good performance of Delobel’s rule for predicting CXCR4-using viruses; the sensitivity was 70% and the specificity was 98%.3 Using the same dataset, the WebPSSM_{X4/R5} was 80% sensitive, but less specific (76%).4 In another study, Delobel’s rule predicted the subtype C CXCR4-using viruses with a sensitivity of 93% and a specificity of 96%, and the subtype C WebPSSM_{X4/R5} was 82% sensitive and 93% specific.5 Further studies are needed to evaluate the performances of genotypic algorithms for specific subtypes. Finally, we agree that genotypic methods are suitable for determining HIV-1 co-receptor usage in both plasma and peripheral blood mononuclear cells before treatment with CCR5 antagonists.

Transparency declarations

None to declare.

References


High sensitivity of specific genotypic tools for detection of X4 variants in antiretroviral-experienced patients suitable to be treated with CCR5 antagonists—authors’ response

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Sir,

We appreciate the comments made by Raymond et al. on our recent study, in which we evaluated the accuracy of several genotypic predictors of HIV tropism, taking as reference the results obtained using a phenotypic assay (Phenoscript®) in 150 plasma samples collected from HIV-1 patients infected with either B (n=75) or non-B clades (n=75). One of the genotypic approaches evaluated was Delobel’s rule, which refers to the interpretation algorithm proposed by Delobel et al. a few years ago. At that time Delobel and colleagues reported an improved genotype-phenotype correlation for predicting HIV tropism by combining the 11/25 and net charge rules. Delobel et al. said ‘the presence of CXCR4-using viruses in HIV-1 quasi-species was suspected when an R or K amino acid at V3 position 11 or 25 was detected in major or minor species on the electropherogram, concomitant with a maximum net charge of +5 (when considering the combination of codons that resulted in the highest net charge)’. Following that description, we did our analyses. Therefore there is no mistake in our interpretation, as samples were labelled as X4 if a basic amino acid (R or K) was recognized at positions 11 or 25 within the V3 region and if the global net charge of the V3 sequence was ≥+5.

In a subsequent publication, Raymond et al. suggested that prediction of CXCR4-coreceptor usage should be made considering ‘either 11R/K or 25K or both; 25R and a net charge of at least +5; or a net charge of at least +6’. We have re-analysed the 150 samples of our study using this new interpretation in order to evaluate its accuracy to predict HIV tropism using Phenoscript® results for comparison. Overall, we found a sensitivity/specificity of 78%/86% for recognition of X4 variants in clade B viruses, which is lower in terms of sensitivity to that found using Garrido’s rule (94%/74%).

The sensitivity/specificity for detecting X4 variants in antiretroviral (ARV)-experienced patients was 75%/85%, but 40%/93% in ARV-naïve individuals. The last figures suggest a lower sensitivity than in the original report by Raymond et al. (63%/97%). The difference could be in part due to the variability between the two different phenotypic methods used to determine HIV tropism in both studies.

The overall sensitivity/specificity to predict X4 variants in non-B subtypes using Raymond’s rule was 42%/92%. These results are not in line with prior data in a different set of non-B subtypes tested by these authors that included A1, F1, G, J, CRF_01, CRF_02 and CRF_06. They found the same genotype-phenotype concordance among B (76/84) and non-B viruses (13/14). However, it is worth noting the limited size of the population examined and the difficulty of getting conclusive results.

In our dataset we have performed a specific analysis of 21 CRF02_AG specimens and found sensitivity/specificity rates of 40%/94%, while Raymond et al. reported figures of 70%/98% for CRF02_AG (n=52). The different sensitivities between studies are most likely due to the limited size of the populations examined and require further attention. It must be highlighted that misclassification of X4 variants may be critical in terms of clinical consequences.

In our dataset we did not have enough clade C specimens (only eight) and therefore could not derive any conclusion. We agree that specific genotypic predictors are needed for determining HIV tropism in patients infected with clade C. Overall, all this information highlights that further studies testing larger cohorts of patients infected with distinct non-B subtypes are required in order to establish the reliability of genotypic tools for assessing HIV tropism in clinical settings and guide the therapeutic use of CCR5 antagonists.

Transparency declarations

None to declare.

References


