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Determination of HIV-1 co-receptor usage in German patients – comparison of genotypic methods with the TROFILE® phenotypic assay

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Background

Maraviroc is a new drug used to treat HIV infection from the new class of drugs called CCR5 entry inhibitors. As the active principle of these drugs is to block the CCR5-receptor on the surface of the target cells, it has to be known if the virus in the patient is using only CCR5 as co-receptor or if there are populations that can also use CXCR4. Therefore, an assay to determine the tropism has to be performed before starting a therapy. Besides phenotypic assays like the TROFILE® assay by Monogram, used in the approval studies, there exist several genotyping systems like geno2pheno-coreceptor, Wetcat (providing five different genotypic tropism schemes) and WebPSSM.

Methods

We compared the results of 310 patient samples using the geno2pheno-coreceptor with the results of the TROFILE assay.

Summary of results

The agreement between the TROFILE assay and geno2pheno[co-receptor] (using a false positive rate of 20%) was 75%, compared to 84% for WebPSSM. Although the performance of geno2pheno-coreceptor seems not superior compared to the other genotypic systems, this approach only classifies 23% of the 104 CXCR4-tropic samples false as CCR5-tropic, whereas WebPSSM and Wetcat have a higher amount of false CCR5-tropic classification. See Figure 1.

Although geno2pheno has the unique ability to add additional laboratory parameters into the analysis, the use of these data has no beneficial effect on the prediction. For 65 of the proviral samples, additional TROFILE results and results from viral RNA sequencing were available. Concordance between viral and proviral results was 74%, with a slightly higher rate of X4 detection (42% vs. 37%).

Conclusion

The results of the genotypic classification approaches show similar results as comparison of phenotypic approaches. Due to our experiences, a differentiated approach using the geno2pheno system provides the best results in CXCR4 usage prediction. For patients with severely limited therapeutic options we suggest the use of CCR5 blockers only if the geno2pheno system, using a FPR of 5%, does not predict CXCR4 usage. The other side of the patient spectrum with many antiretroviral therapy options requires a more stringent setting with a FPR of 20%. For this highly personalized approach, close cooperation between the clinicians and virologists is essential. Sequencing of proviral DNA is leading to similar

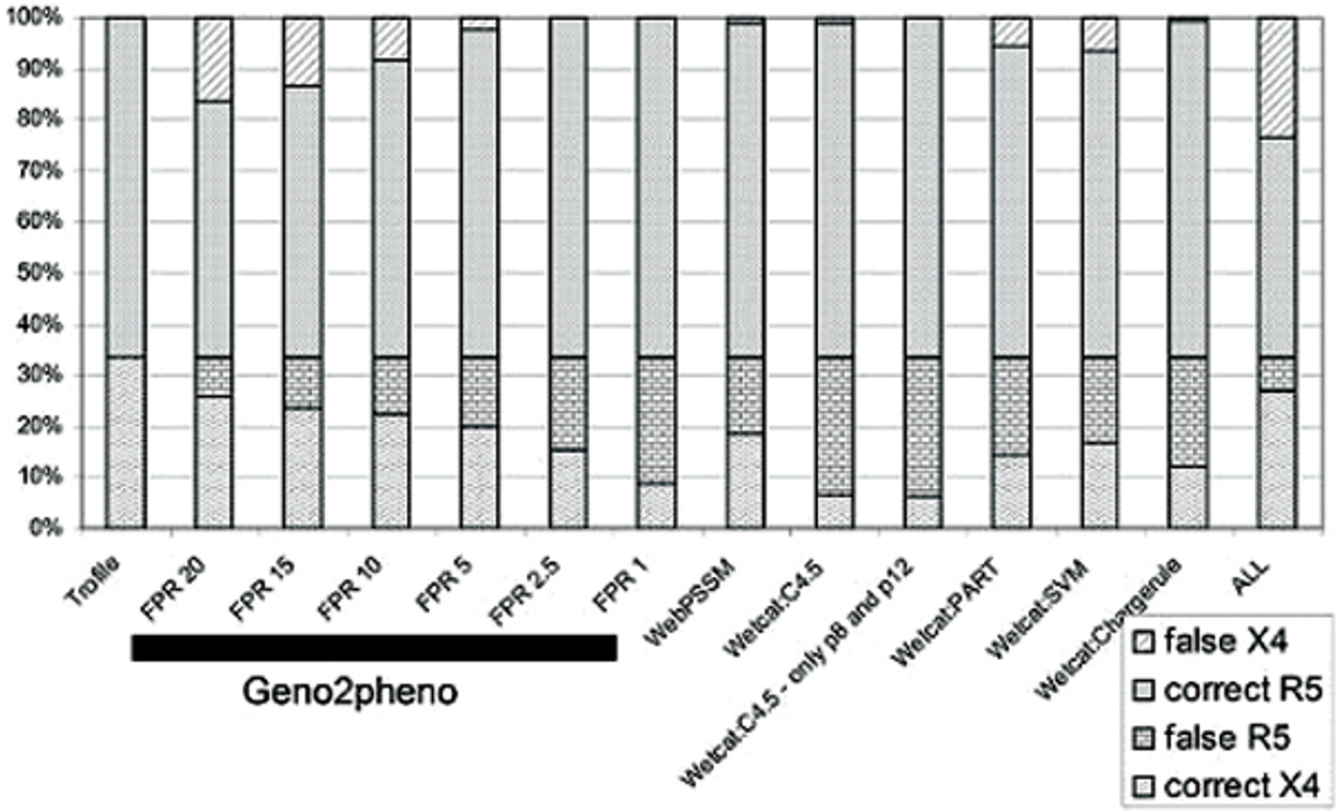

Figure 1
Agreement between genotypic methods and TROFILE® N = 310.

results as sequencing viral plasma RNA, with a slightly higher rate of X4 detection, thus offering an possibility for tropism testing at a plasma viral load below detection limit.