Geno2pheno and the Arevir database: tools for determination of clinically relevant cut-offs and prediction of viral load change from HIV-1 genotype.

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Introduction

There is wide agreement that genotypic and phenotypic definitions of HIV drug resistance should rely on correlation with virological and clinical outcome. Establishing these “clinical cut-offs” has proven to be a significant challenge because (i) monotherapy is obsolete, (ii) treatment response to a drug combination is usually attributed to more than one drug, and (iii) other factors apart from drug resistance may confound the analysis (e.g. drug adherence).

Methods

For determination of clinically relevant cut-offs we combined the quantitative phenotype prediction tool geno2pheno (fig. 1) with the multi-center Arevir database (fig. 2). Geno2pheno is an HIV drug resistance interpretation system based on machine learning techniques. The Arevir database is a relationale database containing clinical and virological data of 4.597 patients. To deduce virologic response to Lopinavir/r (LPV/r) the Arevir database was screened for LPV add-on- and “quasi-monotherapies” (therapies where LPV/r was the only drug estimated to be active). Resistance factors were predicted from HIV-genotypes by geno2pheno with the multi-center Arevir database containing phenotype prediction tool geno2pheno (fig. 1) with the multi-center Arevir database: tools for determination of clinically relevant cut-offs and prediction of viral load change from HIV-1 genotype. Diversity and complexity of HIV-1 drug resistance: A bioinformatics approach to predicting phenotype from genotype. Proceedings of the National Academy of Sciences U.S.A. 2002, 99(12), 7671-7676.

Results and Discussion:

Of the more than 4,500 data sets only 45 fulfilled the criteria for genotyping and viral loads before and after switch. Only 13 of these 45 data sets were estimated a “LPV/r quasi-monotherapy”. The maximum VL reduction after therapy switch was observed for genotypes with LPV-specific resistance factors (RFs) < 10 fold (lower cut-off). Patients with almost no VL reduction harboured viruses with genotypes of predicted RFs >31 fold (upper cut-off). Besides determination of clinically relevant cut-offs, this system enables prediction of VL change from HIV-genotype, which is most helpful in an intermediate level of resistance, where interpretation is most challenging, particularly for patients with limited therapy options.

Results and Discussion:

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<th>d4T</th>
<th>3TC</th>
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Fig. 1: geno2pheno output

Fig. 2: Schematic representation of the relationale Arevir database showing selected entities.

Fig. 3: Correlation of viral load change and resistance factor

References
