HIV DART 2004
Frontiers in Drug Development for Antiretroviral Therapies

Final Program and Abstract Book
Montego Bay, Jamaica
12–16 December 2004

Sponsored by
NORTHWESTERN UNIVERSITY
Feinberg School of Medicine

Official Publication of the International Society for Antiviral Research
RESULTS: Susceptibility to saquinavir is summarized by subtype, for all non-B subtypes and for subtype B in Table 1. Susceptibility of viruses from non-B subtypes was comparable to that observed for the 5 SQV naive subtype B viruses (GM of 1.381 vs. 1.406 nM, respectively).

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Geomean IC₅₀(nM)</th>
<th>IC₅₀ Range (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLADE A</td>
<td>5</td>
<td>0.989</td>
<td>0.90-1.30</td>
</tr>
<tr>
<td>CLADE AE</td>
<td>5</td>
<td>1.318</td>
<td>1.20-1.40</td>
</tr>
<tr>
<td>CLADE C</td>
<td>5</td>
<td>1.357</td>
<td>1.00-1.60</td>
</tr>
<tr>
<td>CLADE D</td>
<td>5</td>
<td>1.441</td>
<td>1.00-1.90</td>
</tr>
<tr>
<td>CLADE F</td>
<td>5</td>
<td>1.726</td>
<td>1.50-2.20</td>
</tr>
<tr>
<td>CLADE G</td>
<td>5</td>
<td>1.526</td>
<td>1.10-2.30</td>
</tr>
<tr>
<td>CLADE H</td>
<td>2</td>
<td>2.000</td>
<td>1.60-2.50</td>
</tr>
<tr>
<td>All Non-B</td>
<td>3</td>
<td>1.406</td>
<td>0.90-2.50</td>
</tr>
<tr>
<td>CLADE B wt</td>
<td>5</td>
<td>1.381</td>
<td>1.10-1.70</td>
</tr>
</tbody>
</table>

CONCLUSIONS: The results presented here indicate that non-subtype B viruses show IC₅₀ values for saquinavir comparable with protease-inhibitor naïve subtype B viruses. These data would suggest that PI untreated non-B subtypes are fully sensitive to treatment with saquinavir and therapy should not be withheld for reasons of viral diversity.

ABSTRACT 043

Prediction of HIV-1 Resistance to NNRTIs: a Computer-aided Molecular-based Rationale

S.Prioli¹, A.Coslanich¹, M.Fermeglia¹, M.Ferrone¹, MS.Panen¹, R.Loddo², A.Cabizza², G.Sanna², M.Murreddu², P.La.Colla²

1 Molecular Simulation Engineering (M.O.S.E.), Department of Chemical Engineering, University of Trieste, Italy; 2 Department of Biomedical Sciences and Technologies, University of Cagliari, Italy

BACKGROUND: The introduction of Highly Active Antiretroviral Therapy (HAART) has had a dramatically positive effect on the natural history of HIV-1 disease in the developed world. However, incomplete suppression leading to drug resistance has often impaired the HAART efficacy. For example, resistance towards non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) develops rapidly in the clinical setting. Accordingly, the optimal use of NNRTIs will require both the appreciation of the potential for the development of drug resistance, and the recognition that this problem can be avoided. Thus, an approach to the issue of rapid emergence of NNRTI resistance could be the attempt to provide sufficient levels of potent inhibitors in order to inhibit not only wild type HIV-1, but also preexisting resistant viral variants found at low levels as a result of de novo mutations during ongoing virus replication, or at high levels as a consequence of NNRTI treatment failure.

METHODS: In this work we developed a computational procedure for the evaluation of the free energy contribution of each residue in the HIV-1 RT in binding to several, different NNRTIs which are known to fail in the presence of given mutations. The purpose of these computations is: 1) to obtain indication for the design of resistance-evading drugs and, 2) to calculate the values of an empirical parameter, GV, which combines free energy calculations and sequence analysis to suggest possible drug resistance mutations on the RT. In practical terms, this parameter is defined as the product of a given residue contribution to the total binding free energy and the variability of that residue. This quantity could, in principle, be used in assisted resistance-evading drug design for HIV-1 RT, as well as for any other proteic viral target.
RESULTS: The developed computational method allowed to correctly predict all the resistance mutations found in vitro and/or in vivo for a substantial number of NNRTIs. Moreover, it was also able to highlight aminoacid residues classified as sensitive to resistance.

CONCLUSIONS: A computer-aided based approach is developed for predicting HIV-1 RT resistance towards NNRTIs. The method is highly predictive in all cases considered. More importantly, for those compounds for which the X-ray structure of the relevant complex with HIV-1 RT is not available, an ab initio procedure is devised, starting from the docking of the drug within the enzyme to the prediction of the relevant site susceptible to mutation. This method can be employed for the a priori prediction of the insurgence of resistance of newly designed drugs, or to aply modify existing drugs towards a more efficacious binding even in the presence of resistant HIV-1 RT mutants.

ABSTRACT 044
Polymorphisms and Drug Resistance Associated Mutations in Subtype C HIV-1 Variants

D Turner1,2, B Brenner1, D Moisi1, Y Sela2, and MA Wainberg1

1 McGill University AIDS Centre, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada, 2 AIDS Center, Tel-Aviv Sourasky Medical Center, Israel

BACKGROUND: Most current knowledge of HIV pathogenesis and responsiveness to antiretroviral therapy (ART) is based on work carried out with subtype B viruses, while relatively little information is available in regard to other viral subtypes. Many polymorphisms are known to be associated with non-B subtypes. Our objectives in this study were to compare the prevalence of mutations in subtype B viruses with viruses of subtype C in treated and untreated patients and to look for the presence of unknown mutations in subtype C viruses associated with ART.

METHODS: Viruses isolated from patients harboring subtype B and C viruses were analyzed by DNA sequencing of DNA PCR products, and the PR and RT regions of viruses from treated and untreated individuals were compared separately for each of subtypes B and C. We asked whether differences between the subtypes might exist in regard to prevalence of drug resistance-associated mutations. Statistical significance was assessed by χ² analysis.

RESULTS: Fifty-six sequences of HIV-1 subtype C (36 treatment naive and 20 post ART) and 290 (79 treatment naïve and 211 post ART) subtype B viral isolates were analyzed. Mutations that were common in RT of the treated patients harboring subtype C viruses included: Q335D (70%), M184V (40%), K173T (30%), T215Y(30%), D67N(25%). None of these mutations were present in naïve patients with the exception of M184V (2.8%). Similar proportions of these mutations were present in the subtype B viruses, except that the latter did not contain either K173T or Q333D in RT, which were also uncommon in the subtype C isolates. No significant differences were observed in the prevalence of mutations associated with PI therapy in patients harboring subtype C (n=12) vs subtype B viruses (n=178).

CONCLUSION: Despite a high level of polymorphisms, patterns of drug resistance-associated mutations do not differ significantly in viruses of subtype C vs subtype B.

Keywords: HIV-1, subtype C, resistance