HIV-1 Clinical Isolates with the E138A Substitution in Reverse Transcriptase Show Full Susceptibility to Emtricitabine and Other Nucleoside Reverse Transcriptase Inhibitors

Danielle P. Porter, Rima Kulkarni, Kirsten L. White
Gilead Sciences, Inc, Foster City, California, USA

A recent report by Sluis-Cremer and colleagues found that HIV-1 site-directed mutants containing the E138A substitution in reverse transcriptase (RT) exhibited decreased susceptibility to the nucleoside reverse transcriptase inhibitors (NRTIs) emtricitabine (FTC) and lamivudine (3TC) in vitro by 4.7-fold and 6.0-fold, respectively, compared to wild-type virus (1). Other amino acid substitutions at position E138, such as G, K, Q, and R, did not show any effect on phenotypic susceptibility to FTC. The authors note that while the clinical significance of these findings is unknown, they postulate that E138A may impact the clinical response to FTC and 3TC. No clinical data are presented in their report to address this possibility.

Here, we report NRTI phenotypic susceptibility data for 20 E138A-containing HIV-1 clinical isolates from 17 individual patients in a clinical trial database (Table 1). Protease and RT genotyping (population sequencing) and phenotyping of the isolates were performed using the PhenoSense GT assay (Monogram Biosciences, South San Francisco, CA). Genotyping results showed that all of these HIV-1 isolates contain E138A and no other known NRTI or nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations in RT. In contrast to the published data using site-directed mutant viruses (1), phenotyping data from these clinical isolates demonstrated that the E138A substitution did not confer reduced susceptibility to FTC, 3TC, or any of the other NRTIs that are currently available for HIV treatment (Table 1). Fold changes for FTC and 3TC for clinical isolates containing E138A were similar to those of a group of over 500 patient isolates lacking any known resistance-associated mutations in RT (mean fold change [range]: FTC, 1.1 [0.55 to 2.2]; 3TC, 1.1 [0.59 to 2.1]).

The E138A substitution in HIV-1 RT is a common polymorphism present in the virus of 0.5% (subtype B) to 5% (subtype C) of treatment-naive HIV-1-infected individuals (HIV Drug Resistance Database, NNRTI Resistance Notes, accessed 2 April 2014 [http://hivdb.stanford.edu/DR/NNRTIResNote.html]). This substitution is included in the International Antiviral Society-USA (IAS-USA) list of NNRTI resistance mutations for etravirine and rilpivirine (RPV) and is thought to contribute to reduced susceptibility to these drugs (2; HIV Drug Resistance Database, NNRTI Resistance Notes, accessed 2 April 2014 [http://hivdb.stanford.edu/DR/NNRTIResNote.html]). Although the emergence of E138A has not been observed in any RPV-treated patients in three large clinical trials, E138A should still be considered a relevant RPV resistance-associated substitution (3–5).

Other amino acid substitutions at position 138 in RT, most notably E138K, are commonly selected in patients failing treatment with RPV and the NNRTIs FTC and tenofovir disoproxil fumarate (TDF), often in combination with the FTC resistance-associated substitutions M184V/I in RT (3–5). E138K alone has been shown to confer reduced susceptibility to RPV but not FTC. The combination of E138K with M184V or -I has reduced susceptibility to FTC that is comparable to the reduced susceptibility to FTC seen with M184V or -I alone (6, 7).

The phenotyping data of patient isolates presented here show that the E138A substitution in RT does not have an impact on FTC susceptibility, and therefore, the presence of this substitution is unlikely to affect treatment outcomes for patients treated with FTC. While E138A plays a role in the in vitro system developed by Sluis-Cremer and colleagues, the clinical relevance of these results remains uncertain.

REFERENCES


TABLE 1 Nucleoside reverse transcriptase inhibitor phenotypic susceptibility of E138A-containing HIV-1 clinical isolates (n = 20)a

<table>
<thead>
<tr>
<th>NRTI</th>
<th>Mean fold change (range)</th>
<th>Assay cutoffb</th>
<th>No. of resistant isolatesc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtricitabine</td>
<td>1.2 (0.59–2.0)</td>
<td>3.5</td>
<td>0</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>1.3 (0.77–2.2)</td>
<td>3.5</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>0.87 (0.66–1.2)</td>
<td>1.4–4</td>
<td>0</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1.1 (0.83–1.3)</td>
<td>4.5–6.5</td>
<td>0</td>
</tr>
<tr>
<td>Didanosine</td>
<td>1.0 (0.67–1.3)</td>
<td>1.3–2.2</td>
<td>1d</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>0.81 (0.34–1.4)</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Stavudine</td>
<td>0.92 (0.64–1.2)</td>
<td>1.7</td>
<td>0</td>
</tr>
</tbody>
</table>

a All isolates were HIV-1 subtype B.
b Assay cutoffs are reported biological or clinical cutoffs for the PhenoSense GT assay.
c Resistance is defined as having a fold change above the assay cutoff for the drug.
d One isolate had a fold change of 1.32 and was reported to be partially resistant.

LETTER TO THE EDITOR

The authors of the published paper did not feel that a response was necessary.

Copyright © 2014, American Society for Microbiology. All Rights Reserved.

Address correspondence to Danielle P. Porter, danielle.porter@gilead.com.