

Human Immunodeficiency Virus Polymorphisms and Zidovudine Resistance

Stürmer et al. presented an interesting paper (1) on the influence of the classic zidovudine (ZDV) mutation patterns and the role of the additional mutations at positions 208, 211, 214, and 333 on phenotypic ZDV resistance. The presence of the 211/214 mutation combination in the background of genotypic highly ZDV-resistant viruses increased ZDV resistance 2.4-fold, and the 208/211/214 combination increased ZDV resistance 8-fold. The authors suspect a stabilization mechanism of the three-dimensional structure of the enzyme that could be explained by the vicinity of the mutations at positions 208, 211, and 214 to the ZDV-associated mutations L210W and T215Y/F. These mutations are likely involved in the compensation of the possible loss of fitness caused by the T215Y/F mutation.

We investigated the drug susceptibility of human immunodeficiency virus (HIV) strains of 19 HIV-infected patients failing double nucleoside reverse transcriptase inhibitor (NRTI) therapy by using the genotypic and the phenotypic assays. We identified four patterns of genotypic resistance (Table 1), namely, pattern 1, in patients with the 184V mutation alone; pattern 2, in patients with the 184V mutation combined with the 208Y, 211K, and/or 214F mutations; pattern 3, in patients with the 184V mutation and thymidine analogue mutations (TAMs) (including 41L, 210W, 215Y/F, and/or 219Q/E); and pattern 4, in patients with TAMs and the 184V mutation combined with the 208Y, 211K, and/or 214F mutations. As expected, genotypic patterns 1 and 3 showed a phenotypic resistant pattern to lamivudine (3TC) alone and to both 3TC and ZDV, respectively. The presence of 208/211/214 polymorphism combined with the 184V mutation (genotypic pattern 2) was related to a high phenotypic cross-resistance within all NRTIs analyzed. The presence of TAMs in addition to this pattern (genotypic pattern 4) showed a reduced phenotypic resistance for stavudine (d4T) and, to a smaller extent, for didanosine, ZDV, and abacavir.

The impact of the 208/211/214 polymorphism in terms of NRTI drug susceptibility on a background of a resistant virus appears to be related to the presence of the 184V mutation alone. High cross-resistance to all NRTIs has been detected only in HIV strains with this polymorphism combined with the 184V mutation in absence of TAMs. This particular genotypic-phenotypic pattern was detected among patients treated with d4T and 3TC. This phenomenon is likely to be related to the presence of different pathways in the emergence of NRTI resistance mutations in HIV-infected patients failing a d4T-3TC or ZDV-3TC regimen. Longitudinal studies are needed to

evaluate the significance of this polymorphism in the clinical outcome of patients treated with highly active antiretroviral therapy.

REFERENCE

1. Stürmer, M., S. Staszewski, H.-W. Doerr, B. Larder, S. Bloor, and K. Hertogs. 2003. Correlation of phenotypic Zidovudine resistance with mutational patterns in the reverse transcriptase of human immunodeficiency virus type 1: interpretation of established mutations and characterization of new polymorphisms at codons 208, 211, and 214. *Antimicrob. Agents Chemother.* 47:54–61.

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Authors' Reply

Nicastrì and colleagues investigated drug susceptibility of HIV type 1 strains isolated from 19 patients using both genotypic and phenotypic assays. They identified four mutational patterns and analyzed the corresponding phenotypes. One mutational pattern including the M184V, H208Y, R211K, and/or L214F changes without TAMs was characterized as conferring high cross-resistance within the group of NRTIs. The authors concluded from their data that the influence of the 208/211/214 polymorphism on NRTI resistance appears to be related to the M184V mutation only.

As we have described in our paper (4), the H208Y change was not detectable in samples without any TAMs (0 of 431). Therefore, we reanalyzed our database, which has been ex-

TABLE 1. Pattern of genotypic and phenotypic resistance of 19 HIV strains of patients failing double NRTI therapy

Pattern of genotypic mutation(s) ^a	No. of samples	No. of samples with phenotypic resistance (IC ₅₀ range [fold]) ^b :				
		d4T	3TC	ddI	AZT	ABC
184V	4	0 (0.6–1.1)	4 (22–1,666)	0 (0.8–1.7)	0 (0.4–2)	2 (1.1–30)
184V and 208Y/211K/214L	4	3 (2.1–226)	4 (354–456)	3 (1.2–277)	4 (10–1,744)	4 (10.6–506)
184V and TAMs	3	0 (0.5–2.1)	3 (132–235)	1 (1.1–8)	3 (5.4–200)	1 (0.7–11.6)
184V and 208Y/211K/214L and TAMs	8	2 (0.6–182)	8 (14–542)	4 (1–53)	5 (0.9–940)	6 (0.9–276)

^a TAMs include 41L, 210W, 215Y/F, and/or 219Q/E mutation(s).

^b ddI, didanosine; ABC, abacavir.

tended in the meantime, and found only two samples (2 of 2,331) from one patient with the mutational pattern described by Nicastrì and colleagues (M184V, H208Y, R211K, and/or L214F without TAMs). We have submitted this sequence to two virtual phenotype-based interpretation systems, Geno2Pheno (1) and VirtualPhenotype (Virco) (2). The following results were obtained for Geno2Pheno (obtained fold change in the 50% inhibitory concentration [IC_{50}]/cutoff): zidovudine, 1.6/8.5; didanosine and zalcitabine, 2.1/2.5; stavudine, 1.4/2.5; lamivudine, 68.6/8.5; and abacavir, 2.9/2.5. Similar results were found using VirtualPhenotype (obtained IC_{50} fold change/cutoff): zidovudine, 0.9/4.0; didanosine, 1.2/2.0; zalcitabine, 1.5/2.0; stavudine, 0.7/1.8; lamivudine, 46.0/4.5; and abacavir, 1.6/3.0. In the case of VirtualPhenotype, the IC_{50} fold changes were calculated using a median of 2,714 matches in the database (range, 1,102 to 2,924). When a sample with only the M184V mutation was analyzed in the VirtualPhenotype system, a similar pattern of IC_{50} fold changes was obtained.

These findings don't support a broad cross-resistance in the group of NRTIs produced by the above-mentioned mutational pattern. The slightly increased IC_{50} fold changes observed for didanosine, zalcitabine, and abacavir are associated with the presence of the M184V change (3) independent of other polymorphisms but could not be interpreted as broad cross-resistance to these drugs. The patient isolates with the mutational pattern described as conferring NRTI cross-resistance by Nicastrì and colleagues should be reanalyzed in consideration of the presence of known multidrug resistance patterns or other mutational patterns yet uncharacterized. Furthermore, the principle of the phenotypic assay used should be made available, and the samples should be retested to clarify these contrary findings.

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