Correspondence

HIV-1 Genotypic Drug-Resistance Interpretation Algorithms Need to Include Hypersusceptibility-Associated Mutations

To the Editor—Tozzi et al. [1] recently reported a retrospective study investigating the effect that mutations associated with hypersusceptibility to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) have on the virological response to efavirenz-based therapies. The authors concluded that "the M41L, M184V, L210W, and T215Y mutations were associated with a better, although transient, virological outcome in patients treated with efavirenz-based regimens" (p. 1688).

Hypersusceptibility is certainly a very interesting concept, and we have checked publicly available HIV-1 genotypic drug-resistance interpretation algorithms for information on hypersusceptibility. The most recent mutations report (October 2003 revision) from the International AIDS Society–USA Drug Resistance Mutations Group [2] includes a footnote that describes M184V as a mutation that is possibly associated with hypersusceptibility to some nucleoside reverse-transcriptase inhibitors, but the report does not include this or any other hypersusceptibility-associated mutations in its main table. Using the algorithm-specific interface of the Stanford Drug Resistance Database [3], we could not find a "hypersusceptible" category in the rules for either the ANRS algorithm (version 2003.10) or the Rega algorithm (version 6.2). The Stanford HIVdb algorithm (version 2004.4) does contain a few hypersusceptibility annotations, but none of the 4 mutations reported by Tozzi et al. is listed as conferring hypersusceptibility to efavirenz or to other NNRTIs. The geno2pheno web server [4] implements 2 machine-learning algorithms (decision tree and support vector machine) for HIV-1 genotypic drug-resistance interpretation, but neither algorithm can provide predictions for hypersusceptibility. We recently developed a linear statistical model for HIV-1 genotypic drug-resistance interpretation [5]. Our model for efavirenz suggests that the presence of M41L or T215Y can potentially decease IC_{50} fold-change values by 38.7% and 33.0%, respectively. Our genotypic algorithm actually predicts the existence of at least 1 hypersusceptibility-associated mutation for all 17 protease inhibitors (PIs) and reverse-transcriptase inhibitors used in our study. Included in our models are the predictions that M41L and T215Y cause hypersusceptibility to delavirdine and that T215Y causes hypersusceptibility to nevirapine.

In surveying the literature, we have come across several articles reporting on mutations associated with hypersusceptibility to NNRTIs. Shulman et al. [6] observed a positive correlation between phenotypic hypersusceptibility to efavirenz and virological responses to regimens that include efavirenz; also, using a multivariate analysis similar to our linear model, they found 215Y/F to be associated with hypersusceptibility. Whitcomb et al. [7] analyzed genotypic, phenotypic, and clinical data on mutations associated with hypersusceptibility to NNRTIs and demonstrated that "M41L and T215Y cause increased susceptibility to delavirdine and efavirenz" (p. F45) and that "M184V causes slight increases in susceptibility to all three NNRTIs" (p. F45). Haubrich et al. [8], Katzenstein et al. [9], and Mellors et al. [10] independently reported the correlation between hypersusceptibility and virological responses. These articles indicate that at least M41L and T215Y are associated with hypersusceptibility to NNRTIs and that such hypersusceptibility is associated with better virological responses. In addition, hypersusceptibility-associated mutations for PIs have been reported in a few cases, although their clinical significance has not been firmly established.

In conclusion, many groups involved in creating HIV-1 genotypic drug-resistance interpretation algorithms have, to date, ignored the issue of hypersusceptibility. In light of the accumulating data that supports the correlation between hypersusceptibility and better virological responses, we suggest that these mutations be included in genotypic algorithms and in rules for choosing combination therapy regimens. Further work should be done to investigate the clinical significance of mutations that are reported to confer hypersusceptibility to other antiretroviral drugs.

Kai Wang, Ram Samudrala, and John E. Mittler

Department of Microbiology, University of Washington, Seattle

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Reprints or correspondence: Dr. John E. Mittler, Dept. of Microbiology, University of Washington, Box 358070, Seattle, WA 98195 (jmittler@u.washington.edu).

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Reply to Wang et al.

To the Editor—Wang et al. [1], on the basis of the correlation between hypersusceptibility to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and improved virological response, have suggested that mutations associated with hypersusceptibility to NNRTIs should be included in genotypic drug-resistance interpretation algorithms and in rules for choosing combination therapy regimens. I agree with their suggestion. The International AIDS Society–USA Drug Resistance Mutations Group, in its most recent mutations report [2], included a footnote stating that the M184V mutation may enhance susceptibility to zidovudine, stavudine, and/or tenofovir. However, the report did not mention any mutation associated with hypersusceptibility to NNRTIs. I believe that nucleoside reverse-transcriptase inhibitor mutations associated with hypersusceptibility to NNRTIs should be considered for inclusion in genotypic algorithms for choosing combination therapy regimens, although some caveats should be kept in mind. First, hypersusceptibility is a complex phenomenon that cannot be fully explained by genotypic assessment. This is particularly important for hypersusceptibility to NNRTIs, because some of the most convincing evidence supporting its potential clinical utility has come from clinical trials of phenotypic assays [3, 4]. Second, the results of the study by my colleagues and I indicated that the beneficial effect on virological response is transient—the correlations between the M41L, M184V, L210W, and T215Y mutations in the reverse-transcriptase gene and the virological response to efavirenz-based therapy were observed only with respect to achieving an undetectable viral load and not with respect to the probability of the viral load remaining undetectable due to a lack of virological rebound [5]. Given the low genetic barrier and the wide cross-resistance of NNRTIs, the risk of virological rebound suggests the need to closely monitor virus load if an NNRTI is used in this setting.

Valerio Tozzi

National Institute for Infectious Diseases Lazzaro Spallanzani, Rome, Italy

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Reprints or correspondence: Dr. Valerio Tozzi, National Institute for Infectious Diseases Lazzaro Spallanzani, Via Portuense 292, 00149 Rome, Italy (tozzi@inmi.it).

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Mutations Associated with Hypersusceptibility… and with Good Adherence

To the Editor—In their excellent article, Tozzi et al. have shown that several nucleoside reverse-transcriptase inhibitor (NRTI) mutations are associated with an increased probability of the virological success of rescue therapy when the rescue therapy includes efavirenz [1]. The authors suggest that this is caused by hypersusceptibility to efavirenz. It is a reasonable interpretation. However, it would have been nice if Tozzi et al. had discussed the possible effect of adherence. My colleagues and I, as well as others, have demonstrated that patients who experience treatment failure and whose rebounding virus harbors resistance mutations more often have good adherence than do patients who experience treatment failure and whose rebounding virus does not harbor resistance mutations [2–5]. Thus, in the study by Tozzi et al., the improved virological response observed in patients with virus strains harboring resistance mutations could be explained, at least in part, by better adherence. Admittedly, the poorer association between NRTI mutations and the response to protease inhibitor (PI)–based therapy does support the hypothesis concerning hypersusceptibility to nonnucleoside reverse-transcriptase inhibitors, but this association could also be explained by the