Correspondence

Nonnucleotide Reverse-Transcriptase Inhibitors and Treatment Interruption

To the Editor—The instructive findings of Hare et al. [1] invite some loosely evidence-based speculation concerning both the pathogenesis of drug resistance and clinical practice pertaining to nonnucleotide reverse-transcriptase inhibitors (NNRTIs) with long half-lives, compared with most other antiretroviral drugs. Simultaneous discontinuation of an entire NNRTI-based regimen exposes the virus to a period of suboptimal NNRTI concentrations. NNRTI resistance may develop (or at least become manifest) in some patients as a consequence of this functional low-dose monotherapy, potentially voiding the future use of the entire NNRTI-drug class. Of course, the theoretical possibility remains that, even in the case of undetectable viremia during combination therapy, there may be enough ongoing viral replication to allow mutations to emerge for drugs with low genetic barriers to resistance (such as NNRTIs) in a few patients with apparently suppressed infections [2]. Nonetheless, because drug resistance is most likely to emerge during the wash-out period after simultaneous complete treatment interruption, staggered discontinuation of treatment has been recommended to decrease this risk [3–5]. Data presented by Hare et al. [1] demonstrate that such a strategy using a 2-day lead time may not be reliably successful in patients with undetectable viremia. A more aggressive approach would be to sequentially discontinue the drugs by first substituting treatment with a non–reverse-transcriptase inhibitor, such as a protease inhibitor, to replace the NNRTI component of the regimen for a duration commensurate with several half-lives of the NNRTI [6]. In circumstances in which a treatment interruption can be anticipated with sufficient advance warning, a non–reverse-transcriptase inhibitor can be added to the regimen shortly before withdrawal of the NNRTI. Because the ideal timing may vary with different NNRTIs and host pharmacogenetics [6], an example would be to initiate a protease inhibitor (probably as a boosted protease inhibitor) at least 8–15 days before the target date for complete treatment interruption [7], followed the next day by exclusive discontinuation of the NNRTI component of the regimen; after a minimum duration of 1–2 weeks of protease inhibitor–based combination therapy, all antiretroviral therapy could be concurrently stopped. The residual plasma and intracellular concentrations of NNRTIs that actually place patients at risk of developing drug resistance and the characteristics of the ideal non–reverse-transcriptase inhibitor to substitute for the NNRTI remain to be determined. Pending the ready availability of cytochrome P450 (CYP) 2B6 genotyping and/or therapeutic drug–level monitoring, ethnicity might be used as a surrogate marker for the presence or absence of a homozygous CYP 2B6 516G→T polymorphism associated with slower clearance of efavirenz, to inform real-time bedside decisions about the appropriate length of the NNRTI wash-out period in individual patients. Antiretroviral regimens in any future studies involving short-term repetitive treatment interruptions should probably not include NNRTIs [8].

Acknowledgments

Potential conflicts of interest. M.J.D. is an employee of and owns stock options in Merck.

Mark J. DiNubile
Merck Research Laboratories,
West Point, Pennsylvania

References