Correspondence

Lamivudine and Second-Line Antiretroviral Regimens

To the Editor—Sungkanuparph et al. [1] confirm the nearly ubiquitous presence of the M184V mutation in patients for whom antiretroviral regimens containing lamivudine fail. In this discussion, they go on to suggest that the high prevalence of this mutation among those for whom the initial regimen failed should preclude consideration of lamivudine as “an active NRTI in the second-line regimen” (p. 451). The data listed in their table 2 (p. 450) supports this assertion by not listing lamivudine as a second-line nucleoside reverse-transcriptase inhibitor option when the M184V mutation is documented [1]. The choice to include lamivudine in the second-line regimen is not so unambiguous. As Dr. Gallant [2] suggests in his editorial commentary, the rational sequencing of antiretroviral agents in the developing world is nearly impossible given current severe limitations in antiretroviral agent availability and viral load monitoring. However, contrary to the assertion of Sungkanuparph et al. [1], the maintenance of lamivudine in a second-line regimen and the ensuing persistence of the M184V mutation can serve an important purpose in preserving zidovudine sensitivity and potentially limiting viral fitness. Clinicians working in developing countries should not be so roundly discouraged from incorporating lamivudine into second-line regimens. Rather, rational incorporation of lamivudine into second-line regimens should be encouraged. Even in settings of limited options, lamivudine may remain useful in second-line regimens by protecting potential nucleoside reverse-transcriptase inhibitor backbone options and avoiding protease inhibitor monotherapy.

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References


Reply to Vogenthaler

To the Editor—We thank Dr. Vogenthaler [1] for his interest in our recent article describing the options for a second-line antiretroviral regimen after the failure of an initial regimen of a fixed-dose combination of stavudine, lamivudine, and nevirapine [2]. Vogenthaler raises the question of whether lamivudine should be included as a nucleoside reverse-transcriptase inhibitor in a second-line regimen (table 2 of [2]). He notes that maintenance of lamivudine in a second-line regimen and ensuing persistence of the M184V mutation can serve an important purpose in preserving zidovudine sensitivity and potentially limiting viral fitness.

The M184V substitution in the HIV-1 reverse-transcriptase gene confers high-level phenotypic drug resistance; an in vitro study [3] has shown that viruses harboring this mutation replicate less efficiently. A small pilot study by Campbell et al. [4] reported that lamivudine exerts some antiviral activity as a part of an incompletely suppressive regimen in patients with multidrug-resistant HIV-1 infection who harbored the M184V mutation. Castagna et al. [5] established that lamivudine monotherapy may lead to a better immunological and clinical outcome than complete therapy interruption in HIV-1–infected patients who harbored M184V. Of note, these 2 studies demonstrate the benefit of maintaining lamivudine therapy in patients with multidrug-resistant HIV-1 infection and that the goal for complete viral suppression is at least possible. Should we continue lamivudine therapy in a patient who is taking an incompletely suppressive regimen or who has no options for fully suppressive therapy? The answer is yes, on the basis of available data.

In contrast, a second-line antiretroviral regimen for patients for whom their initial first regimen failed should aim for complete viral suppression. Recent guidelines have indicated that the goal of treatment for patients with prior limited drug exposure and drug resistance is to reestablish complete viral suppression [6, 7]. Although these guidelines are primarily designed for use in developed countries, realization of this goal should at least be attempted in resource-limited countries as well, particularly if it is not impossible. A primary objective of our study [2] was to address concerns about HIV-1 drug resistance and its effect on the options of second-line therapy that aims for complete viral suppression. Thus, the nucleoside reverse-transcriptase options in a second-line regimen should not include lamivudine when M184V is present. The results of the Continued Lamivudine Twice Daily

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References


QT Interval Prolongation and Antiretroviral Treatment: Another Point of Interest

To the Editor—In their recent brilliant article, Owens and Nolin [1] described how the QT interval can be prolonged by use of antimicrobials, such as macrolides and ketolides, certain fluoroquinolones and antimalarials, pentamidine, and the azole antifungals. The antimicrobials mentioned by Owens and Nolin [1] are largely administered worldwide, although for limited periods of time. On the other hand, ~2 million persons are continually exposed to antiretroviral therapy worldwide, and this number will probably increase as the HIV epidemic continues to spread and as antiretroviral therapy becomes available for more people, especially in developing countries. Indeed, from 2001 to 2005, the number of persons receiving antiretroviral therapy in low- and middle-income countries increased >5-fold from 240,000 to ~1.3 million [2].

In recent years, there has been increasing concern with regard to QT interval prolongation in HIV-infected patients. Indeed, an increased prevalence of QT interval prolongation and a longer QT interval have been described in HIV-infected patients, compared with HIV-uninfected subjects [3–5]. QT interval prolongation in HIV-positive patients has been associated with alterations in cardiac innervation as a result of autonomic neuropathy [4, 6]. Moreover, several drugs administered to HIV-infected patients can cause a prolongation of the QT interval, including pentamidine [7], pyrimethamine [8], trimethoprim–sulfamethoxazole [9], methadone [10], clarithromycin [11], and ciprofloxacin [12, 13]. Furthermore, among antiretroviral drugs, efavirenz [14] and protease inhibitors [15, 16] have been reported as potential QT interval prolongers.

In a recent case-control study conducted at our institute, we were able to demonstrate an association between the administration of efavirenz or nelfinavir and the development of QT interval prolongation in HIV-infected individuals [17]. Moreover, we provided evidence that the risk of QT prolongation increased when efavirenz or nelfinavir therapy was combined with zidovudine therapy. In our opinion, clinicians who care for HIV-infected persons should be aware of the risk of QT interval prolongation, particularly when antiretroviral therapy is combined with drugs with known potential to prolong the QT interval.

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