Management of antiretroviral-related neuropsychiatric adverse effects

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The introduction of highly active antiretroviral therapy has led to sustained suppression of viral replication, immune reconstitution and improved clinical outcomes. Clinical trials (1,2) have informed recommendations for specific regimens as preferred therapy in treatment-naïve HIV-infected individuals. Observational cohort studies (3-5) have indicated that the rate of viral rebound after initial suppression to an undetectable (less than 50 copies/mL) viral load varies according to specific antiretroviral agents. In these cohort studies, efavirenz in combination with a dual nucleoside backbone continues to be an effective third agent. In addition, clinical trials (6-8) have demonstrated that efavirenz can be combined in a nucleoside-sparing regimen with boosted protease inhibitors, and can be successfully substituted for protease inhibitors and maintain viral suppression (9). Efavirenz is generally well tolerated, with the most frequent side effects being neuropsychiatric, including dizziness, insomnia, somnolence, impaired concentration and vivid dreams. These symptoms are usually mild to moderate, usually self-limiting, and resolve after the first two to four weeks of efavirenz use. In one clinical trial (10), central nervous system (CNS) symptoms occurred in more than 50% of efavirenz-treated patients. In a substudy of the ACTG 5095 trial (A5095 [11]) in which patients were randomly assigned to receive efavirenz with or without abacavir, 6% of those patients receiving efavirenz experienced CNS symptoms or mood disorders that led to discontinuation of the agent. Symptoms occurred within the first week of therapy in those on efavirenz; however, these resolved within the first month with no evidence of significant differences in neuropsychological performance. No significant changes in anxiety or depressed mood were found (11-14). Longer term toxicity has been observed with persistence of neuropsychiatric disorders after a mean of two years on efavirenz therapy, but these disturbances were mild and clinically tolerable, and did not impair the patients' quality of life and psychological status (15). Among efavirenz-treated patients, serious psychiatric events have been reported, such as severe depression, suicidal ideation, nonfatal suicide attempts, aggressive behaviour, paranoid reactions and manic reactions, all of which occurred in low frequency (16). Hence, management of depression and related neuropsychiatric symptoms associated with HIV infection and antiretroviral therapy is essential.

In the A5095 study, there was an association with higher efavirenz trough blood levels and neurological symptoms, but this occurred only in the first week of treatment. Another study (17) confirmed these findings: patients with higher efavirenz trough blood levels were at increased risk of CNS side effects. The neuropsychiatric toxicities have been associated with a CYP2B6 (G516T) genotype and other polymorphisms,

which affect drug clearance, resulting in higher blood concentration levels. The CYP2B6⁵¹⁶ TT genotype may be found in 20% of African-American patients (18-20). CYP2B6 genotyping can lead to recognition of patients at risk of neuropsychiatric symptoms and to targeted interventions with the initiation of efavirenz therapy. The role of therapeutic drug monitoring to decrease the incidence of these symptoms requires evaluation.

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