Hot News

Chronic Neuropsychiatric Symptoms in Patients on Long-Term Efavirenz

Efavirenz (EFV) is one of the most widely used antiretroviral drugs. Australian researchers have recently conducted a cross-sectional, case-controlled study comparing patients treated with EFV for at least six months with a matched control group (Rihs, et al. HIV Med 2006;7:544-8). Self-administered, standardized questionnaires including the Depression Anxiety Stress Scales (DASS), the Cognitive Failures Questionnaire (CFQ) and a questionnaire on unusual dreams, insomnia, fatigue, dizziness, depersonalization, and derealization were administered to the study patients. Data for 32 matched pairs were analyzed. Overall, significantly higher total stress scores were found in the EFV group compared to controls ($p = 0.008$). Of subjects with elevated stress scores, 19% also reported severe to extremely severe symptoms ($p = 0.014$), indicating increased difficulty in relaxing, and being more irritable, impatient, agitated, and easily upset.

On the other hand, 19% of patients treated with EFV also reported severe levels of anxiety as assessed by the DASS scale compared to controls ($p = 0.059$). This patient group also reported a higher rate of unusual dreams ($p = 0.049$). No significant differences between groups were found for measures of cognitive impairment, fatigue, dizziness, derealization, or depersonalization.

In conclusion, patients exposed to EFV for long periods experience higher levels of stress and anxiety as well as a higher rate of unusual dreams than patients not treated with EFV. These differences may reflect persisting central nervous system side effects of the drug.

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Microbicides: a Long and Bumpy Road to Success?

The need to develop additional HIV prevention tools, under the control of women, is urgent[1]. The search for an effective vaginal microbicide started in the early 1990s[2] and has been accelerated in recent years[3]. On January 31, 2007, CONRAD announced the discontinuation of their Cellulose Sulphate (CS) microbicide phase III effectiveness trial because "preliminary data indicated that cellulose sulphate could lead to an increased risk in HIV infection". This press announcement was received with disappointment and shock. It is yet another reminder that the road to success may be longer and more complex than anticipated. In the 1990s, high hopes were based on N-9 based spermicides. These cheap products were readily available on the market, approved as vaginal contraceptives, and data on anti-HIV activity from *in vitro* and animal models were promising. In 1996, after extensive safety studies[4-7], an HIV prevention phase III trial was launched, showing an increased risk of HIV among the N-9 users versus the placebo[8,9]. Important lessons were learned about local toxicity of vaginal detergents when used frequently and for a longer period of time[9]. Newer *in vitro* models confirmed that the "therapeutic window" between toxicity and anti-HIV efficacy was very narrow for N-9[10].

Screening of products, development of new *in vitro* and animal models more relevant for vaginal transmission of HIV, and multiple consultations between experts led to the identification and evaluation of potentially more effective and less toxic candidate products. The polyanians CS, Carraguard®, PRO 2000 and the acidifying agent Buffergel® entered phase III trials in 2004/2005 and investments in microbicides of the newer generations including the nonnucleoside reverse transcriptase inhibitors and newer versions of small molecular HIV-specific entry inhibitors strengthened[11]. As said, the CS trial was prematurely interrupted and the results of the other nonspecific entry inhibitors trials are eagerly awaited. What are the lessons learned? The negative effect of CS was a surprise. Expectations on the efficacy of CS varied from "promising" to "no effect", depending on which *in vitro* studies were referred to, but the increase in HIV risk was not expected, and no immediate explanation can be given.

This surprising result nevertheless brings us to a central issue in microbicide research: how can we best predict efficacy and toxicity of new candidate products and what is the relevance of the different *in vitro, ex vivo* and *in vivo* models in this context? The models can provide us with a good idea of the relative potency and toxicity of various candidates, but none of the present *in vitro* models is truly able to mimic completely transmission *in vivo* and many basic questions on vaginal transmission remain to be solved. It is a matter of proof of concept to allow for the various *in vitro* models to be validated.

Given the complexity of a phase III trial (cost, ethics, organization), only the very best products should move to this development stage. Therefore we need to invest in research on all levels:

- In the lab, to improve *in vitro* models for efficacy and toxicity, to be able to select the best possible candidates for future phase III trials.
- In the clinic, to rethink safety evaluations.
- In epidemiologic methods, to better understand the data on sexual transmission, and to maximize the phase III trial methodology for HIV prevention trials.

Probably most important is that there is fertilizing cross-discipline exchange! The challenges are enormous, but doing nothing would be the worst for the millions of vulnerable women and men in the world!

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The NEFA Study: Results at Three Years

The concept of simplification emerged as a need for adherent, HIV-infected patients receiving successful, complex or inconvenient antiretroviral regimens and it has now been incorporated into the updated recommendations for the use of antiretroviral therapy. The NEFA (Nevirapine, Efavirenz and Abacavir) Study was a multicenter, randomized, controlled, open-label clinical trial initially designed for one year of follow-up (Martinez, et al. N Engl J Med 2003;349:1036-46), although follow-up was extended up to three years following recommendations from the European Health Authorities in studies of maintenance therapy with simplified regimens in patients showing adequate virologic control. Eligible patients were HIV-1-infected adults who were receiving triple antiretroviral therapy consisting of at least one protease inhibitor (PI) plus two nucleoside reverse transcriptase inhibitors (NRTI), who had had plasma HIV-RNA < 200 copies/ml for at least the previous six months, and who wished to change the PI component of their regimen. Patients were randomly assigned to receive nevirapine, efavirenz, or abacavir instead of the PI used in their current antiretroviral regimen, while their NRTI remained unchanged. The sample size was computed to detect equivalence among the treatment groups in the proportion of patients with undetectable (< 200 HIV-RNA copies/ml) plasma viremia at one year.

The response rates did not differ significantly between nevirapine and efavirenz after one year of follow-up, and these results were maintained after three years of follow-up. At three years, the Kaplan-Meier estimates to reach a protocol-defined endpoint in the nevirapine (n = 155), efavirenz (n = 156) and abacavir (n = 149) arms were, respectively, 33, 46, and 40% in the intent-to-treat analysis (generalized log-rank test, p = 0.068). These figures were 17, 25, and 29% when “missing equal to failure” (generalized log-rank test, p = 0.031); and 12, 21, and 26% when a more conservative intent-to-treat analysis was made (generalized log-rank test, p = 0.020).

Remarkable differences were seen not only in the time to development of adverse effects. Side effects leading to discontinuation of nevirapine and abacavir concentrated almost exclusively in the first weeks of the study, whereas minor but persistent neuropsychiatric adverse effects led to late discontinuation of efavirenz during the entire study follow-up (Martinez, et al. AIDS 2007;21:367-9).

In summary, simplification of PI-containing HAART in patients with sustained virologic response had a higher probability of maintaining the suppression of viral replication after three years of follow-up when nevirapine or efavirenz were substituted for PI as compared with abacavir. However, in contrast with patients on nevirapine who had excellent long-term tolerability, patients on efavirenz showed a low but continuous discontinuation of the study drug due to minor but persistent neuropsychiatric adverse effects.

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Nevirapine or Efavirenz for Replacing Protease Inhibitors?

The recent observational study by Abgrall, et al.[1] reporting that patients with undetectable viral load switching from a first protease inhibitor (PI)-containing regimen to an efavirenz (EFV)-containing regimen are more likely to maintain virologic suppression than switching to an abacavir or nevirapine (NVP)-containing regimen merits a careful discussion. A previous observational study from EuroSIDA comparing NVP and EFV in a large group of mainly antiretroviral-experienced patients[2] also showed a better virologic outcome with EFV than with NVP, although the authors acknowledged that for most patients the NNRTI had not been optimally used as there was prior extensive exposure to NRTI and PI. In fact, they emphasized the need for adequate randomized trials comparing NVP and EFV. The NEFA (Nevirapine, Efavirenz and Abacavir) Study[3] was a randomized, controlled trial that showed similar efficacy between NVP and EFV when they were substituted for PI after three years of follow-up. However, in contrast with patients on NVP who had excellent long-term tolerability, patients on EFV showed a low but stable discontinuation rate due to minor but persistent neuropsychiatric adverse effects[4].

Although the study by Abgrall, et al. included a high number of patients and was adjusted for numerous potential confounding factors, it was a retrospective, observational study. The role of observational studies in the evaluation of treatments is a long-standing and contentious topic. All observational studies have one crucial deficiency: the design is not an experimental one. Each patient's treatment is deliberately chosen rather than randomly assigned, so there is an unavoidable risk of selection bias and of systematic differences in outcomes that are not due to the treatment itself. Although in data analysis adjustments for identifiable differences can be made, it is impossible to be certain that such adjustments are adequate or whether all relevant characteristics of the study population have been taken into account[5,6]. An older study conducted using the large database of EuroSIDA, the French Hospital Database on HIV (the one used in the study by Abgrall, et al.), and the Swiss Cohort Study[7], found serious biases on the effectiveness of antiretroviral therapies when comparing outcomes in these cohorts with the results derived from randomized clinical trials[8].

Given the profound discrepancy in the results reported by Abgrall, et al. and those from the NEFA study, any clinician or any patient may wonder whether NVP is really as virologically effective as EFV in replacing PI in patients who have sustained virologic suppression. To adequately resolve this question, clinicians and patients need to consider what is being done in any new healthcare intervention, founding their decisions on the most scientifically sound and rigorous methods available. Although observational studies may be cheaper, quicker, and less difficult to carry out, and they may be the best evidence when adequate randomized, controlled trials are lacking, we should not lose sight of one simple fact: lack of knowledge calls for careful experimentation. And this means high-quality randomized, controlled trials, not observations that may reflect personal choices and beliefs.

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