The relationship of CPE to HIV dementia
Slain by an ugly fact?

Thomas Henry Huxley, known as “Darwin’s bulldog” for his staunch advocacy of the theory of evolution, is credited with the following statement: “The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact.” The study by Caniglia et al.1 in this issue of Neurology® demonstrating that HIV-infected individuals treated with antiretroviral regimens exhibiting better CNS penetration had higher rates of HIV dementia is perhaps the “ugly fact” that might slay a beautiful and widely touted hypothesis. The finding is not only unexpected, but counterintuitive.

The authors analyzed a large dataset comprising nearly 62,000 HIV-infected persons from Europe and the United States and classified them into 3 groups (high, medium, and low) depending on the CNS penetration effectiveness (CPE) of their antiretroviral regimen. Hazard ratios for HIV dementia and several other neurologic complications of AIDS including toxoplasmosis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy were calculated using a pooled logistic regression model for each of the 3 groups. Not surprisingly, the CPE of the antiretroviral regimen did not affect the likelihood of developing AIDS-related CNS opportunistic infections. After all, the predominant driver for the development of these problems is the degree and duration of cellular immunosuppression, not HIV replication in the CNS. Unanticipated was the observation of a direct correlation between high CPE and HIV dementia. The hazard ratio (95% confidence interval) for initiating a combined antiretroviral regimen with a high vs low CPE regimen was 1.74 (1.15, 2.65) for HIV dementia. The authors suggest that the mechanism is the consequence of HIV infection where viral escape, 

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neurologic performance measures and no prospective study has yet validated it. Nonetheless, it remains frequently cited as an approach for selecting effective therapy. This study emphasizes that such recommendations are premature. Generally, the most tolerable, potent, and effective cART should be selected, regardless of CPE. In rare instances of viral escape in CSF, selection of cART based on viral resistance of the CSF isolate is necessary.

A dogmatic approach in selecting cART to prevent or treat HAND at the current time seems unwarranted. Further development of ranking schemes for effectiveness in brain may be useful, perhaps including considerations for alternative mechanisms competing with cART efficacy against the virus. The brain is a large potential reservoir for HIV infection and may be responsible for the generation of mutations and resistant HIV strains that reseed the body. Effective treatment of HIV must include controlling HAND and clearing the virus from the brain. More detailed prospective studies, encompassing broader possible mechanisms of action, will be needed to clearly define the risk and benefit of our therapeutic regimens. Meanwhile, it remains remarkable that most cART regimens successfully control the virus when taken faithfully. It would be inappropriate for fear of toxicity to become an excuse for noncompliance with the successful HIV therapies available.

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D. Clifford has served/serves on scientific advisory boards for Amgen, Biogen Idec/Quintiles, BMS, Genentech, Genzyme, Pfizer, Millennium, and Sanofi; received a speaker honorarium from Sun Pharmaceuticals; serves as a consultant for Millennium, Genzyme, Biogen Idec, IAS-USA, CMSC/ACTRIMS, ECTRIMS, Drinker, Buddle, Reath, and Cytheris; receives research support from Lilly, Roche, the NIH (NIMH, NIND), and the Alzheimer Association; and has provided consultation in medicolegal cases. J. Berger has served on scientific advisory boards for Millenium/Takeda and Amgen; receives honoraria from Genzyme; and has served as a consultant to Millennium/Takeda, Amgen, Genzyme, Eisai, and Novartis. Go to Neurology.org for full disclosures.

**REFERENCES**

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