Reply to Haddow et al

To the Editor—Haddow and colleagues [1] have expressed 2 concerns regarding interpretation of the longitudinal CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study of neurocognitive (NC) outcomes in 436 human immunodeficiency virus (HIV)-infected patients—namely, that "NC change is common in HIV infection and appears to be driven by a complex set of risk factors involving HIV disease, its treatment, and comorbid conditions" [2].

Haddow et al are correct that the probability of a person experiencing NC decline at any point across multiple visits is somewhat greater than the 5% defined by the published norms for NC change [3] at a single follow-up. However, these authors' use of standard binomial probability estimates to arrive at an overall chance-based "decliner" rate of 20.4% over 6 follow-up visits is inaccurate (excessive), because of the acknowledged assumption that all visits for any individual patient are independent. In fact, in the survival analysis used in our article, "decline" was an absorbing state. Visits were not independent: Once a patient was first classified as a "decliner," the endpoint of interest in our study, that person had no opportunities to (or chance-based risk for) decline at any future visit. Also, of the 99 decliners in our study, 62.3% had declined by their second follow-up visit, and 85% had declined by their third. In the published study that provided norms for NC change in controls [3], the overall prevalence of "decliner" status for participants with ≥4 visits (required for the CHARTER study) was 12.3%. The 22.7% rate of decliners in CHARTER is almost double that in the normative study, a consequential difference that is not easily attributable to chance.

Importantly, if the 99 participants in the CHARTER longitudinal study had evidenced NC declines on the basis of chance alone, one would not expect the large number of observed, statistically significant associations with disease and treatment variables.

The second issue raised by Haddow et al was our failure to consider that the observed association between NC decline and antiretroviral therapy (ART) status could be bidirectional: being off ART (as a time-dependent predictor) could increase risk for NC decline, or NC decline and impairment could cause disengagement from care and nonadherence to ART. Regarding the term "risk," this terminology is used in an associational rather than causative sense in the scientific literature in a variety of settings. For example, when an epidemiologist says that "being male increases the risk of subsequent incarceration for criminal activity," it does not mean that "maleness" causes criminality, nor does one question the validity of the original statement.

Although we have acknowledged that causal associations cannot be established in an observational study such as this, we would note that our "off ART" variable was not an adherence indicator but, instead, reflected the fact that that these participants were not being prescribed ART at the times of their NC declines. While not impossible, it seems unlikely that patients' NC impairment, when detected clinically, led medical providers to avoid prescribing ART.

We appreciate the opportunity to address the concerns raised by Haddow et al [1], but maintain that the conclusion quoted above is warranted.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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