HAD and the need for new trial design methodology

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The study by Schifitto et al. in this issue raises important points in relation to AIDS dementia complex – now known as HIV associated dementia (HAD) – and its less severe forms of minor and asymptomatic neurocognitive impairment. These new terms are the result of a consensus working group convened under the auspices of the National Institutes of Mental Health to reappraise HAD in the HAART era. Schifitto et al. conducted a randomized double-blind placebo controlled trial of adding memantine, a weak N-methyl D-aspartate receptor antagonist, to stable background HAART in HAD patients. Unfortunately, there was no benefit at week 16 although at week 20, in the washout period off the drug, there was some evidence of benefit. In general, the Schifitto et al. paper raises issues related to the importance of HAD itself in the context of HAART and methodological issues associated with clinical trials of novel agents in HAD. This journal is to be lauded for its decision to publish the study despite its negative results.

It is commonly held in the HIV treating community that HAD is no longer important in the era of HAART. The halving of the incidence of HAD and evidence of neuropsychological improvement with the introduction of HAART [1,2] have supported this optimistic view. However, the disorder still occurs and remains functionally compromising to the patient. The prevalence of HAD has increased with HAART [3], while the prevalence of neuropsychological impairment without HAD has not changed and remains common [4]. Furthermore, in clinical practice only approximately 60% of patients with HAD will respond to HAART [5]. Even mild cognitive impairment impacts on the ability to perform activities of daily living and work [6]. Such impairment is frequently missed because clinicians do not specifically assess it and because patients are reluctant to admit there is a problem. Moreover, there is evidence that the disorder is changing, perhaps because of the presence of new underappreciated confounding conditions [7,8].

Thus HAD and its milder forms are still significant despite the introduction of HAART. Clinical trials of novel agents for the disorder must continue. But conducting such trials in the context of HAART raises problems as illustrated by the Schifitto et al. study and by abacavir in the AIDS dementia complex trial [9,10]. The latter was a large multicentre randomized placebo controlled study of the efficacy of the addition of abacavir to stable background antiretroviral therapy in HAD. Both had negative results in the sense that the addition of the novel agent did not lead to improvement. It is fortunate that at least the Schifitto et al. study has been published despite the negative results.

Both studies have brought to light two factors that are now critical to establish at the beginning of any future clinical trial of any novel agent for HAD. The first is that of the activity of HAD, that is to say is the disorder still active or do the deficits reflect old ‘burnt out’ inactive disease? This was first appreciated in the abacavir AIDS dementia complex study [9,10] and later in the NEAD cohort [11]. Its significance should be clear: if the majority of patients in a proposed trial have inactive disease then the efficacy of a novel agent cannot be assessed. Indeed, in such a case if disease inactivity goes unrecognized a potentially efficacious novel agent will be needlessly discarded. The
second is a derivative of the first, namely what is the nature of disease activity? Is it deteriorating, improving, or stable? Deteriorating disease is self-explanatory but can the disorder still be improving even months after commencement of HAART? It appears to be so. Indeed, improvement can extend over many months—at least five months in the abacavir study. Stable disease means that compensatory mechanisms are able to hold the activity in check so that there is no clinical change [12]. These concepts have largely been captured in the revised criteria for HAD which are soon to be published.

The Schifitto et al. study did not address either of these issues. But this should not be seen as a criticism as the study was designed and implemented before these factors were evident. Rather it should serve to emphasize the importance of these newly appreciated factors. Indeed, the negative results may have been related to one or both of these factors. To their credit the authors tried to use magnetic resonance spectroscopy as a surrogate tool for efficacy. This highlights the need for such new biomarkers.

Hence future clinical trials should ensure that HAD is active and not improving. While it is theoretically true that issues of disease activity may be circumvented by recruiting large numbers of patients into trials, practically this is unlikely to be a fruitful strategy given previous HAD trial difficulties. Reliable markers of active HAD in HAART treated patients are not currently available. Presently, activity is implied if there is detectable HIV RNA in the cerebrospinal fluid along with elevated concentrations of immune activation markers. However, this may not be correct in HAART treated patients [12,13]. Ensuring that the patients are not improving is also difficult but ideally patients should have been on their optimal HAART regimen without alteration for at least 5 months prior to entry into the clinical trial.

These difficulties will of course be surmounted when more accurate biomarkers have been developed. In this regard, emerging data on the cerebrospinal fluid concentrations of the neuronal markers neurofilament and perhaps t-tau are promising [14–16]. They potentially will allow detection of activity at trial screening and perhaps stability—if they are unchanged with repeat assessment at a second time point several weeks later. Imaging techniques such as 1H-MRS also hold promise but at present these can only detect disease activity by comparative data from two time points: a reduction in the neuronal marker N-acetyl aspartate can either signify neuronal ‘drop out’ (possibly inactive disease) or ‘sick’ neurons (possibly active disease) Nonetheless, clinical trials for novel agents cannot be stalled while such biomarkers are developed. They can and must proceed albeit with new design methodology.

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**References**


