*Older Age and HIV-Associated Neurocognitive Disorder (HAND)

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Screening for cognitive impairment is important. A two-tiered approach assessing symptoms with follow-up testing is a reasonable paradigm to follow for busy practices, although screening of all patients is recommended whenever possible. Cognitive disorder remains a frequent problem despite effective antiretroviral therapy. Up to 50% of HIV patients will perform in an impaired range on neuropsychological testing batteries; however, only about a quarter of these patients will endorse symptoms and less than half of those are estimated to have HIV-associated dementia (HAD) (Heaton et al. 2010). Patients at particular risk are those with previous CNS disease, a low nadir of the CD4 cell count, detectable plasma viral load, and a low current CD4 cell count (Heaton et al. 2010; Cysique et al. 2010). Co-existing morbidities contribute to poor neuropsychological performance. These include diabetes, hypertension, HCV co-infection, medication toxicities, and psychoactive substance use disorders (Goodkin 2009). Among older HIV infected individuals, one must also consider concurrent neurodegenerative disorders, principally Alzheimer's disease, and the cognitive impact of cerebrovascular disease (Valcour et al. 2004). The demonstrated disease heterogeneity and the relatively high frequency of asymptomatic cognitive impairment must inform screening approaches for them to be effective, and the selection of optimal screening instruments remains an issue in the field to date (Goodkin et al. in press).

The diagnosis of HAD for research studies now requires: (a) acquired moderate-to- severe neuropsychological testing impairment, documented by a score at least 2 SDs below demographically corrected normative means in at least 2 different cognitive domains, (b) moderate-to-severe difficulty in functional status in activities of daily living due specifically to this impairment, (c) a duration of at least one month, (d) absence of delirium and (e) absence of confounding conditions capable of otherwise explaining the impairment (Antinori et al. 2007). Mild Neurocognitive Disorder (MND) is defined by the following features: (a) an acquired mild level of neuropsychological testing impairment documented by a score of at least 1 SD below demographically-corrected norms on tests in at least 2 different cognitive domains, (b) the impairment interferes at a mild level with functional status, and (c) through (e) -- as above for HAD. Finally, the impairment cannot occur solely as part of a delirium and, as in the American Academy of Neurology-defined criteria, the diagnosis is possible only if the impairment cannot be explained by comorbid conditions. Asymptomatic Neurocognitive Impairment (ANI) requires the same level of cognitive impairment as MND, but without any functional status deficit. The differential diagnosis of these

diagnostic entities cannot be determined by screening instruments but require more in-depth neuropsychological testing. Brief clinical screening techniques can and should be employed before more formal and comprehensive NP testing is sought. Overall, for HAD, it appears that there is consistent evidence for aging as a risk factor (Janssen et al. 1992; McArthur et al. 1993; Chiesi et al. 1996; Valcour et al. 2004). This association of aging with HAND appears to be dependent upon the level of severity of HAND – greatest with HAD, less prominent with MND (formerly minor cognitive-motor disorder) (Goodkin et al. 2001; Larussa et al. 2006; Wilkie et al. 2003; Cherner et al. 2004) and least consistent with overall cognitive impairment (Hardy et al. 1999; Hinkin et al. 2001; Wilkie et al. 2003; Cherner et al. 2004).

Cognitive Screening and HAND

The high frequency of impairment and the knowledge that poor neuropsychological testing performance correlates to impaired performance on functional status tests and adherence to antiretroviral medications confirms cognitive screening to be clinically important. Quick and simple screening instruments exist for the most severe form of HAND (which is HAD) and Alzheimer's disease (AD) and vascular cognitive impairment. However, the overlap in content of these tests is necessarily limited given the differing presentations, particularly for AD (cortical impairment) versus HAND (sub-cortical impairment). Thus, optimal screening strategies for older HIV infected adults need to cover broader areas than individual screens allow. Unfortunately, The tests designed to identify HAD perform considerably less well for milder conditions (MND and ANI)

and cannot be recommended for this purpose. and may need to be supplemented by other tests (such as the Trail Making Test) for this purpose (Chalermchai et al., 2013; ,Goodkin et al., in press).

Regarding the available screening tests, the Montreal Cognitive Assessment (MOCA) Test might be suggested to best match the requirements for a screening instrument in an older HIV infected population. This is because it taps areas of cognitive performance involving executive functioning and other higher cognitive abilities thought to be most vulnerable in milder HIV-associated impairment, while remaining broad enough to detect diseases such as AD. However, validation studies are lacking, and early findings suggest that this test may have sizable limitations; some of which may be improved by augmentation with other tests, particularly those of information processing speed. The HIV Dementia Scale (HDS) is a well established test in HIV infection with a psychometrically sound introductory validation study from the pre-HAART era; however most studies in the current era demonstrate that it fails to identify all but the more severe forms of impairment. The International HIV Dementia Scale (IHDS) is useful within the USA for patients from other cultures, of which Hispanics would be the most numerous, but maintains similar limitations as does the HDS (Sacktor et al. 2005) (Bottiggi et al. 2007; Richardson et al. 2005; Smith et al. 2003; Morgan et al. 2008; Davis et al. 2002). Since the Mini Mental State Examination does not tap domains that are typically impaired in HAND and since there are data demonstrating its lack of efficacy, it should not be used for screening in this setting.

Currently, consensus recommendations on the treatment of HAND are concordant in a focus on the use of a stable, effective ART regimen. Beyond

this, the American Psychiatric Association Practice Guidelines for HIV/AIDS (Folstein et al. 2006; OARAC DHHS Panel Working Group of the Office of AIDS Research 2011) (McDaniel et al. 2000; Forstein et al. 2006) and the Guide for HIV/AIDS Clinical Care (DHHS, 2011) recommend the use of CNS-penetrating antiretroviral therapy regimens and the psychostimulants. However, it should be noted that there is considerable variability in how this approach is applied since there are no large-scale intervention trials that have consistently demonstrated efficacy for these recommendations and since a randomized controlled study designed to investigate a CNS-penetration effectiveness intensification approach failed to show benefit and actually identified worse performance in the CNS intensified (Marra et al. 2009). Yet, these results should be related to the limitations of using a measure of penetration rather than achieving the IC95 for that specific ARV in the CSF and to the limitations of the CSF a window into the processes occurring in brain tissue.

These approaches need to be considered in the context of medication side-effect, antiretroviral adherence and the risk of exposure to new medications that could alter resistance profiles and long-term HIV outcomes. More research is needed. An exclusionary work-up for non-HIV-associated treatable causes of neurocognitive disorder, such as thyroid disease, syphilis, and B12 deficiency as well as conditions specific to HIV infection is important. Patients with presentations suggestive of CNS opportunistic infection or tumor, such as focal neurological findings, require careful evaluation, as do cases with more rapid neurological progression. Use of medications with higher CNS penetration effectiveness have clearly demonstrated utility in these focused situations, particularly in rare cases of CNS

escape where virus is identified in CSF despite suppression in plasma. In addition, the psychostimulants have some evidence for efficacy in smaller studies (Fernandez et al. 1988; Van Dyck et al. 1997; Hinkin et al. 2001) Other therapies that may have promise for research studies include the use of anti-inflammatory agents, neurotrophic factors, nutritional supplements, and antioxidants, although a recent trial using minocycline as a novel antioxidant did not demonstrate efficacy. More research is clearly needed. Based on general recommendations applied to HIV-negative populations, exercise [both physical (Fazeli, et al., 2014) and mental], remaining socially engaged, monitoring for depression, and monitoring for cerebrovascular risk factors are relatively safe and possibly effective adjunctive strategies.

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