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With combination antiretroviral therapy (cART), human immunodeficiency virus (HIV) associated morbidity and mortality has decreased remarkably. Although life expectancy has increased, the frequently reported milder forms of HIV-associated cognitive impairment remain a concern and its pathogenesis is poorly understood. We have examined a cohort of middle-aged and older HIV-infected patients with sustained suppressed viremia on cART and found that HIV-associated cognitive impairment was prevalent in 17%. This corresponds with the lower end of the spectrum of HIV-associated cognitive impairment prevalence previously reported in the literature. The observed subtle cognitive deficits included decreased attention, executive function and information processing speed. A diverse set of risk factors for HIV-associated cognitive impairment was identified within this cohort, including factors relating to disease and treatment history, risk for vascular/metabolic disease and life style. In addition, we found that HIV-infected patients have an increased burden of white matter lesions of presumed vascular origin, a diffuse pattern of microstructural white matter abnormalities, and reduced grey matter cerebral blood flow. Such macro-structural, microstructural and hemodynamic brain alterations were associated with measures of past immune deficiency and vascular/metabolic risk factors. Taken together, these findings suggest that the brain alterations found may represent irreversible neuronal and vascular damage that has occurred during previous periods of immune deficiency, and the current vascular/metabolic risk factors, as well as physiological aging, possibly continuing to contribute to further neuronal and vascular damage. White matter lesions of presumed vascular origin are found to be the best correlate of HIV-associated cognitive impairment.