Cocaine use is associated with high-risk sexual practices that accelerate the spread of human immunodeficiency virus (HIV) infection. Substantial literature has demonstrated that active substance use leads to impairment on assessments of executive function. Inhibitory control—the ability to withhold a thought, feeling, or action—is a central construct involved in the minimization of risk-taking behaviors and is frequently blunted both by active substance use and by neurocognitive impairment. While the effects of HIV on the brain are largely progressive, performance in many of the cognitive domains affected by active substance use normalize following drug abstinence. It is unknown whether this same abstinence-related neurocognitive recovery trajectory persists in former users with comorbid HIV. Converging findings from the three studies composing the current work indicate that HIV+ individuals with a history of cocaine dependence (CD) experience persistent deficits in both inhibitory control capabilities and their underlying neural substrates despite current cocaine-abstinence. These deficits exceed those observed in age-matched HIV+ individuals with no history of substance dependence, as well as age-matched HIV- individuals in recovery from CD. In Chapter 2, I used diffusion tensor imaging (DTI) to understand the effect of combined HIV+ serostatus and former cocaine dependence on cerebral white matter integrity. I observed widespread decreases in diffusion measures across major white-matter tracts in the brain relative to healthy control participants, indicating an extensive neuropathological effect of HIV and former CD on white matter. In Chapters 3 and 4, I investigate the neural substrates of inhibitory control using electroencephalography (EEG) (Chapter 3) and functional magnetic resonance imaging (fMRI) (Chapter 4) as individuals perform a “Go-NoGo” response inhibition task requiring participants to exercise inhibitory control in the presence of drug and non-drug cues. Results from Chapters 3 and 4 indicate complex and interactive alterations in neural activation during response inhibition and highlight the importance of examining the neurocognitive effects of co-morbid conditions. Taken together, these results suggest that abstinence-related recovery of inhibitory control is attenuated in patients with comorbid HIV, suggesting that further or more targeted interventions may be needed to facilitate positive health outcomes in this population.