Introduction: Epidemiological studies on drug abusers with AIDS link abuse of cocaine, even more than other drugs, to increased incidence of HIV sero prevalence and progression to AIDS. In the era of highly active antiretroviral therapy (HAART), although the incidence of HIV-associated dementia (HAD) has declined, HIV-associated neurocognitive disorders (HAND) remain a significant health problem. Literature Review: The neuroinflammation associated with HAND appears to be exacerbated by drugs of abuse, as demonstrated by brain autopsy studies revealing a higher prevalence of HIV encephalitis (microglia activation, presence of multinucleated giant cells, and blood–brain barrier) disruption in drug-abusing HIV-positive individuals in comparison with nonabusing HIV-positive controls. These findings suggest that drug abuse exerts an additive (if not synergistic) effect with HIV within the CNS. Additional studies on the molecular mechanisms underlying the interaction between cocaine and gp120 have demonstrated that exposure of rat primary neurons to both cocaine and gp120 resulted in increased cell toxicity compared to cells treated with either factor alone. The combinatorial toxicity of cocaine and gp120 was accompanied by an increase in both caspase-3 activity and expression of the proapoptotic protein Bax. Furthermore, increased neurotoxicity in the presence of both the agents was associated with a concomitant increase in the production of intracellular reactive oxygen species and loss of mitochondrial membrane potential. Conclusion: Thus, drugs of abuse, particularly cocaine, are strongly associated with enhanced brain injury in HIV positive individuals, which is expressed as enhanced risk for HAND and other neurologic complications.