Introduction: Animal models for HIV infection have proved very useful for understanding of HIV associated CNS disorders, such as depression. These models are mainly transgenic and humanized mice. Literature Review: People living with HIV-1 (PLHIV) exhibit a 2-fold increase in prevalence of depression compared with HIV-uninfected individuals. The contributions of immuno-inflammatory, monoaminergic, neurodegenerative and neurotrophic pathways to HIV-associated depression have recently been reviewed. A number of strategies for studying the relationship of HIV to depression is possible with animal models. They could be used to identify potential biomarkers for HIV depression in CSF and serum, identify the magnitude of the influence of depression and related psychosocial factors have in the course of HIV infection through altering biochemical and immune pathways. The animal models can also be used to determine if and how HIV infection creates a propensity for depression. The predisposition, effects on hippocampus and learning behavior and molecular markers for neuroplasticity may be evaluated in humanized mouse model for HIV. One more goal for such model may be test and compares therapeutic responses of conventional antidepressants and potential HIV depression-specific agents, such as antibodies anti-INF-8, or anti-gp120. Conclusion: An optimal model for HIV depression may be a challenge because the virus-specific mechanisms, the neuroinflammatory and neurodegenerative processes that need to be added into the model. However, translational research may represent a great opportunity of moving forward in the attempt to give a better quality of life for PLHIV.