Human immunodeficiency virus (HIV)-infected patients are at an increased risk of co-infection with human papilloma virus (HPV), and subsequent malignancies such as oral cancer. To determine the role of HIV-associated immune suppression on HPV persistence and pathogenesis, we developed a mathematical model of HIV/HPV co-infection and used it to investigate the mechanisms underlying the modulation of HPV infection and oral cancer by HIV. Our model captures known immunological and molecular features such as impaired HPV-specific effector T helper 1 (Th1) cell responses, and enhanced HPV infection due to HIV. We used the model to determine HPV prognosis in the presence of HIV infection, and identified conditions under which HIV infection alters HPV persistence in the oral mucosal system. The model predicts that conditions leading to HPV persistence during HIV/HPV co-infection are the permissive immune environment created by HIV and molecular interactions between the two viruses. The model also determines when HPV infection continues to persist in the short run in a co-infected patient undergoing antiretroviral therapy. Lastly, the model predicts that under efficacious antiretroviral treatment HPV infections will decrease in the long run due to the restoration of CD4+ T cell levels. (Received September 18, 2016)