Lentiviruses like HIV need to evade intrinsic host restrictions that prevent their replication. The collection of restriction factors produced in cells constitutes the innate immune response to viruses. Lentiviruses encode accessory proteins that serve to counteract specific restriction factors. SAMHD1 is one such restriction factor that restricts lentivirus replication in myeloid cells and resting T cells. Lentiviruses such as SIV encode the accessory protein Vpx which induces the degradation of SAMHD1. The talk will discuss the mechanisms by which SAMHD1 restricts lentivirus replication and the mechanism by which Vpx counteracts SAMHD1. The studies have led to a new approach to the development of a therapeutic vaccine against HIV.