HIV-1 (no Vpx) and SIVsm/HIV-2 (with Vpx) can infect human myeloid-lineage cells differently. In the case of HIV-1, reverse transcription leads to restrictive infection due to SAMHD1. In contrast, SIVsm/HIV-2 with Vpx enables permissive infection by promoting proteasomal degradation of SAMHD1 through the ubiquitin-proteasome pathway.