

POSTER 34**CELL-CYCLE DEPENDENT HIV-1 KILLING IS MEDIATED THROUGH THE VIRAL PROTEASE**

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HIV-1 infection in vivo is characterized by the profound, cytopathic depletion of CD4+ helper T cells. Different mechanisms have been proposed to underlie HIV-1 cell killing. High multiplicity HIV-1 infection is thought to kill cells via toxic levels of unintegrated vDNA or lethal integration events. Killing by low multiplicity HIV-1 infection is thought to require the accumulation of toxic gene products. Using an HIV-1 vector that lacks several cytotoxic genes (*vif*, *vpr*, *env*) and can be stably transduced, we observed killing of human cells at infection frequencies as low as one hit per cell. Interestingly, slowly dividing cells were less rapidly killed after infection. Consistent with this observation, cells growth arrested with anti-proliferative drugs were not killed by HIV-1 vector infection. However removal of drugs and relief of the cell-cycle block rapidly led to death in the infected cells. HIV-1 vector expression was found to be required for the killing. A comparison of cells stably or acutely infected with the HIV-1 vector revealed higher viral protein expression during acute infection and more efficient proteolysis of Gag. Treatment of cells with HIV-1 PR inhibitors (PIs) alleviated killing during acute infection but did not reduce overall viral protein expression. PIs also protected initially growth-arrested HIV-1 vector infected cells after relief of the cell-cycle block. By contrast, HIV-1 vectors encoding drug-resistant PR killed dividing cells in the presence of PIs. Collectively, our data indicate that HIV-1 PR expressed from a single provirus is a cytotoxic hazard to proliferating cells.