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**SPL7013, A DENDRIMER-BASED MICROBICIDE, DEMONSTRATES A HIGH
GENETIC BARRIER FOR THE DEVELOPMENT OF
DRUG-RESISTANT HIV-1 *IN VITRO***

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SPL7013, the active component of VivaGel[®], is a dendrimer-based microbicide with broad-spectrum antiviral activity which is currently undergoing clinical evaluation for the prevention of HIV and HSV-2. The aim of this study was to select HIV-1 with reduced susceptibility to SPL7013 to determine the genetic barrier to resistance and to validate gp120 as the drug target. HIV-1 was passaged in the presence of increasing concentrations of SPL7013. Following 44 passages, virus was selected (SPL7013p44) that displayed 2.8-fold resistance to SPL7013 compared to wild-type (WT) virus passaged a similar number of times in the absence of drug. Parallel experiments using the same strategy selected HIV with >500-fold resistance to the NNRTI, nevirapine after 13 passages. Nucleotide sequence analysis of SPL7013p44 revealed the presence of two mutations in gp120 that were not present in WT virus passaged in the absence of drug, in the V3 region and the CD4 binding site respectively. Introduction of both mutations into WT NL4.3 recapitulated the 2-3 fold decrease in SPL7013 susceptibility observed with SPL7013p44 compared to WT. These data suggest that the gp120 CD4 binding site and V3 region, which mediates binding to the CXCR4 and CCR5 chemokine co-receptors, are likely targets of SPL7013. SPL7013p44 also displayed low-level cross-resistance to dextran sulphate and the fusion inhibitor T20, but was not cross-resistant to the CXCR4 antagonist AMD3100. The relative difficulty in selecting high-level resistance to SPL7013 compared to nevirapine demonstrates that there is a higher genetic barrier for the generation of SPL7013 resistant HIV *in vitro* and suggests that it may be difficult to select for HIV with high level resistance to SPL7013 *in vivo*.