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Entry Inhibitors Are Less Effective at Preventing Cell-Associated HIV-2 Infection than HIV-1

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Abstract : Cell-to-cell transmission plays a critical role in the spread of HIV-1 infection in vitro and in vivo. Inhibition of HIV-1 cell-associated infection by antiretroviral drugs and neutralizing antibodies (NAbs) is more difficult compared to cell-free infection. Limited data exists on cell-associated infection by HIV-2 and its inhibition. In this work, we determined the ability of entry inhibitors to inhibit HIV-1 and HIV-2 cell-to cell fusion as a proxy to cell-associated infection. We developed a method in which Hela-CD4-cells are first transfected with a Tat expressing plasmid (pcDNA3.1+/Tat101) and infected with recombinant vaccinia viruses expressing either the HIV-1 (vPE16: from isolate HTLV-IIIB, clone BH8, X4 tropism) or HIV-2 (vSC50: from HIV-2SBL/ISY, R5 and X4 tropism) envelope glycoproteins (M.O.I.=1 PFU/cell).These cells are added to TZM-bl cells. When cell-to-cell fusion (syncytia) occurs the Tat protein diffuses to the TZM-bl cells activating the expression of a reporter gene (luciferase). We tested several entry inhibitors including the fusion inhibitors T1249, T20 and P3, the CCR5 antagonists MVC and TAK-779, the CXCR4 antagonist AMD3100 and several HIV-2 neutralizing antibodies (Nabs). All compounds inhibited HIV-1 and HIV-2 cell fusion albeit to different levels. Maximum percentage of HIV-2 inhibition (MPI) was higher for fusion inhibitors (T1249- 99.8%; P3- 95%, T20-90%) followed by co-receptor antagonists (MVC- 63%; TAK-779- 55%; AMD3100- 45%). NAbs from HIV-2 infected patients did not prevent cell fusion up to the tested concentration of 4µg/ml. As for HIV-1, MPI reached 100% with TAK-779 and T1249. For the other antivirals, MPIs were: P3-79%; T20-75%; AMD3100-61%; MVC-65%.These results are consistent with published data. Maraviroc had the lowest IC50 both for HIV-2 and HIV-1 (IC50 HIV-2= 0.06 µM; HIV-1=0.0076µM). Highest IC50 were observed with T20 for HIV-2 (3.86µM) and with TAK-779 for HIV-1 (12.64µM). Overall, our results show that entry inhibitors in clinical use are less effective at preventing Env mediated cell-to-cell-fusion in HIV-2 than in HIV-1 which suggests that cell-associated HIV-2 infection will be more difficult to inhibit compared to HIV-1. The method described here will be useful to screen for new HIV entry inhibitors.

Keywords : cell-to-cell fusion, entry inhibitors, HIV, NAbs, vaccinia virus
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