HIV-1 infection of female primary genital epithelial cells after pseudotyping with HTLV-1:

Potential driver of sexual transmission of HIV-1

Abstract #: 214
CROI 2015

Funding support: NIH, grant No. 8DP1HD075625 to JEKH

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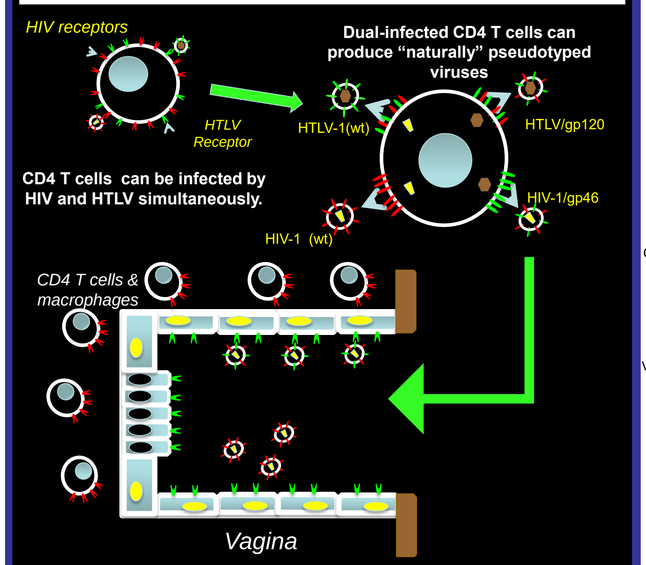
Background: Young females are at high risk of HIV infection and constitute 75% of infected individuals in some sub-Saharan African countries. Some regions with high prevalence of HIV-1 are often also highly endemic for HTLV. HIV/HTLV co-infection in Africa, Latin America and the Caribbean basin is increasing and has emerged as a global health problem. In our recently published study we demonstrated that HIV-1 is able to acquire envelope glycoproteins of a gammaretrovirus during co-infection, in a process we called "natural pseudotyping", and expand its cellular tropism enabling it to infect primary female genital epithelial cells. Natural pseudotyping may dramatically increase risk of female HIV-1 infection during sexual intercourse and therefore could be a biological factor contributing to the devastating spread of HIV in young females in Africa and other regions of the world.

Results: Progeny virus from HTLV-1/HIV-1 co-infected T cells was capable of infecting primary vaginal and cervical epithelial cells via both cell-associated and free virus mediated infection. No HIV-1 infection was observed from epithelial cells exposed to progeny virus from T cells infected with HIV-1 alone. Infection of primary genital cells was significantly reduced by antisera against the HTLV-1 glycoprotein, indicating that HIV-1 infection was mediated by the HTLV glycoprotein. Active HIV-1 replication infection in primary genital epithelial cells was confirmed by using protease inhibitors. However, HIV-1 reverse transcriptase inhibitors AZT or Rilpivirine only partially blocked HIV-1 infection in primary genital epithelial cells. Further analysis indicated that AZT or Rilpivirine treatment blocked HIV-1 infection in cells infected with HIV-1 alone but not in cells infected by both HIV-1 and HTLV-1.

Conclusions:

Co-infection with HIV-1 and HTLV-1 produces naturally pseudotyped HIV-1 capable of directly infecting primary female lower genital epithelial cells; HIV-1 is resistant to HIV RT inhibitors when cells are co-infected with HTLV-1.

Natural pseudotyping hypothesis predicts that HIV can bypass mechanical barrier by infecting mucosal epithelial cells



Pseudotyping expands HIV-1 tropism and enables virus to directly infect genital mucosal epithelial cell

Figure 1: HIV-1/HTLV-1 co-replicated in CD4+T cell lines

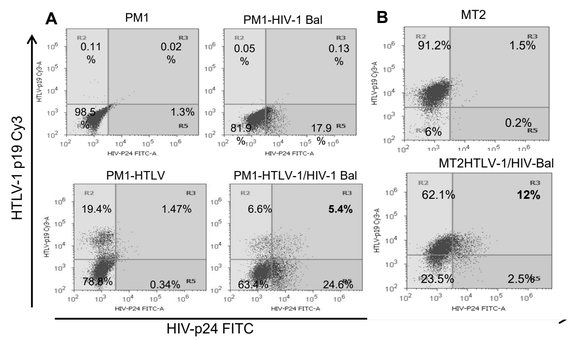


Figure 1. A. PM1 cells were exposed to HTLV-1 by co-cultivation with mitomycin C treated HTLV-1 chronic infected cell line MT2. Two days later cells were superinfected with HIV-1 Bal. **B**. MT2 cells were infected with HIV-1 Bal. HIV-1 and HTLV-1 infection in PM1 and MT2 cells were determined by dual immunofluorescence staining with anti-HIV-1p24 and anti-HTLV-1 p19 antibodies followed by flow cytometry analysis.

Figure 2. Progeny virus from HTLV-1/HIV-1 co-infected T cells is able to infect primary female lower genital epithelial cells

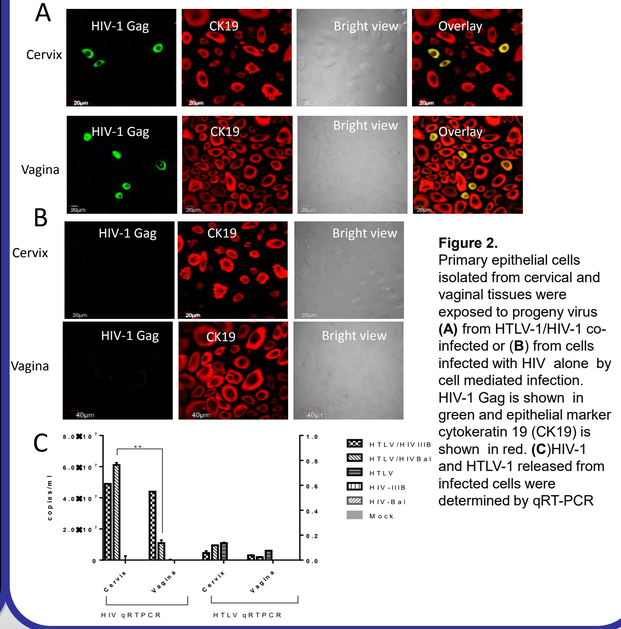


Figure 2. Primary epithelial cells isolated from cervical and vaginal tissues were exposed to progeny virus **(A)** from HTLV-1/HIV-1 co-infected or (**B**) from cells infected with HIV alone by cell mediated infection. HIV-1 Gag is shown in green and epithelial marker cytokeratin 19 (CK19) is shown in red. (**C**)HIV-1 and HTLV-1 released from infected cells were determined by qRT-PCR

Figure 3. Active HIV-1 replication in primary genital epithelial cells was inhibited with protease inhibitors but not with reverse transcriptase inhibitors

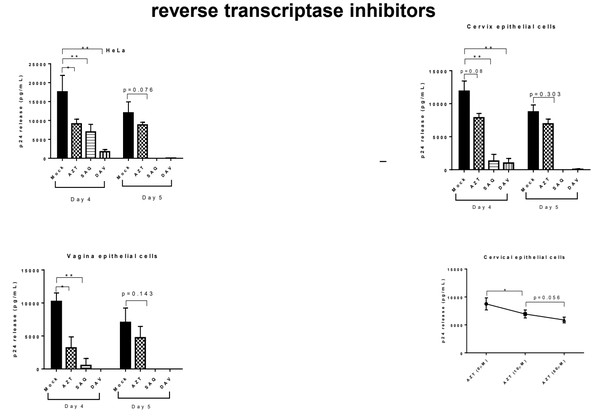


Figure 3. Epithelial cells were exposed to progeny virus from HIV-1/HTLV-1 co-infected T cells in the presence of the indicated drug. Viral release from epithelial cells was quantified by p24 ELISA. AZT, Zidovudine; SAQ, saquinavir and DAV, darunavir

Figure 4. HIV-1 is resistant to RT inhibitors in HIV-1/HTLV-1 dually infected genital mucosal epithelial cells

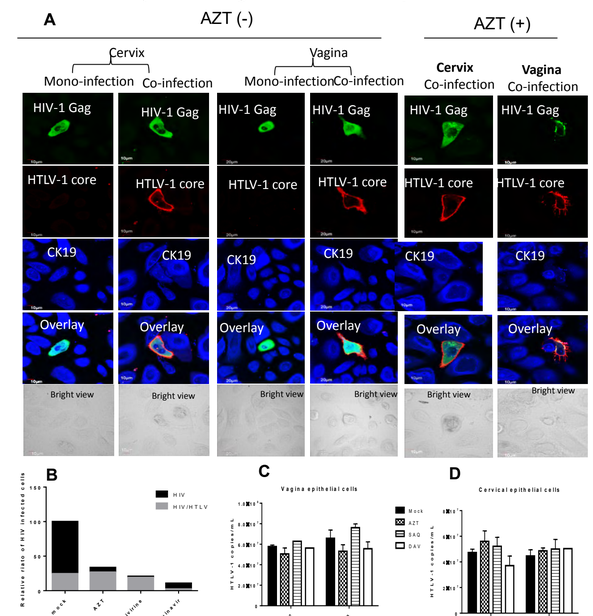


Figure 4. (A) Representative images of HIV-1 mono-infected or HIV-1/HTLV co-infected epithelial cells after exposed to progeny virus from dually infected T cells in the absence or presence of AZT. (**B**) Cervical epithelial cells were exposed to progeny virus from HTLV/HIV co-infected T cells. The relative ratio of HIV mono-infected and HIV/HTLV co-infected epithelial cells treated with the indicated inhibitors are shown. The infection events were determined by flow cytometry. **(C,D)** HIV-1 protease inhibitors and reverse transcriptase inhibitors don't affect HTLV-1 infection in epithelial cells

Figure 5. HIV-1 infection of primary genital epithelial cells was significantly reduced by antisera against HTLV-1 glycoprotein

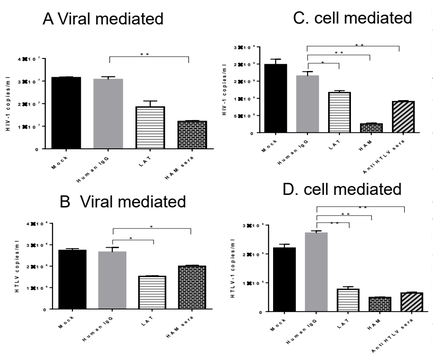


Figure 5.Cervical epithelial cells were exposed to progeny virus from HTLV-1/HIV-1 co-infected T cells in the presence of indicated antibodies (A,C, free virus infection; B,D epithelial cells exposed to HTLV-1/HIV-1 co-infected T cells). HIV-1 (A,B) and HTLV-1 (C,D) viral release from infected epithelial cells were determined by qRT-PCR. LAT, a rat monoclonal antibody (mAb) against HTLV-1 envelope gp46; HAM human polyclonal IgG purified from sera of HTLV-1-associated myelopathy (HAM) patients