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Proof-of-concept of new carbosilane dendrimers with dual-prevention against HIV-1/HSV-2 co-infection as topical microbicided

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A safe and effective prophylactic vaccine for HSV-2/HIV-1 remains elusive. The vulnerability of women to the HSV-2/HIV-1 co-infection due to cultural/social aspects does not provide women power to negotiate the use of a condom, discuss fidelity with their partners or leave risky relationships. The development of new prevention strategies aimed at halting the spread of HSV-2/HIV-1 in regions such as sub-Saharan Africa are clearly needed. One of these strategies includes the development of safe, effective, and low-priced topical microbicides that should prevent the HSV-2/HIV-1 entry and maintain the integrity of the vaginal epithelial barrier. The field of nanotechnology, specifically dendrimers, plays an important role in addressing this challenge. The generations of polyanionic carbosilane dendrimers with silicon atom core, (G1-S4 generation zero, 4 sulphate end-groups) and G2-S16 (1st-generation, 16 sulfonate end-groups) have showed a potent and broad-spectrum anti-HIV-1/HSV-2 activity *in vitro* and *in vivo*. Thus, when applied intravaginally to h-BLT mice 3% G2-S16 gel protected against the R5-HIV-1_{JR-CSF} vaginal transmission in 84%. Topical 3% G2-S16 and 3% G1-S4 proved capable to prevent the HSV-2 infection vaginally at 100% and 90% in female BALB/c mice, respectively. No irritation or inflammation processes were detected in female mice after seven consecutive doses vaginally. G2-S16 and G1-S4 prevented the rectal HSV-2 transmission over 90% in BALB/c mice. Our results suggest that G1-S4 and G2-S16 exert anti-HSV-2/HIV-1 activity at early stages of the viral replication inactivating the virus, blocking the adsorption, and the HSV-2/HIV-1 entry. We showed that dendrimers are active against semen-exposed HIV-1 particles, which their infectivity has been enhanced by the presence of amyloid fibrils of semen.

Our study represents the first demonstration indicating that HIV-1 vaginally infects humanized BLT mice and that transmission of the virus can be efficiently blocked by

vaginally applied G2-S16. Our results indicate that polyanionic carbosilane dendrimers have an excellent potential to prevent the vaginal transmission of HSV-2/HIV-1. These results provide strong experimental evidence in the development of dendrimers based topical microbicides to prevent vaginal the HSV-2/HIV-1 transmission in humans.

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