Mobility of Transmitted/Founder HIV-1 Variants in Human Cervicovaginal Mucus

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BACKGROUND

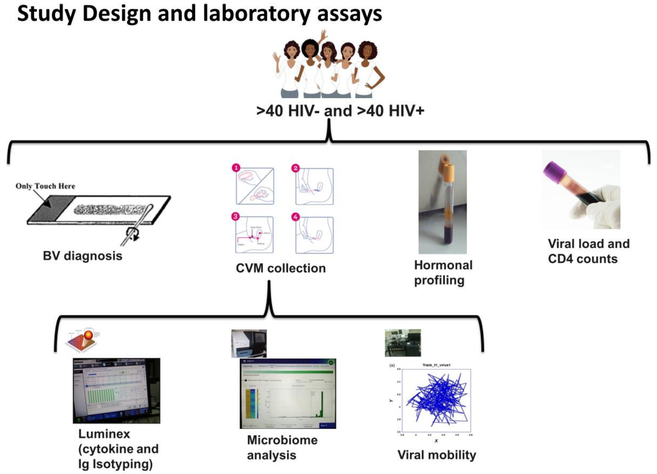
HIV must traverse the mucus barrier overlaying the mucosal epithelia for infection of the target cells to occur. A single or a limited number of HIV-1 variant(s), known as Transmitted/founder (T/F) HIV-1, are typically responsible for successive infections, overcoming the mucosal barriers, including the protective mucus layer. Factors affecting this mucus physical and chemical properties may influence its barrier function and how this influences the mobility of T/F HIV-1 in the mucus is yet to be determined. Our study seeks to unravel how factors affecting the cervicovaginal mucus (CVM) properties, such as serum levels of reproductive hormones, cervicovaginal pH, microbiome diversity, immunoglobulin content and cytokines milieu, may influence the mobility of T/F HIV-1 variants in cervicovaginal mucus. We therefore hypothesized that CVM physical and biochemical properties may influence the mobility of T/F HIV-1 in the CVM.

We specifically aim to:

1. To assess impact of HIV-1 envelop glycoprotein on mobility of T/F HIV-1 variants.
2. To correlate the microbiome diversity, Immunoglobulin contents and the cytokine milieu to the mobility of T/F HIV-1 variants in CVM.
3. To correlate serum sex hormone profile to the mobility of T/F HIV-1 variants in CVM.

METHODS

Study Design and laboratory assays



RESULTS

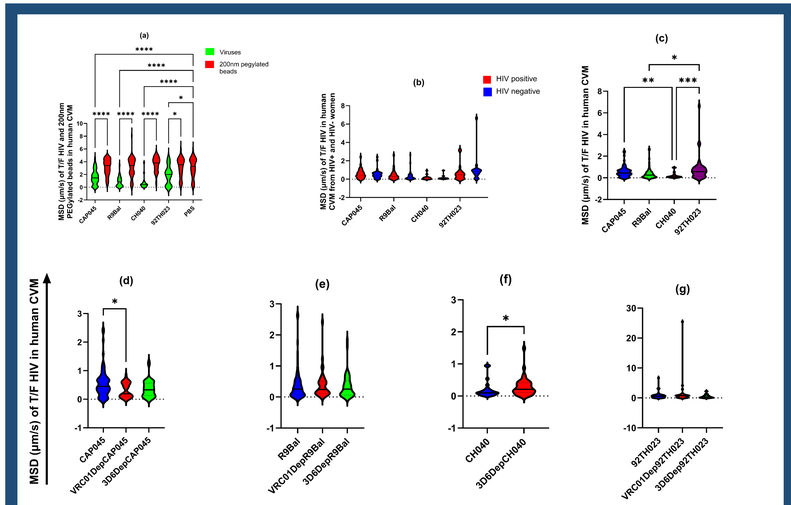


Figure 1: Mean squared displacement (MSD) in micrometers (µm) over time in seconds (s) of fluorescently labelled particles in human CVM. Comparison between viral particles and 200nm PEGylated beads (a); comparison between trapping of the viral particle in human CVM from HIV+ vs HIV- women (b); comparison of T/H HIV trapping in human CVM among the different tested clades (c); and evaluation of the influence of T/F HIV envelopment glycoprotein on virla trapping of the different tested clade: clade C CAP045 (d); laboratory adopted clade B R9Bal (e); clade B CH040 (f) and circulating recombinant form clade A/E 92TH023 (g). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

- The was trapping of T/F HIV in Human CVM with no different of the trapping in CVM obtained from either HIV infected or uninfected women.
- Clade B (CH040) T/F HIV-1 and the laboratory adapted R9Bal were more vulnerable to the trapping compared to the clade C (CAP045) and the recombinant clade A/E (92TH023).
- There could be an existence of cross reacting antibodies in human CVM that target T/F HIV-1 gp41 (VRC01 depleted virions).

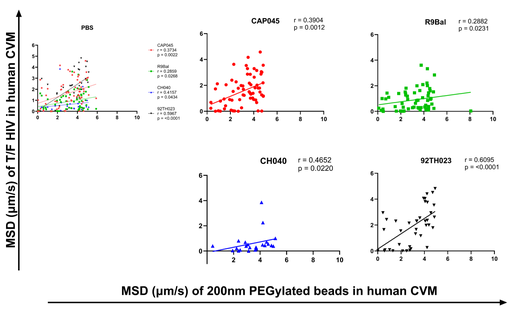


Figure 2: Correlation of the mobility (MSD) of T/F HIV to that of the 200nm PEGylated beads in the absence of the viral particles (PBS control) or in the presence of the different tested viral particles.

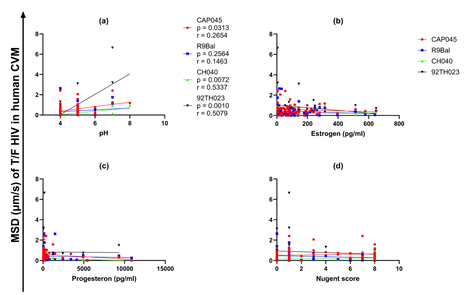


Figure 3: Correlation of the different factors influencing CVM physical and biochemical properties pH (a); serum estrogen concentration (b); serum progesteron concentration (c) and bacterial vaginosis nugent scores (d) to the mobility of the fluorescently labelled T/F HIV in the CVM measured as mean squred displacement (MSD) in micrometers (µm) of the T/F HIV over time (s)

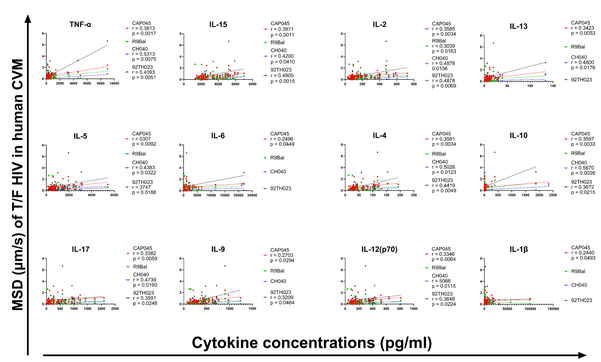


Figure 4: Correlation of the mobility of T/F HIV in human CVM measured as the mean squared displacement (MSD) in micro meters (m) per time in seconds (s) to the cytokine concentrations (pg/ml) in the human CVM.

- Trapping of the T/F HIV-1 in the CVM positively correlated to the viscosity of the CVM (figure 2). Apart from the lab adapted R9Bal, mobility of all the tested T/F HIV-1 positively correlated to the pH and concentrations of some cytokines in the CVM. There was no correlation to the serum reproductive hormone levels and the Nugent scores of the CVM (figure 3 and figure 4).

CONCLUSIONS

- Our study results demonstrate that CVM impedes the mobility of T/F HIV-1 variants which varies among different clades as observed in the significant reduced mobility of the virions when compared to the 200nm PEGylated beads.
- The results also show that cervicovaginal microenvironment may influence the mucus barrier function
- These results are crucial for gaining insights into the biological traits of T/F HIV-1 variants, enabling them to bypass the mucosal immune bottleneck
- By understanding the early interaction events at the mucosal sites upon HIV-1 exposure, we can facilitate the development of preventive strategies and treatments that enhance mucosal barrier function, thus reducing the transmission of HIV-1.

ADDITIONAL KEY INFORMATION

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