# Chapter 8.5

# Global level:
# A multi-layered model to describe HIV-1 transmission

*Multi-layered model to describe global HIV-1* transmission

In order to understand the HIV-1 pandemic and design preventive therapies, it is essential to further define HIV-1 transmission. From literature it is clear that there is confusion and debate on the mechanisms that are involved in the global spread of HIV-1, including the primary target cells and receptors[7,25,52,56]. Based on previous chapters, we postulate that global sexual transmission of HIV-1 is not a static process that involves one type of target cell and receptors. We propose a multi-layered model to represent HIV-1 transmission, predict the likelihood of infection, define the first target cell and receptors involved, and to ultimately design effective methods to prevent transmission (Table 8.5; Figure 8.5).

**Layer 0: Sexual practice and resistance factors**

A key factor influencing sexual HIV-1 transmission in the global population is unsafe receptive intercourse. Furthermore, sex with multiple partners and traumatic sex largely increase sexual HIV-1 transmission. Resistance factors, such as CCR5 mutations[63], also affect HIV-1 transmission, however most of these factors are still undetermined[63,66,92]. Awareness of safe-sex, distribution of condoms and easy access to HIV-1 test-facilities can still be improved to increase global protection against HIV-1.

**1st layer: Viral load, Langerin polymorphisms, body fluid factors**

High viral loads increase HIV-1 transmission. The viral load of the partner increases HIV-1 transmission by saturating Langerin function, by increasing the chance of bypassing the epithelial layers and by increasing the likelihood of infection of other target cells. Furthermore, Langerin polymorphisms decrease the interaction of this C-type lectin with carbohydrate structures[110] and this will decrease protection by the LC barrier. Furthermore, compounds in body fluids might affect the function of the C-type lectins (Chapter 8.4). Antiretroviral therapy decreases plasma viral loads and as such decreases the susceptibility of the population to HIV-1.

*Table 8.5 Multi-layered HIV-1 transmission model*

| Layer 0: Safe-sex/ resistance factors | Layer 1: Viral load partner | Layer 2: Exposed tissue | Layer 3: Genital "fitness" | Transmission | First target cell | Receptors involved |
|---|---|---|---|---|---|---|
| NO/NO | Low | • Rectum<br>• Endocervix | Steady-state | + | Epithelial *trans*migration/*trans*cytosis and DC-SIGN$^+$-DCs | HSPGs, DC-SIGN, ?CD4/CCR5/CXCR4 ? GalCer |
| | High | | | ++ | | |
| | Low | | Trauma/Inflammation | ++ | DC-SIGN$^+$-DCs | HSPGs, DC-SIGN, ?CD4/CCR5/CXCR4 ? GalCer |
| | High | | | +++ | | |
| | Low | • Anus<br>• Vagina<br>• Ectocervix<br>• Foreskin | Steady-state | - | - | Langerin protects |
| | High | | | + | LCs | CD4/CCR5 |
| | Low | | Ulcerative inflammation, loss epithelium, loss LCs (hormones) or disruption epithelium (trauma) | ++ | DC-SIGN$^+$ DCs, subepithelial macrophages, CD4$^+$ T cells | HSPGs, DC-SIGN, ?CD4/CCR5/CXCR4 ? MR/GalCer |
| | High | | | +++ | LCs | |
| | Low | | Non-Ulcerative Inflammation | + | LCs, DC-SIGN$^+$ DCs, subepithelial Macrophages, T cells | HSPGs, DC-SIGN, ?CD4/CCR5/CXCR4 ? MR/GalCer |
| | High | | | +++ | | |

**2nd layer: Exposure site**

Penile-anal and penile-vaginal intercourse expose different tissues to HIV-1, affecting HIV-1 transmission and the first target cells and receptors involved. During anal sex, HIV-1 encounters the rectal epithelium, and this will probably result in HIV-1 capture by DC-SIGN$^+$ DCs. Vaginal and cervical tissues contain different target cells, including Langerhans cells and CD4$^+$ T cells, of which the densities are highly variable and which are thought to be subject to environmental triggers. Circumcision inhibits the likelihood to acquire HIV-1[23]. This implicates that the most sensitive tissue for HIV-1 transmission on the penis is the foreskin epithelium. Strikingly, the density of target cells, including LCs, is comparable in foreskin epithelium and glans epidermis, suggesting that the amount of target cells does not determine the higher susceptibility of foreskin. However, foreskin epithelium lacks the protective keratin layer of skin[73] and due to the mucosal structure, the epithelial/LC barrier is easier traumatized, allowing interaction of the virus with the cells in the subepithelium. Penile-vaginal and penile-anal contact may require specific microbicides to prevent HIV-1 transmission via the anal or the vaginal route.

**3rd layer: Genital "fitness"**

Under steady-state conditions the epithelial layer protects against HIV-1 transmission. However, under inflammatory conditions or during trauma the epithelial barrier can be disrupted, exposing subepithelial target cells to HIV-1. Furthermore, inflammation may attract target cells towards the genital epithelia and inflammatory factors might enhance HIV-1 transmission by LCs (**Section 6**) and other target cells[23]. In the 1990s two major clinical trials investigated whether treatment of sexual transmitted infections (STI) reduced HIV-1 transmission. In one trial HIV-1 transmission was decreased by 38%. Unexpectedly, the other trial only marginally affected the number of HIV-1 infections[38,42,111]. Low incidence of STIs and low-risk behaviour are thought to have attributed to the results in the second trial. Therefore, it now thought that in population with high-risk behaviour and high STI rates, STI treatment might significantly reduce HIV-1 transmission[62,112].

*Future directions to investigate HIV-1 using the multi-layered model*

**Population genetics.** Population genetics have a great potential in providing answers about the involvement of different proteins in sexual HIV-1 transmission. Distinctions are needed to assess a role of different factors according to layer 1-3, comparing homosexual with heterosexual cohorts, viral loads of the infected partner and people suffering from genital inflammation compared with healthy persons.

***In vivo.*** Primate infection with immune deficiency viruses could be a valuable mode to asses the role of the different layers by comparing the rectal, vaginal and penile route of infection, using different viral concentrations, in steady-state conditions and inflammatory conditions. In previous work, different methods were used to achieve high rates of infection using limit animal group sizes, including high viral loads and hormonal treatments. This high infectivity does not reflect the *in vivo* chance to acquire HIV-1 by sexual contact and may underestimate protective factors *in vivo*. Recently, a research group demonstrated efficient infection of macaque by SHIV using repeated low-dose exposures during several weeks[100]. This may provide a valuable model to investigate viral transmission. Small animals are not susceptible to infection by HIV or SIV. Progress has been made towards a genetically engineered murine model that is susceptible to HIV-1 via the anal and vaginal route[10]. If successful, these models could provide interesting answers using knock-out for genes and cells involved in transmission[9,50,55].

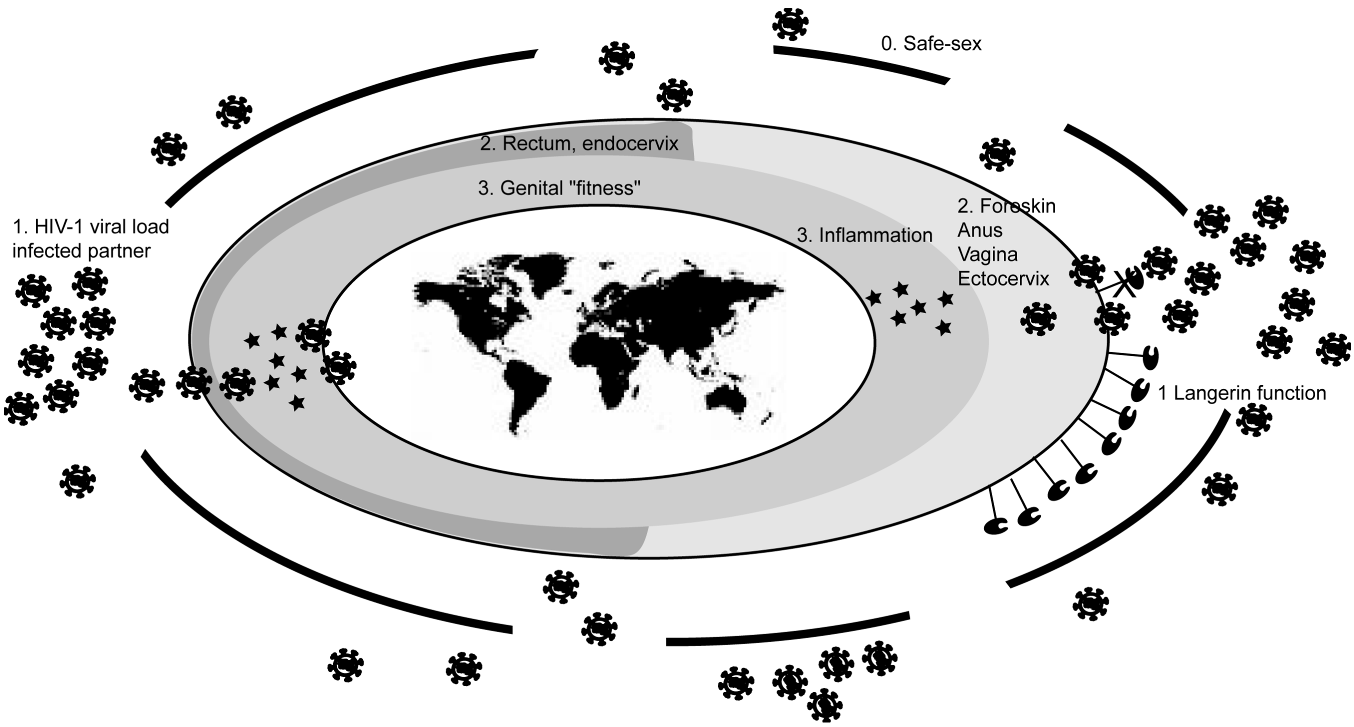


**Figure 8.5 A multi-layered model to describe global HIV-1 transmission.**
HIV-1 transmission is a multifactorial process. (0) Safe-sex is a major protective variable in the global population and increasing awareness on safe-sex will highly decrease HIV-1 transmission. (1) Viral load of the infected partner is strongly associated with HIV-1 transmission. High viral loads saturate the protective Langerin function and other processes that mediate transmission are enhanced. Moreover, Langerin polymorphisms or soluble factors in body fluids might affect the function of this receptor. (2)The tissue exposed to HIV-1 determines the mechanisms that are involved in HIV-1 transmission. In the rectum and endocervix the LC barrier is not present and DC-SIGN$^{+}$ DCs that efficiently mediate transmission are closely located to the lumen. In the foreskin, vagina and ectocervix, Langerin function clears invading particles protecting the host. In some females, however, high amounts of CD4$^{+}$ T cells are observed in the epithelia and subepithelia of the genital tissues. (3) Inflammation in all genital tissues increases HIV-1 transmission by the interaction of microbes with TLRs and the production of cytokines. Furthermore, the epithelium might be disrupted and target cells attracted towards the epithelium.

*In vitro* studies using primary or DC-like single cells are essential to discover new receptors and pathways. The receptors and factors that are revealed using these single cells might be essential targets for microbicides. It is important to always confirm these targets and pathways in primary cells, using different physiological concentrations of virus. More physiological concentrations of virus reveal a protective function for the C-type lectin Langerin, which is not observed using higher viral concentrations. *In vitro* studies may implement the different layers by isolation of primary cells from different target tissue, by stimulating cells with different stress-factors and by using different virus concentrations.

*Design of a sensitive viral transmission model.*

To ultimately draw conclusions on the first target cell and the pathways involved during transmission of HIV-1, it is essential to develop and use models that translate to the human *in vivo* situation. Transmission of the low-infectious HIV-1 is thought to be mediated by a one hit event. Unfortunately, we cannot sit down with a 'super'-microscope that visualizes this event in the human genital tract, including the identity of the cell that is targeted and the biological processes involved. This is further complicated since *trans*-infection is a process that can only be visualized using the *trans*-infected cell as a read-out. The sensitivity of our models can be increased using recombinant viruses, such as the work of Hladik *et al.* in which they infected vagina explants with HIV-1-GFP[43]. However, this group used high concentrations of this recombinant virus and spinoculation, a method to increase infection, demonstrating that only the use of recombinant viruses is not enough to work under physiological conditions. Multiple exposure of the HIV-1-susceptible mouse[23] to physiological concentrations of HIV-1 in combination with knock-out of single HIV-1 target cell types, might reveal the contribution of the different cell types. However, the translation of this murine model to humans is not evaluated yet.

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