Section 6: Risk factors to acquire HIV-1: A role for Langerhans cells?
Chapter 6.1

Risk factors to acquire HIV-1

Bridge

In Section 5, we have demonstrated that Langerhans cells protect against HIV-1 transmission by capture of the virus via the receptor Langerin. However, by using high viral concentrations or blocking Langerin function LCs are infected by HIV-1 and mediate transmission to CD4+ T cells. Epidemiological studies have revealed that different risk- but also protective factors are involved in the susceptibility to sexually acquire HIV-1. In Section 6 we have investigated how risk factors increase the susceptibility to acquire HIV-1, according to the mechanisms previously described in this thesis.
**Sexual mode and risk factors**

Sexual transmission of HIV-1 per exposure is low compared to parental and vertical transmission and depends on the mode of sexual contact (Table 6.1). Furthermore, different risk- but also protective factors are involved in the susceptibility to sexually acquire HIV-1 (Table 6.2). This results in a variable risk to acquire HIV-1 per individual, dependent on sexual practices, ‘genital fitness’ and the viral load of the infected partner. The identification of risk factors to acquire HIV-1 is important for the design of preventive strategies but might also unmask underlying mechanisms that are involved in HIV-1 transmission.

**Table 6.1 The chance to acquire HIV-1 per exposure (adapted from 38,58,88)**

<table>
<thead>
<tr>
<th></th>
<th>Chance per exposure:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sexual transmission</strong></td>
<td></td>
</tr>
<tr>
<td>Female-to-male</td>
<td>0.03-0.14%</td>
</tr>
<tr>
<td>Male-to-female</td>
<td>0.05-0.5%*</td>
</tr>
<tr>
<td>Male-to-male</td>
<td>0.16%-10%</td>
</tr>
<tr>
<td><strong>Parental transmission</strong></td>
<td></td>
</tr>
<tr>
<td>Transfusion of infected blood</td>
<td>95%</td>
</tr>
<tr>
<td>Needle sharing</td>
<td>0.7%</td>
</tr>
<tr>
<td>Needle accident</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Vertical transmission (mother-child)</strong></td>
<td></td>
</tr>
<tr>
<td>Without retroviral therapy</td>
<td>25%</td>
</tr>
<tr>
<td>Retroviral therapy</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

(*) However, mathematical modeling suggests a chance of 7%-24% that female partners acquire HIV-1 during the first two months of infection of their sexual partner (with even higher risks if either partner has an STD), referred to as amplified transmission\(^15,80\)

**High viral loads**

The correlation between plasma viral loads and the acquisition of HIV-1 are evident and are thought to account for the high risk to acquire HIV-1 during primary infection or late stage disease of the infected partner.\(^{38,83,88,110}\) Viral loads in the body fluids are generally lower than in blood.\(^{63,108}\) However, plasma viral loads correlate with the levels of HIV-1 in both semen and cervicovaginal fluid.\(^{92}\) High concentrations of HIV-1 in these body fluids are likely to enhance all possible mechanisms that have proposed to account for sexual HIV-1 transmission, including epithelial transcytosis, DC-SIGN\(^+\) DC-mediated transmission, direct T cell and macrophage infection in the lamina propria. Moreover, high viral loads might be particularly important for Langerin function. Section 4 has demonstrated that high concentrations of HIV-1 saturate the protective function of Langerin. Subsequently, LCs are infected by HIV-1 and mediate transmission instead of protection through viral clearance.

**Susceptibility to HIV-1 of different genital tissues and the influence of hormones**

The mode of sexual contact, genital trauma, menstruation, intra-uterine devices and cervical ectopy influence the susceptibility to HIV-1 (Table 6.1 and 6.2). These observations suggest that different
genital tissues and tissues in different conditions are variably susceptible to HIV-1 and that the integrity of the epithelium is crucial. Indeed, sexual practices that disrupt the epithelial barrier, such as dry sex, increase the susceptibility to HIV-1\textsuperscript{42}. Intra-uterine devices might influence the amount of co-infections, disrupt the epithelial layers or affect the composition of the cervical epithelial tissues. The endocervix and the rectal epithelium contain a thin columnar epithelial layer, which contain numerous DC-SIGN\textsuperscript{*} DCs that may mediate HIV-1 transmission, lacking LCs that clear HIV-1 (Figure 2.2.1). Increased susceptibility to HIV-1 in men-having-sex-with-men or in women with cervical ectopy or practising anal intercourse\textsuperscript{1,59,76,88} might be explained by the exposure of the endocervical epithelium and the rectum to HIV-1.

Table 6.2: The impact of risk/protective factor on HIV-1 transmission (adapted from\textsuperscript{88,110})

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Infectiousness (*)</th>
<th>Susceptibility (**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High viral loads (***)</td>
<td>++</td>
<td>N.A.</td>
</tr>
<tr>
<td>Late stage HIV infection/Primary HIV infection</td>
<td>++</td>
<td>N.A.</td>
</tr>
<tr>
<td>Antiretroviral therapy</td>
<td>--</td>
<td>?</td>
</tr>
<tr>
<td>Genital inflammation (+ (**))</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Cervical ectopy (***)</td>
<td>+?</td>
<td>++</td>
</tr>
<tr>
<td>Hormonal anti-conceptives</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Intrauterine devices</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Genital tract trauma</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Menstruation</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Circumcision</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Condom use</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CCR5 mutation</td>
<td>?</td>
<td>---</td>
</tr>
</tbody>
</table>

(*) Chance to spread HIV-1 (+** represents an increase in chance, --** a decrease)
(**) Chance to acquire HIV-1 (+* represents an increase in chance, --* a decrease)
(***) Especially important in female to male transmission\textsuperscript{24}
(****) The presence of endocervical columnar epithelial cells on the ectocervix

Menstruation, female age, pregnancy and sex-hormones alter the susceptibility to HIV-1, suggesting an important role for the composition of the vaginal/cervical epithelium and the influence of sex hormones\textsuperscript{1,37,70,93}. Oestrogen and progesterone have distinct functions on the thickness of the epithelium, and primate experiments indicated that oestrogen is responsible for vaginal epithelial thickening and maturation and protects against HIV-1 transmission\textsuperscript{70,93}. During menstruation alterations in the vaginal milieu or genital tissues or direct blood contact might enhance infection.

In chapter 6.2 we have investigated the distribution and phenotype of the target cells for HIV-1 in the genital tissues and the role of androgens for the composition of these tissues.

**Genital inflammation**

Epidemiological studies have demonstrated that genital inflammation increases HIV-1 infectivity as well as the HIV-1 susceptibility (Table 6.1). Especially ulcerative infections have been linked to increased susceptibility\textsuperscript{14,29,41}. These infections disrupt the epithelial integrity and the LC barrier and expose DC-SIGN\textsuperscript{*} DCs, macrophages and CD4\textsuperscript{*} T cells to HIV-1. Non-ulcerative infections, such as bacterial
vaginosis, have also been associated with higher rates of HIV-1 acquisition\textsuperscript{39,97}. This suggests that genital inflammation increases susceptibility without disrupting the epithelial barrier. These conditions might attract target cells for HIV-1 towards the epithelial layer or down-regulate Langerin function resulting in less HIV-1 clearance and more LC infection.

In chapter 6.3 and 6.4 we have investigated the role of bacterial co-infection and herpes simplex virus infection on HIV-1 transmission by LCs.

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**Figure 6.1 Different risk factors might attribute to HIV-1 transmission.**

(a) Vagina, foreskin and ectocervix contain a stratified epithelium in which LCs are present. In these tissues DC-SIGN\textsuperscript{+} DCs reside in the subepithelium. The epithelial layer and viral clearance via Langerin protect against HIV-1 transmission by DC-SIGN\textsuperscript{+} DCs or other target cells (b) High viral loads of the infected partner increase HIV-1 transmission. Langerin function might be saturated, resulting in a loss of the protective function of LCs, which in turn can become infected. Moreover, inefficient processes such as epithelial transcytosis and subsequent interaction with other target cells are increased. (c) Rectum and endocervix contain a thin columnar epithelial layer, which lacks LCs. In these tissues DC-SIGN\textsuperscript{+} DCs are located close the lumen, and might therefore often encounter HIV-1 for transmission. (d) During trauma or ulceration the epithelium is damaged and the HIV-1 can interact with DC-SIGN\textsuperscript{+} DCs and other target cells in the subepithelium.

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**Condom use, CCR5 mutation and circumcision**

Safe sex using condoms is the most effective active method to prevent HIV-1 transmission to date. However, circumcision has been demonstrated to moderately protect against HIV-1 infection\textsuperscript{36}. Circumcision removes the part of the penis with the most fragile epithelium containing of LCs, T cells and DC-SIGN\textsuperscript{+} DCs (Chapter 4.2)\textsuperscript{66}. Moreover, foreskin might serve for a temporary warm reservoir where virus is not washed away.

Interestingly, different protective host factors have been demonstrated to protect against HIV-1 infection, such as a homozygous CCR5 mutation\textsuperscript{62}. Only a part of the high-risk seronegative individuals can be explained by this mutation, suggesting that unidentified factors, or a combination of modest factors, protect these persons for acquiring HIV-1\textsuperscript{57,80,89}. 

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References