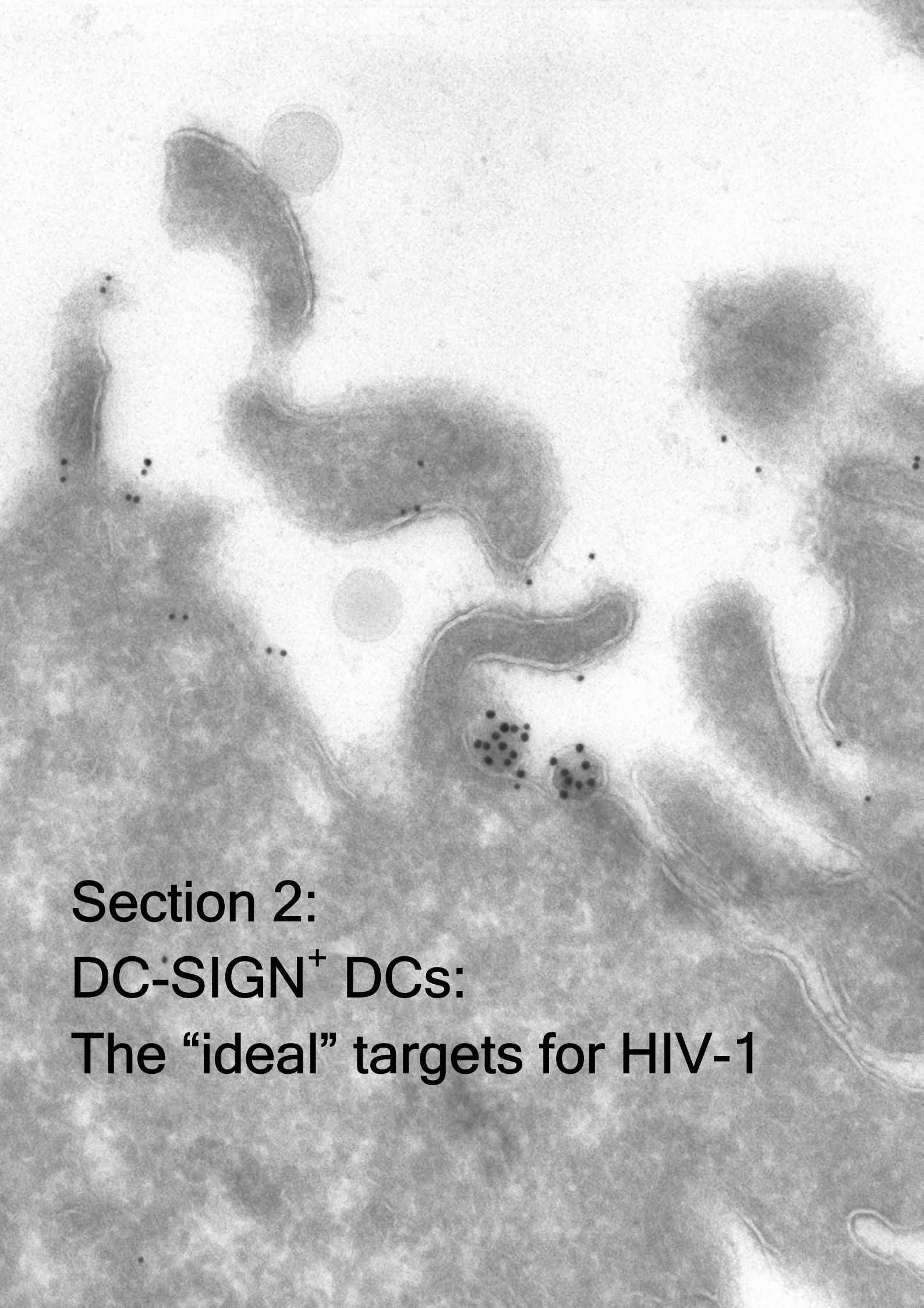

Section 2:
DC-SIGN^{+} DCs:
The “ideal” targets for HIV-1

Chapter 2.1

Human immunodeficiency virus type 1: Structure, pathogenesis and the pandemic

Bridge

In **Section 1** we have introduced the different subsets of DCs, the function of DCs in the immune system and the role of DCs during viral infections. In **Section 2,** we will discuss the interaction of HIV-1 and a specific DC subset, the DC-SIGN^{+} DCs. This DC subset is thought to induce antiviral adaptive immune responses, but might also mediate transmission of the virus from the site of infection into the lymphoid tissues. The DC receptors that are involved in these processes are under debate and were further investigated.

The HIV-1 pandemic

Infection with HIV-1 may lead to acquired immune deficiency syndrome (AIDS), one of the major death causes worldwide. The WHO estimated that in 2007 2.5 million people acquired HIV-1, leading to a total of 30.6-36.1 million infected people, which counts for a prevalence of 0.8% of the global population. Last year, AIDS claimed an estimated of 2.1 million deaths, of which 330,000 were children. Sub-Saharan Africa accounts for more than 60% of the infected individuals and more than 75% of the HIV-1 related deaths. Today, no region is untouched by the HIV-1 pandemic (Table 2.1)[21,34].

Table 2.1: The HIV-1 pandemic in different parts of the world

	Prevalence	AIDS-related Mortality ($x10^3$)	Main mode of transmission
Sub-Saharan Africa	5.0	1600	Unprotected sex>parental
Northern Africa/Middle east	0.3	25	Unprotected sex>parental
Asia	0.3	302	Unclear
Latin America	0.5	58	Unprotected sex>parental
North America	0.6	21	Unprotected sex>parental
West/Central Europe	0.3	12	Unprotected sex>parental
Eastern Europe/Central Asia	0.9	55	Parental >unprotected sex
Oceania	0.4	1.2	Unprotected sex>parental
Caribbean	1	11	Unprotected sex>parental
Total	0.8	2100	Unprotected sex>parental

Human immunodeficiency virus type 1 structure and life cycle

HIV-1 is an enveloped RNA virus and belongs to the family of *retroviridae,* genus *lentivirus*. The virus consists of two identical positive sense RNA molecules surrounded by a spherical capsid and a host cell-derived envelope. The RNA consists of nine genes, which encode for structural proteins (*gag, env),* proteins essential for viral replication (*pol),* regulatory proteins (*tat, rev)* and accessory proteins (*vif, vpr, vpu, nef)* (Figure 2.1.1).

Retroviruses have a complex life cycle: upon entry of a target cell, viral RNA is converted into double-stranded DNA by the viral enzyme reverse transcriptase. Subsequently, viral DNA is transported into the nucleus and integrated into DNA of the host cell by the enzyme integrase. Transcription of the viral genes is started using host cell derived RNA polymerase. Viral RNA copies and viral proteins are produced, which together form new viral particles that are released from the host cell by budding[11,13,15] (Figure 2.1.1).

HIV-1 entry receptors and tropism

The entry receptors for HIV-1 can be divided into attachment and fusion receptors. The attachment receptor is CD4, which binds the HIV-1 envelope glycoprotein 120 (gp120). The fusion receptors are me mbers of the seven membrane-spanning C-C or CXC families of chemokines receptors, and mediate fusion of the viral and cell membrane[5,9]. The main chemokine receptors involved are chemokine (C-C motif) receptor 5 (CCR5) or chemokine (CXC) receptor 4 (CXCR4)[12]. HIV-1 infects cells of the immune system that express these attachment and fusion receptors: $CD4^+$ T cells, macrophages, dendritic cells (DCs), microglia and thymocytes[4,18,32]. Sexual transmission of HIV-1 is predominantly caused by CCR5-using HIV-1[4,10,13,37]. This is underscored by data that individuals homozygous for a defective CCR5

allele (delta-32) are highly resistant to acquire HIV-1[25]. During end-stage disease the virus may evolve to a CXCR-4 using virus, which is associated with rapid disease progression[7].

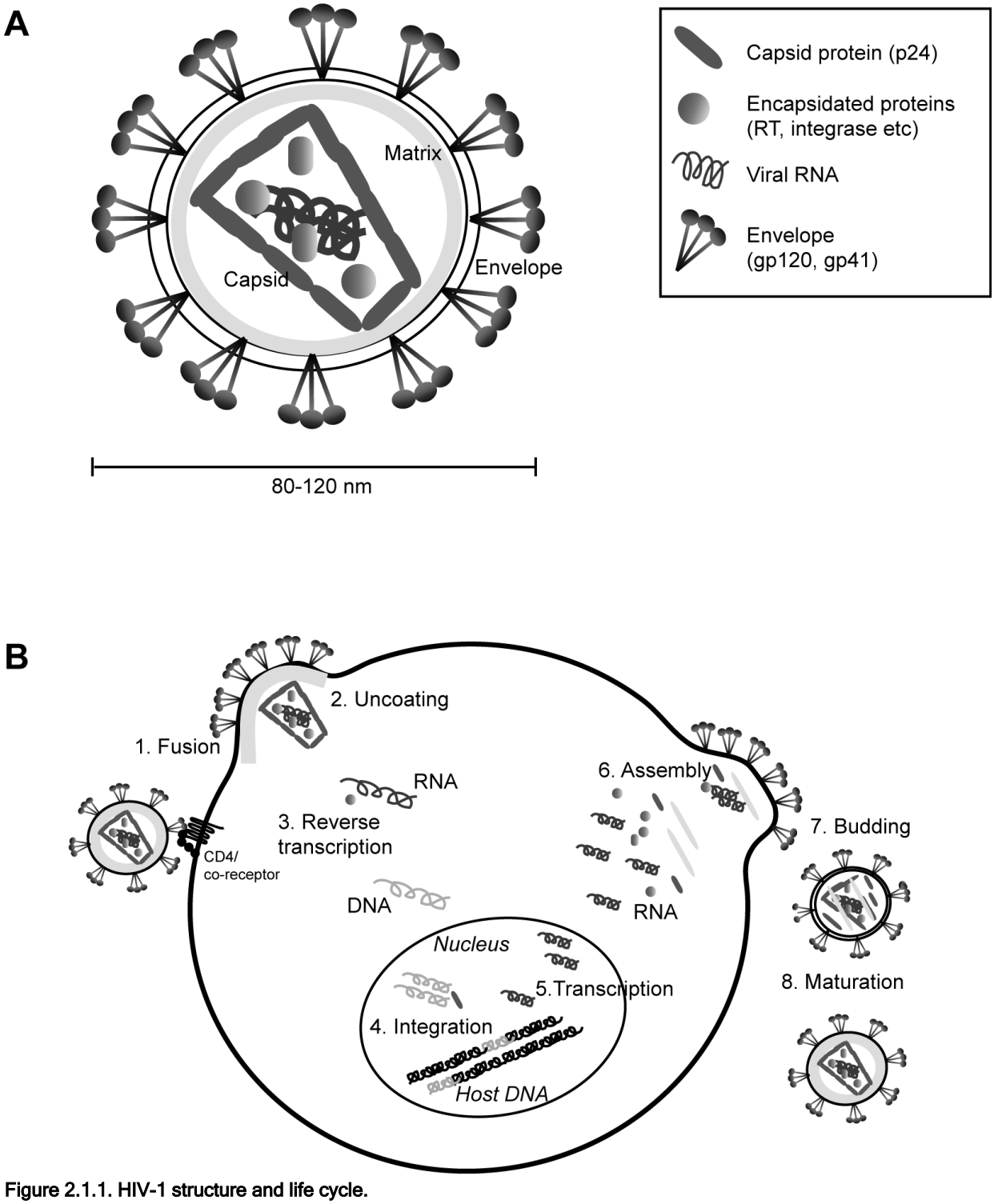

Figure 2.1.1. HIV-1 structure and life cycle.
(a) HIV-1 is a relatively small virus (80-120nm) that consists of two RNA molecules and structural proteins; surrounded by a capsid and an envelope that contains the envelope glycoproteins (gp120 and gp41). (b) HIV-1 interacts with CD4 and a co-receptor to enter a target cell. Viral RNA is converted into double-stranded DNA by reverse transcriptase, transported into the nucleus and integrated into DNA of the host cell by the enzyme integrase. Viral RNA copies and viral polyproteins are produced, and new viral particles are released from the host cell by budding. During maturation, HIV-1 proteases cleave the polyproteins into functional HIV proteins and enzymes.

HIV-1 pathogenesis

After transmission, initial replication takes place in the regional lymphoid organs. Subsequently, the virus is disseminated throughout the body. A massive infection of susceptible cells results in high viral loads and a rapid drop of $CD4^+$ T cell counts, which might cause clinical symptoms[10,,34]. The immune system responds with a strong HIV-1-specific immune response, including virus-specific CTLs and seroconversion. Viral replication is suppressed to lower levels, resulting in clinical latency. As infection with HIV-1 progresses, the level of $CD4^+$ effector and memory T cells gradual decreases and the cell-mediated immunity is impaired, resulting in opportunistic infections. Different mechanisms have been proposed for this depletion, including direct apoptosis due to viral infection, CTL killing and generalized immune hyperactivation[6,8]. HIV-1 infection ultimately leads to severe immunosuppression and the development of AIDS. The onset of AIDS varies considerably between infected individuals and ranges from 6 months to more than 25 years. Host factors are thought to attribute to fast or slow disease progression[6,11].

Transmission of HIV-1

Cell-free HIV-1 and HIV-1-infected cells are present in body fluids, including blood, semen, cervico-vaginal fluid and breast milk[2,26,29,30,33]. HIV-1 is therefore transmitted via unprotected hetero- and homosexual intercourse, use of contaminated needles, contaminated blood transfusion as well as from mother to child at birth and through breast-feeding[34]. The major route of acquiring HIV-1 worldwide is sexual transmission, accounting for about 85% of all HIV-1 infections (Box 2.1)[31,34]. Sexual transmission involves contact of infected semen, saliva or cervicovaginal fluid with the genital, oral, or rectal mucosa of an uninfected person. The chance of acquiring HIV-1 per sexual act with an infected person is thought to range between 0.01% and 1%, dependent on the mode of sexual intercourse, the viral load of the infected partner, and different host factors, including presence of co-infection and genetic factors[16,21,23,28,31,38,38]. (Risk factors for the sexual transmission of HIV-1 are further discussed in section 6).

Multiple theories

The sequential events that occur from the moment HIV-1 encounters the genital epithelial barrier until the virus has caused a systemic infection remain obscure. Backtracking from systemic HIV-1 infection until viral entry of the host, results in an increase in uncertainties and remaining questions. Systemic HIV-1 infection is characterized by massive infection of both primary and peripheral lymphoid tissues[1]. Preceding generalized disease, HIV-1 is thought to replicate several rounds in the regional lymphoid tissues draining the site of entry[34]. The phase before regional infection is not elucidated yet. Multiple theories exist about the events occurring at the moment the virus invades the body. These theories include different receptors, target cells and pathways that are involved in transmission of the virus to the lymphoid tissues (Text box 2.1).

Treatment and prevention of HIV-1

Unfortunately, a cure for HIV-1 infection has not yet been discovered. However, anti-retroviral drugs have been developed that suppress infection, reduce morbidity and highly increase the life expectancy of HIV-1 patients. These drugs inhibit replication at different steps of the viral life cycle. High mutation speed of the virus, results in rapid drug resistance and therefore a combination of three or more antiviral drugs is required for long-term effectiveness[6,19,34]. So far, retroviral therapy does not cure HIV-1

infection. To stop the pandemic it is therefore essential to prevent new HIV-1 infections. The most effective method would be immunization with a vaccine capable of inducing life-long protection. Despite huge efforts such a vaccine has not been discovered yet. An alternative method to prevent infection would be the use of microbicides, topical drugs that inhibit vaginal, penile or rectal transmission of the virus[3,24]. To develop an effective HIV-1 vaccine or microbicide it is essential to understand the mechanisms governing HIV-1 transmission. Microbicides will be discussed in detail in section 7.

Text box 2.1: Sexual transmission of HIV-1

What do we know?

- Sexual transmission is the main mode of HIV-1 infection worldwide (Table 2.1)[21,31].
- The chance to acquire HIV-1 per sexual act with an infected individual is low[16,31], and therefore underlying processes are either inefficient or dependent on certain circumstances
- Host factors are involved in the sexual transmission of HIV-1[31].
- Sexual HIV-1 transmission is primarily caused by CCR5 using viruses[25,40].
- The genital epithelium is an important barrier against invading HIV-1.
- CD4$^+$ T cells, the primary target cells for HIV-1 are scarce in the genital epithelial tissues[27]. (However might be variable, section 6)
- Langerhans cells (LCs) are the majority of cells in the epithelium that express HIV-1 entry receptors
- Dendritic cells, abundantly present in the submucosal tissues migrate towards the lymphoid tissues.

What are the different theories?

- HIV-1 is captured by subepithelial DC-SIGN$^+$ DCs, these DCs migrate to lymphoid tissues and mediate HIV-1 transmission of captured virus or *de novo* produced virus[14,36], this will be further discussed in this section.
- HIV-1 infects LCs in the mucosal epithelia, infected cells migrate to lymphoid tissues and mediate transmission (This is further discussed in section 4)[22].
- HIV-1 is transcytosed through the epithelial layer and then infects macrophages and T cells in the lamina propria[17,20,25,35,39,40]. After a first round of replication the virus reaches the lymphoid tissue by diffusion.
- A combination of the mechanisms above

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