Vertical transmission of Human Immunodeficiency Virus

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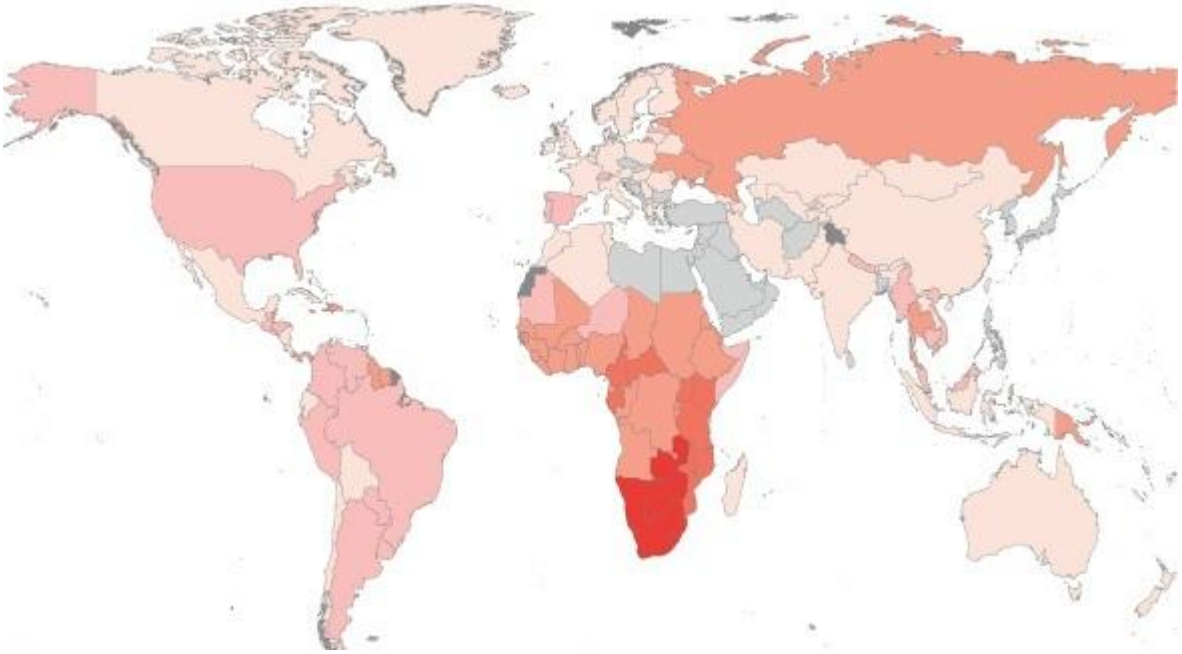


Abstract

The mother-to-child route of transmission of Human Immunodeficiency Virus (HIV) causes many new HIV infections. Mother to child transmission (MTCT) of HIV is most prevalent in sub-Saharan Africa. It can be transmitted in the uterus, at time of delivery and during breastfeeding. Important risk factors for MTCT of HIV are a high viral load and a low $CD4^+$ cell count in the mother, mode of delivery (vaginal delivery versus caesarean section), virus type and genetic variability, maternal nutrition and maternal co-infection with malaria. But a child exposed to HIV does not always contract the infection. This may be due to HIV-specific $CD8^+$ T cells and natural killer cells in the immune system of the newborn. Prevention of MTCT of HIV is important because an HIV infection cannot yet be cured. The most effective way to prevent MTCT is to keep the viral load of the mother low by Combined Anti Retroviral Therapy (CART) The problem with this, however is, that many pregnant woman in high-prevalence areas do not receive HIV counseling or HIV testing. And when HIV counseling and testing has been done, access to anti-retroviral drugs is often insufficient. Therefore more HIV counseling and testing should be available in high risk areas and HIV treatment should be accessible for HIV positive pregnant woman.

http://www.who.int/hiv/data/global_data/en/index.html

Contents

Introduction

The virus

Human Immunodeficiency virus (HIV) is a lentivirus and belongs to the family of the R*etroviridae*, it causes acquired immunodeficiency syndrome (AIDS) (Douek et al 2009). In AIDS the immune system starts to fail, leading to potentially lethal opportunistic infections. HIV causes AIDS by entering and replicating in $CD4^+$ cells of the immune system. The $CD4^+$ cells are then eliminated either by the virus or by $CD8^+$ T cells which react to the infection by inducing apoptosis in infected $CD4^+$ cells (Weiss, 1993). When HIV reduces the quantity of $CD4^+$ cells below a critical level, the immune system is no longer capable of inducing a proper immune response to eliminate an invading pathogen.

According to the World Health Organization (WHO), HIV is now considered a pandemic, with a death rate of more than 25 million people between 1981 and 2006 and infecting 0.6% of the global population (Joint United Nations Programme on HIV/AIDS, 2006). HIV is transmitted via blood, semen, vaginal fluids, pre-ejaculate and breast milk (Peterman et al 1985). The virus originates from non-human primates and started to infect people probably in the late 19^{th} or early 20^{th} century (Worobey et al, 2008). Two subtypes of HIV are known: HIV-1 and HIV-2. HIV-1 originates from chimpanzees and HIV-2 from the Sooty Mangabey (Sharp et al 2001). HIV-1 is prevalent globally, while HIV-2 is only present in sub-Saharan Africa (Reeves et al, 2002). Furthermore HIV-1 is more infectious and virulent (Gilbert et al, 2003).

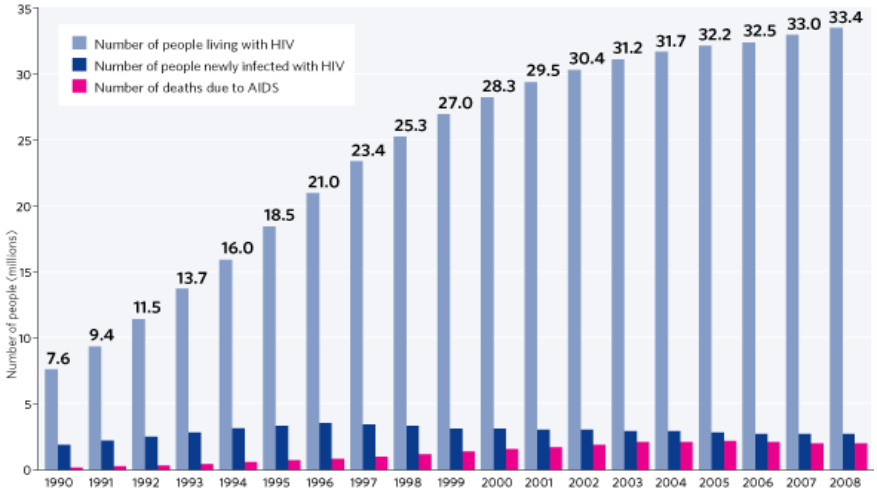


Figure 1. Prevalence of HIV.
The number of HIV infected people worldwide in the past two decades. The number of infected people is leveling and the number of new infections per year is slightly declining.
http://www.who.int/hiv/data/global_data/en/index.html

Demographic prevalence of HIV

According to the WHO there were an estimated 33.4 million people infected with HIV in 2008 (Fig. 1). The prevalence was rising in the past decades, but is now leveling off. High prevalence areas for HIV are sub-Saharan Africa, Russia and South East Asia (Fig. 2). In this review the focus will be sub-Saharan Africa because HIV is most problematic in this area. This is confirmed by numbers of the WHO estimating that 64% of all people infected by HIV live in sub-Saharan Africa. South Africa with 5.2 million infected people has currently the most HIV infections, followed by Nigeria and India (Behaviour and Communication Survey, 2008; McNeil, Jr., 2007). Reasons for the high prevalence are insufficient condom use and low rate's of male circumcision according to the report of the Experts Think Tank Meeting on HIV Prevention in High-Prevalence Countries in Southern Africa (SADC, 2006). Other possible reasons could be: low male involvement in HIV infection prevention, high prevalence of sexual violence, low HIV risk perception, and pervasiveness of transactional sex among young people, insufficient access to HIV counseling and testing and access to condoms (Halperin et al, 2007)

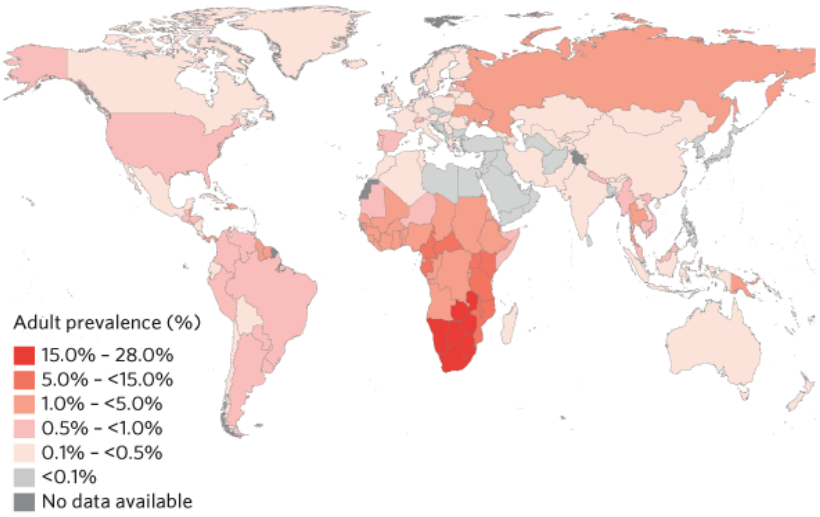


Figure 2. Prevalence of HIV

High prevalence areas are sub-Saharan Africa, Russia and south east Asia. http://www.who.int/hiv/data/global_data/en/index.html

Aim

The aim of this paper is to give an overview of the MTCT of HIV, with a focus on (I) different mechanisms of infection, (II) influences of the mother and infant on transmission rate,(III) the prevention of MTCT of HIV.

Human Immunodeficiency Virus

Structure of the virus

In its structure, HIV is different from other *Retroviridae.* It is spherical and has a diameter of 120 nm (McGovern et al, 2002). The membrane of HIV consists of several glycoprotein's (gp's) which are important in cell entry of the virus as elaborated later. These gp's are called gp120 and gp41. Gp120 is located above gp41 and therefore gp41 is not visible for other molecules. Gp41 is the anchor in the membrane of the gp120 and gp41 protein complex. The membrane of the virus is made out of lipids.

Within the virion, HIV has a capsid which contains 2 copies of positive single stranded RNA genome tightly bound to four enzymes, one of which is the reverse transcriptase. After cell entry this enzyme converts RNA to copy DNA after which the HIV genome can be replicated and transcribed by the hosts transcription factors. The viral genome consists of nine genes (Mc Govern et al 2002), which code for a total of 19 proteins necessary for HIV replication.

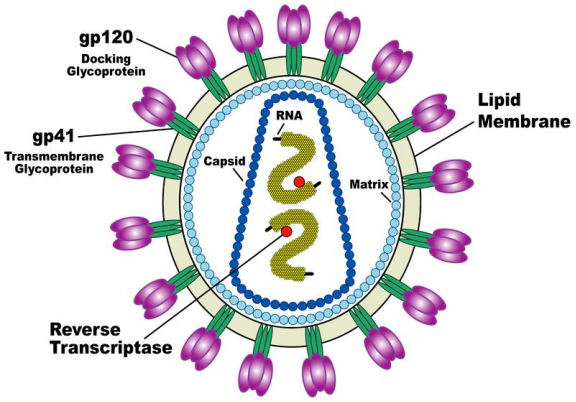


Figure 3. HIV
Schematic overview of the virus. Two copies of the RNA bound to reverse transcriptase in the capsid and gp 120 and gp41 on its surface.

Infection mechanism

When HIV has entered the host, it binds its gp120 (Fig. 3) to the CD4 receptor of either macrophages or $CD4^+$ T cells. This is a strong binding which facilitates a structural change of the viral envelope, this binding reveals the chemokine binding site of gp120 which binds to the co-receptor of CD4. This attachment allows gp41 (Fig. 3) to bring the virus and the host cell closer together so their membranes can fuse. HIV is capable of entering the target host cell in two different ways. Firstly, it can enter the target cell directly by the previous explained route. This route of infection is called a cis infection. Secondly, HIV can enter a target cell by first binding DC-SIGN of a dendritic cell at the site of viral entry in the host. This dendritic cell, with HIV bound to it, then migrates to a lymph node and presents HIV to a $CD4^+$ cell, which then can become infected (Steinman et al., 2003). This route of infection is called trans infection.

After the membranes are fused the viral RNA and the enzymes reverse transcriptase, integrase, ribonuclease, and protease are transported to the nucleus via a microtubule transport (Chan et al, 1998; Wyatt et al, 1998). During this transport reverse transcriptase transcribes the viral RNA into copy DNA. This process is very error prone because it happens in the cytosol where host mechanisms to repair mutations do not exist. Therefore the HIV genome mutates relatively rapid, which may cause HIV to become resistant to drugs and help it evade the hosts immune system. After reverse transcription, the so-called proviral DNA is inserted in the hosts genome by integrase (Zheng et al, 2005).

When the proviral DNA is inserted in to the host's genome it is not yet transcribed and the virus is in a latent state. To replicate the viral genome, some host cellular transcription factors are necessary. The most important factor is NF-*κ*B which is up-regulated when T cells are activated. This means that HIV reproduction begins when T cells are fighting an infection, thereby providing a second load for the host's immune system (Hiscott et al, 2001). When the viral genome is transcribed from DNA to mRNA it first produces the Tat and Rev proteins. Tat proteins regulate the formation of new viral proteins (Ruben et al, 1989) and Rev proteins regulate other proteins which eventually lead to the transcription and transport of new viral RNA genomes (Pollard et al, 1998). After viral protein formation, protease cuts the proteins in the correct sizes. These proteins form a HIV membrane on the membrane of the host cell, than the RNA genome and proteins are transported to the HIV membrane and new virus particles are being assembled. After completion of the particle, they are released from the host cell membrane by budding.

Transmission of HIV

Sexual contact

Most HIV transmissions occur during sexual intercourse. The chance of contracting HIV when having sexual intercourse with an HIV-positive person is 0.04% per act when the virus transmits from a female to a male. When the transmission is from a male to a female the transmission rate is 0.08% per act. This is however in high-income countries and in low-income countries the chance of contracting HIV when having sexual intercourse with an HIV-positive person is 0.38% per act when the virus transmits from a female to a male. When the transmission is from a male to a female the transmission is 0.30% per act. This difference is probably due to the lower access to condoms and anti-retroviral drugs in low-income countries. The lower access to anti-retroviral drugs means that the mean viral load of HIV

infected people is higher in these areas, therefore transmission is more prevalent. When adjusted for commercial sex exposure these estimates were higher. Also genital ulcers, either in the past or present, in one of the sexual partners increase the risk of transmission. Studies on HIV transmission in anal intercourse showed that the chance of transmission is 1,7% per act, so a lot higher than during heterosexual intercourse (Boily et al, 2009).

Prevention of HIV transmission in sexual contact can be managed by using a condom. Other strategies to reduce HIV transmission via sexual contact are lowering viral load by anti-retroviral therapy and male circumcision. Male circumcision can be useful in lowering the rate of transmission because HIV can be present under the foreskin of HIV infected males, therefore increasing the rate of transmission. But after all practicing safe sex by using a condom remains the easiest, cheapest and best solution.

Blood to blood contact

Besides sexual context, HIV can also be transmitted by blood to blood contact. This can happen with blood transfusions, needle reuse and open wound contact. In the developed world, blood is almost always checked for HIV and needles are never reused in hospital. Therefore the chance of contracting HIV via that route is rather small. Drug addicts however, often reuse needles of other addicts and thus contribute to the transmission of HIV. In undeveloped countries the medical system is often not as strict as in developed countries and therefore the rate of HIV infection by blood to blood contact is much higher in those countries. The rate of transmission in blood transfusion with infected blood is approximately 90% per case (Donegan et al, 1990).

Vertical transmission

A third way of HIV transmission is vertical transmission. This means that the virus is transmitted from the mother to her child. Without any intervention the chance of transmission to a newborn from a HIV infected mother is about 25% (Coovadia, 2004). Transmission can happen before, during or shortly after birth as discussed in detail in the next chapter. The risk of infection is greatest during birth, because then the newborn contacts many possibly infected maternal substances (Coedert et al, 1991). The prevalence of vertical transmission during pregnancy is relatively low. A study by Brossard et al examined 100 aborted fetuses from HIV-1 infected mothers. Fetal thymuses were tested for HIV DNA by Polymerase Chain Reaction (PCR) and it appeared that only two fetuses were positive (Brossard et al, 1995). Far more prevalent is transmission during birth, there are several possibilities for transmission to occur. For example in vaginal delivery the risk of infection is greatest when

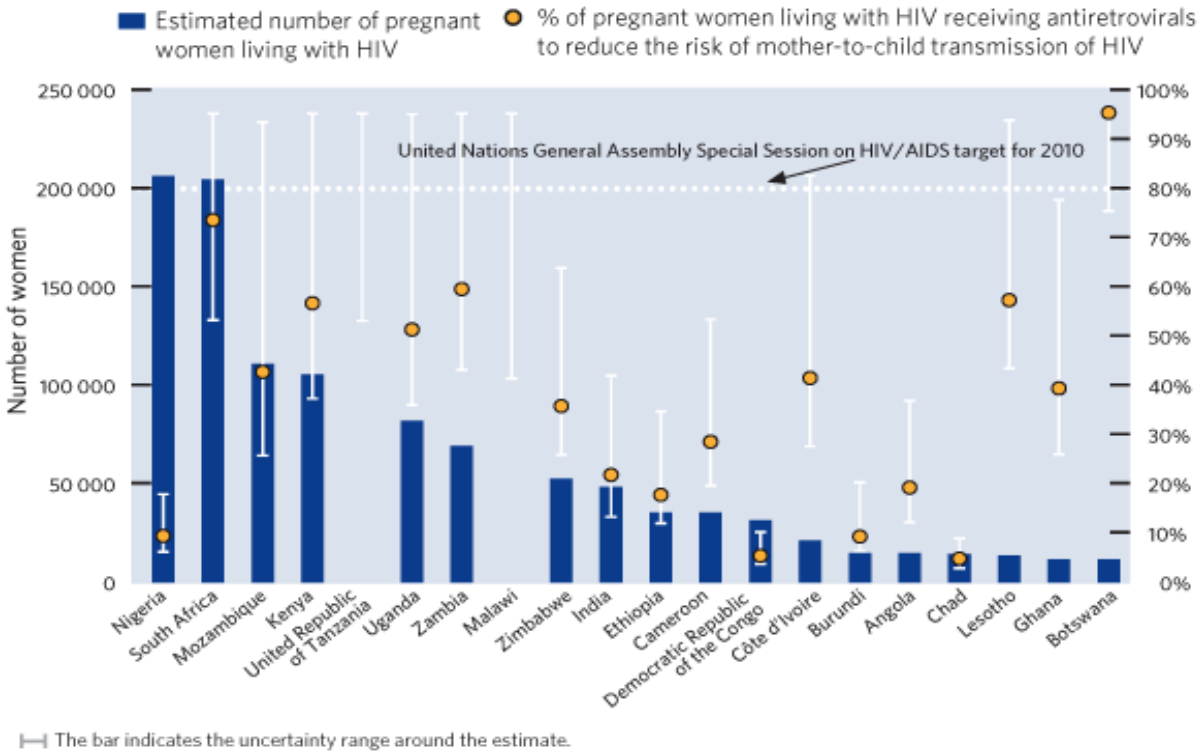


Figure 4. Number of pregnant woman living with HIV and percentage of HIV infected pregnant woman receiving anti-retroviral drugs in high prevalence countries. Nigeria and South Africa scoring high on prevalence of pregnant woman living with HIV. In Nigeria coverage of anti-retroviral therapy is about 10%, which is very low.

the baby passes the vagina and contacts cervicovaginal secretions, which may contain virus (Henin et al, 1993; Krevine et al, 1992). HIV transmission in the first year after birth is commonly due to breast feeding (Stiehm et al, 1991). This route of transmission poses a problem in developing countries because bottled milk is scarce and expensive, while water is often contaminated (Cutting, 1994). Because of this, breast feeding with a risk of HIV transmission often outweighs the risks posed by alternatives (Morrison et al, 1994; Coutsoudis et al, 2008).

Demographic prevalence for MTCT is closely related to the prevalence for HIV. Figure 4 shows that countries like Nigeria, South Africa and other countries in sub-Saharan Africa have significant numbers of pregnant women infected with HIV. Furthermore figure 4 shows that countries in this area of the world have low numbers of HIV positive pregnant women who receive combination anti retroviral therapy (cART). This is probably due to economical factors, but major challenges also exist in identifying pregnant women suffering from HIV. Furthermore cultural believes may have an impact, as does the scarcity in clean water and formula to give the newborn alternative feeding (Størdal, 2010).

Mechanisms of Vertical transmission

Perinatal transmission

Although most of the vertical HIV transmissions occur during birth, some 1.5 – 2.0% of the MTCT transmissions happen before birth (Dorenbaum, 2001). These are called trans-placental transmissions, because the virus has to cross the normally impermeable placental barrier. The placental barrier consists of Hofbauer cells (the macrophages of the placenta) which are shielded from the capillaries by a layer of trophoblast cells (Fig. 5). This barrier is permeable for nutrients and some immune components, but HIV is simply too large to cross the epithelial barrier in the maternal placental arteries by diffusion.

There is however evidence that HIV is capable of infecting Hofbauer cells, the macrophages of the placenta, in vitro (Newell et al, 1998). Further evidence shows that trophoblast cells can also be infected by HIV. Trophoblast cells seem to be only moderately susceptible to HIV infection (Moussa et al, 1999). Other research however shows that trophoblast cells are not HIV infected in pregnant woman with HIV (Soilleux et al, 2001; Tscherning-Casper et al, 1999). This would mean that the placenta is a good barrier against HIV and that previously mentioned results are due to insufficient techniques (Soilleux et al, 2003). But how then does HIV infect a fetus?

Research done with newer techniques suggest that Hofbauer cells can be infected, in the placenta during pregnancy of HIV-positive woman, by another route (Soilleux et al, 2003). It was shown that the HIV binding lectin DC-SIGN is present on Hofbauer cells in the placenta. Earlier literature states that these lectins are able to bind gp120, which is expressed at the envelope of the HIV virus and used in cis infection (Curtis et al, 1992). Other research indicates that HIV is capable of infecting fetal Hofbauer cells using the DC-SIGN lectin

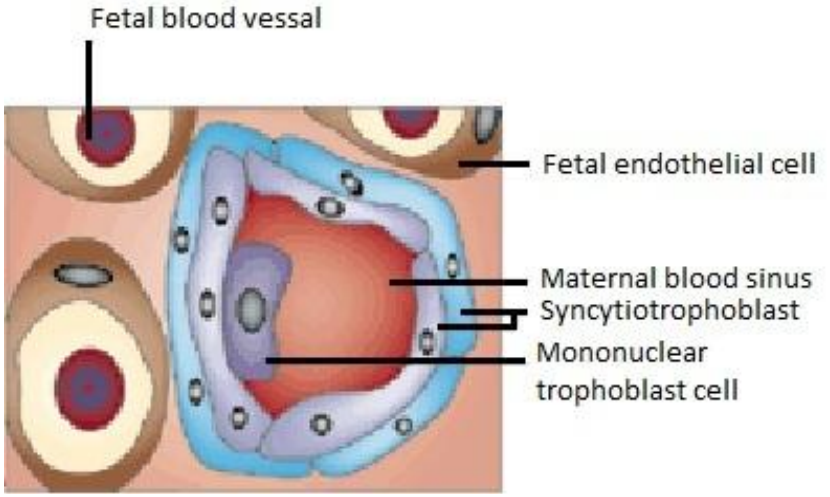


Figure 5. Anatomy of the placenta.
Nutrients are transferred from the maternal blood sinus to the fetal blood vessel. Hofbauer cells are present in the space between the maternal and fetal blood vessels. In MTCT of HIV, the virus is able to transfer from the mother to the fetus. The exact mechanism is however not known.
http://www.nature.com/nrg/journal/v2/n7/fig_tab/nrg0701_538a_F2.html

(Geijtenbeek et al, 2000). So it may be that via infecting Hofbauer cells, HIV is capable to transmit from the maternal blood vessel to the fetal blood vessel and so infect $CD4^+$ cells in the fetus.

Furthermore it has been shown in vitro that direct contact between the trophoblast barrier and a HIV infected cell can lead to transcytosis of the virus (Lagaye et al, 2001). This transcytosis can be either by infecting the trophoblast cell and budding on the basolateral side, or entering the trophoblast cell in a vesicle and be released on the basolateral side without infecting the cell. If transcytosis is possible in vivo is not yet known, but it could be that Hofbauer cells are infected in this way.

Once the virus has infected the Hofbauer cells, there are multiple theories about how the fetus is infected. The first theory is that HIV infected Hofbauer cells may enter the umbilical vein and migrate from there to the fetus. Secondly, infected Hofbauer cells remain in the chorionic villi where they present HIV to fetal T-lymphocytes and infect them, there is however evidence that T lymphocytes are not prominent in the chorionic villi so this theory seems unlikely (Soilleux et al, 2001). Thirdly, HIV may replicate and bud from Hofbauer cells so the free viral particles can bind to DC-SIGNR which is present on the endothelium of the capillaries leading to the fetus. This DC-SIGNR receptor is like DC-SIGN capable of binding HIV. Still the exact mechanism of trans-placental infection is not uncovered and more advanced research has to be done (Al-Husaini, 2009)

Intrapartum transmission

MTCT of HIV occurs most frequently during birth, especially when the newborn is passing the birth canal. Evidence for this comes from studies with twins, born from an HIV-positive mother. In twin birth, the first born twin spends more time in the birth canal and research indicated that these first born twins had an increased risk of contracting an HIV-1 infection (Coedert et al, 1991). A possible explanation is that cervical epithelial cell support HIV infection and HIV is found in cervical secretions in 40% of HIV positive pregnant woman (Tan et al, 1991; Henin et al, 1993). These cervical secretions are able to come into direct contact with the mucous membranes of the newborn and infect it. More evidence for transmission via cervical secretions comes from research where the time between rupture of the membranes and delivery was measured. It appeared that when this period lasted more than 4 hours, the risk of transmission to the baby was increased (Landesman et al, 1996). Another study done with women, positive for HIV, delivering vaginally or with non elective Caesarean section, showed that every extra hour between rupture of the membranes and delivery, the chances for the baby to contract HIV increased with 2%. (The International Perinatal HIV Group, 2001)

Besides cervical secretions, it is also possible that a newborn is infected during birth by infected blood from the mother, as a result of the transfusion of infected blood when the uterus contracts. This as a result of maternal blood loss due to the ruptured membrane or blood in the birth canal (Andiman et al, 2002). Because of the infection risk, vaginal delivery is nowadays generally avoided in the developed world. Instead a Caesarean section is now the common mode of delivery with HIV-positive pregnant women in these areas. But the risk with a Caesarean section is, that the baby contracts HIV via blood contact, due to the incision of the womb. But nevertheless in a large study it was shown that elective Caesarean section can reduce HIV transmission during birth by approximately 50% in comparison with other modes of delivery (The European Collaborative Study, 1994).

Breast feeding

Breast feeding is the way in which HIV is able to infect a child postnatally. This form of transmitting HIV was first discovered in 1985 and still poses a problem around the world (Ziegler et al, 1985; Horvath et al, 2010). Infection via breast milk is relatively easy to prevent by feeding the newborn with alternative feeding like formula and other breast milk substitutes. This however poses a problem in Third World countries, because alternative feeding is expensive and water is often contaminated causing diarrhea. Furthermore the benefits of breast feeding are well recognized including decreased infant morbidity and mortality rates by protecting against common childhood infections (Kramer et al, 2001). Moreover HIV-positive mothers who opt to feed their child with replacement feeding are stigmatized in many cultures, further complicating the prevention program concerning post-natal MTCT HIV infection (Rankin et al, 2005).

One important factor in breast feeding is the duration of the feeding. A meta-analysis of nine clinical trials in HIV-positive women in sub-Saharan Africa revealed that 42% of the MTCT of HIV was due to breast feeding and the cumulative probability increased as the duration of the breast feeding increased (from 1.6% at three months of age to 9.3% at 18 months of age)(Breastfeeding and HIV International Transmission Study Group, 2004). Other contributing factors increasing the probability of transmission by breast feeding are younger maternal age, higher parity, lower $CD4^+$ count and breast abnormalities (Miotti et al, 1999; Semba et al, 1999; Pillay et al, 2000; Embree et al, 2000). Breast abnormalities include for example inflammations, in which more immune cells are present in the breast, increasing HIV transmission.

Besides these maternal factors there also is a possible association between breast milk characteristics and MTCT of HIV. For example, Donovan and colleges found that lower concentrations of epidermal growth factor increase the risk of HIV-transmission. This effect

is probably due to the fact that epidermal growth factor decreases the permeability of the gastrointestinal tract for viral particles (Donovan et al, 1994). More factors in breast milk which possibly affect HIV transmission include lactoferrin, lysozyme and secretory leukocyte protease inhibitor (Harmsen et al 1995; Swart et al, 1996; Hocini et al, 2000).

Role of the mother in transmission

Viral load

The risk of vertical transmission depends maternally on a number of factors, one of them is viral load. Viral load is the number of virus particles per ml of blood. The viral load is very high in the beginning of infection and decreases over time. It rises again with the onset of AIDS. When an HIV-infected person is on treatment, the viral load can be close to zero. This however does not mean that the infection is cleared, because HIV is still present in cells in the immune system of the host. Besides viral load a second measurement of HIV severity is developed, namely the $CD4^+$ count. The $CD4^+$ count measures the number of $CD4^+$ cells per unit of blood and because HIV destroys $CD4^+$ cells when it reproduces, a decrease in $CD4^+$ cells means an increase in disease severity. Because of this it is harder for the mother to fight infections. These infections may harm the fetus and therefore a high maternal $CD4^+$ count and a less severe HIV infection is beneficial for the newborn (Ryder et al, 1988).

HIV subtype and genetic variability of the virus

Another factor involved in the rate of MTCT of HIV is the subtype of the virus. As said earlier HIV-1 is more infectious and virulent than HIV-2 (Gilbert et al, 2003), but is HIV-1 also the most prevalent in MTCT? In a study in Gambia, researchers took samples of pregnant women and did a PCR to determine the concentration of viral RNA. The results appeared to be that HIV-1 RNA concentrations are on average a 31-fold higher than HIV-2 RNA concentrations (O'Donovan et al, 2000). This result is in line with observations by Gilbert and colleges and suggests that HIV-2 MTCT rates will be lower. Many studies indeed found this effect and even failed to identify MTCT of HIV-2 (Coulter, 1993 ; Gayle et al, 1992 ; Poulsen et al, 1993). There are however some cases of MTCT of HIV-2, but they remain rather scarce (Buseyne et al, 1993; Morgan et al, 1990).

Besides HIV subtype, the genetic variability of HIV-1 also plays an important role in MTCT prevalence. Research done on the genetic variability of HIV-1 showed that genetic variation affects pathogenicity of the virus, by for example being able to replicate more

efficiently and so make more copies of the virus (Feyno et al, 1988; Roques et al, 1993; Klicks et al, 1994). Research in Rwanda also showed that having multiple partners prior to delivering a child increases the risk of MTCT (Bulterys et al, 1993). This is probably due to the contracting of HIV-1 multiple times with possibly different genetic makeup. This adds to the chance of contracting a higher virulent HIV-1 type.

Maternal nutrition

Adequate nutrition is essential for pregnant woman, especially when they are infected with HIV, because basal metabolism raises during infection (Ellen et al, 2005). Furthermore, research suggests that maternal malnutrition influences MTCT of HIV. It may do so by impairing fetal growth and the fetal immune system, therefore making the fetus more susceptible to HIV infection. Besides that, maternal malnutrition may impair the integrity of the placenta and the genital mucosal barrier of the mother and the gastrointestinal tract of the unborn. These things may facilitate MTCT of HIV, but data confirming these relationships are rather limited (Dreyfuss et al, 2002).

A lot of research has been done on the influence of maternal vitamin A levels on MTCT of HIV. Some researchers found that low levels of serum vitamin A is associated with shedding of HIV in genital-tract secretions and in breast milk (Nduati et al, 1995; Mostad et al, 1997). This however is in contrast with research done among non-pregnant and pregnant women in Kenya and Tanzania, where daily supplements of vitamin A had no effect or even an adverse effect on HIV shedding in the lower genital tract (Baeten et al, 2002; Fawzi et al, 2004). Another Tanzanian study showed that multivitamin supplements, consisting of vitamin B,C and E, during pregnancy and the breast feeding period improved the infants immune system. This vitamin therapy led to lower rates of MTCT of HIV in nutritionally and immunologically vulnerable pregnant woman, increased $CD4^+$ counts and delayed HIV disease progression (Fawzi et al, 2002; Fawzi et al, 2003; Fawzi et al, 2004). The beneficial effects of maternal nutrition could be due to the effects of micronutrients on the integrity of the epithelium in the placenta. Nutritional intake may also reduce inflammation of the breast tissue which can cause viral shedding (Dreyfuss et al, 2002)

Maternal co-infection

Research on the effect of co-infection with HIV in MTCT has particularly focused on infection with malaria. Because of the high prevalence of both HIV and malaria in sub-Saharan Africa, co-infections with the two are very common. In malaria co-infection with HIV, it has been shown that there is a trade-off between malaria and HIV, because malaria seems

to affect HIV infection and vice versa (Ter Kuile et al, 2004). Steketee and colleagues have shown that HIV infection increases the risk of malaria parasitemia at the time of delivery and in the placenta. Besides that, research also showed that malaria parasite density was increased in pregnant HIV positive woman (Steketee et al, 1996). This effect is predominantly seen in multigravidae, but is in lesser extent present in primigravidae and secundigravidae.

It was indicated by Hoffman and colleagues that malaria co-infection increases HIV viral load. It does so by activating the immune system and therefore the transcription factor NF-*κ*B which is necessary for HIV to start its replication cycle (Hoffman et al, 1999). This increase in viral load of HIV also occurs in pregnant HIV and malaria-positive women (Inion et al, 2003). Viral load is an important factor in MTCT of HIV, but research results are heterogeneous (Ter Kuile et al, 2004). So it is not clear whether maternal malaria enhances MTCT of HIV. Research in Kisumu in western Kenya even indicates that maternal malaria may have a protective effect on MTCT of HIV in some cases (Ayisi et al, 2004).

Role of the infant in vertical transmission

Cytotoxic T cells and natural killer cells

HIV infection of the infant does not occur in the majority of pregnancies with an HIV-positive mother. This is partly due to the low infectiousness of HIV, but research has indicated that the immune system of the newborn may play a role in preventing vertical transmission, despite its immaturity (Morrison et al, 1994). A study done with 29 HIV-1 mother-to-child infected newborns showed that four children became sero-reverted after several months (Buseyne et al, 1993). The problem, however, with this study is that maternal HIV antibodies are present several months in the infant after birth, which makes the study unreliable. However in another study it was found that, in 25% of the uninfected children born from HIV-1 infected mothers, had HIV-specific cytotoxic T cell activity against different proteins like enf and gag (De Maria et al, 1994). How this specific activity of cytotoxic T cells can occur is however not clear.

A recent study found that mothers and infants who have natural killer cells targeted against HIV-1 proteins are less susceptible for HIV-1 transmission and infection. These natural killer cells respond to the Env and Reg proteins, while T cells in chronic infection target more conserved proteins of HIV (Tiemessen et al, 2009). This difference in antigen targeting could be the link why without intervention only 25% of the children, born from HIV infected mothers, are infected. This is strengthened by other researchers who found that

infants with an acute infection of HIV displayed HIV specific responses of $CD8^+$ and $CD4^+$ T cells (Shalekoff et al, 2009). How these findings relate to the earlier described findings of De Maria and colleagues, that a $CD8^+$ cytotoxic T cell response is seen in uninfected children from infected mothers, is not yet clear.

Prevention of mother to child transmission of HIV

Anti-retroviral therapy

Today MTCT of HIV is a rather rare event in developed countries, but still in 2008 370000 newborns were infected with HIV due to MTCT, of which 90% lives in sub-Saharan Africa (UNAIDS, 2008). Anti-retroviral therapy access has improved drastically in low-and middle-income countries during the last 3 years, reaching up to 42% of the population in need of therapy. But the other two third of the 9,6 million people in need of therapy have yet to get access (Fig. 6). A great problem in MTCT of HIV is that only 18% of the pregnant women in low-and middle-income countries received an HIV test in 2007, although it has increased in the past years (WHO, 2008). Furthermore, once an HIV-infected pregnant woman is identified, there are not always resources to put her on therapy. Partly because of that, only 45% of the pregnant HIV-positive woman in sub/Saharan Africa received HIV therapy in 2008. (Towards universal access. WHO. 2009)

Nowadays HIV-infected people are treated with combination antiretroviral therapy (cART). Because of this therapy, MTCT of HIV in well resourced countries has dropped to below 1-2% (UNAIDS, 2008). This treatment is however scarce in sub Saharan Africa so HIV infected pregnant woman there are not always able to get cART. But research suggests that a simple single dose nevirapine-based treatment is also effective, averting an estimated 30000 MTC infections in 2004 and 2005. This is however limited because HIV becomes

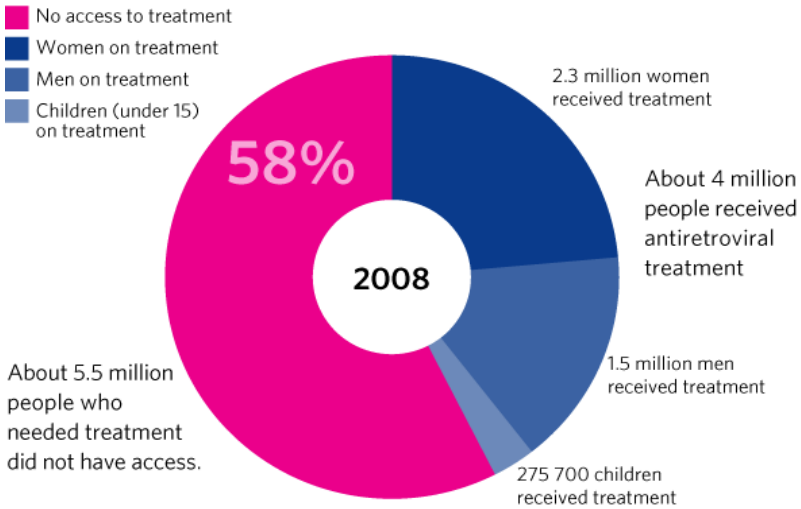
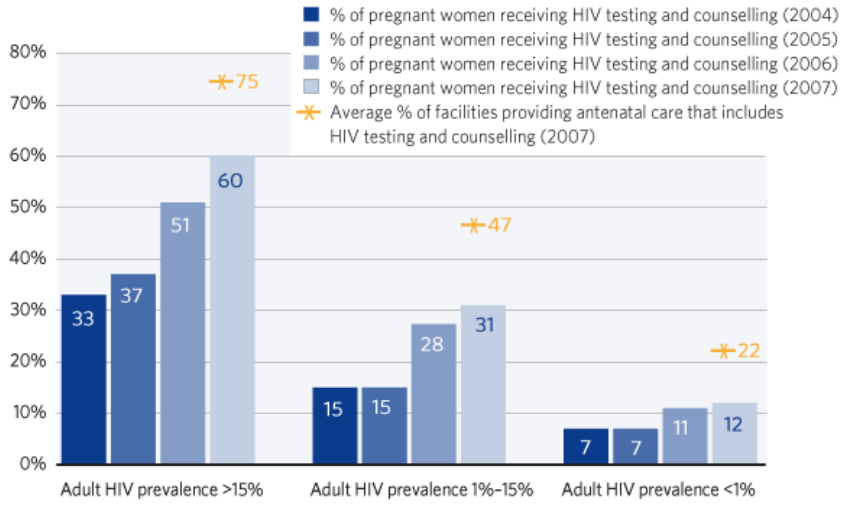


Figure 6. People in need of HIV therapy in low and middle income countries.
9.6 million people were in need of HIV treatment in low and middle income countries in 2008. Only 42% has access to treatment.

quickly resistant to treatment with only one antiretroviral drug , like nevirapine. (Lehman et al, 2009). Nevertheless experts assume that the number of averted MTCT's will probably rise in the future, because the increase in anti-retroviral drug access like cART in low income countries (Boeke et al, 2008).

As earlier mentioned, breast feeding of the infant often remains the only choice in HIV infected mother in sub-Saharan Africa, increasing the risk of HIV transmission. But recent studies show that cART treatment of the mother during breastfeeding reduces the risk of transmitting HIV, achieving a transmission rate of only 1,9% after 18 months of age (WHO, 2008; Mofenson, 2008). In another study it was shown that short term CART even had an effect in mothers with low $CD4^+$ cell counts between 200-350 cells/µl, achieving a transmission rate of 6.1% at 12 months of age. CART appeared however to be less effective, among mothers with a $CD4^+$ count between 350-500 cells/µl, in decreasing the rate of MTCT via breast milk (de Vincenzi, 2009)



Figuur 7. Percentage of pregnant women tested for HIV, by prevalence level in adult population.
HIV testing and counseling from 2004 to 2007, sorted by area prevalence. In the high prevalence areas and significant increase is seen in testing and counseling, up to 60% in 2007.

Mode of delivery

Elective Caesarean section at 38 weeks of pregnancy, before rupture of the membranes or onset of labor, can reduce the MTCT by 50-80% (Brockleburst, 1999) and can even by further reduced by combining caesarean section with anti-retroviral therapy to approximately 2%. But when the viral load is below 1000 virus particles per ml, there is no evidence that Caesarean section outweighs vaginal delivery in reducing MTCT of HIV. In fact, the risk of infectious complications raises severely (Surjushe et al, 2008). Therefore

Caesarean section should only be done when the mother is unable to reach a viral load of <1000 viral particles per ml. Furthermore Caesarean section is expensive, especially in Third World countries and is therefore not an ideal prevention method in these areas.

Informing HIV positive pregnant woman and mothers

To prevent MTCT of HIV, counseling for child bearing aged woman is necessary. In Africa many people live in rural areas where counseling and HIV testing is not readily available, and therefore pregnant woman do not always have resources to be tested for HIV. Therefore projects have been started to increase counseling and HIV testing in undeveloped countries. For example in Kenya where the testing policy was changed from opt-in to opt-out. But because of poor managing , HIV testing kits storages were soon depleted (Sripipatana, 2006). In a study in Malawi in 2005, the University of North Carolina changed from a opt-in to a opt-out policy. This change resulted in a increase of counseling up to 75-100%, and in a HIV testing rate of 98% of the counseled woman (Zimba et al , 2006). Overall coverage of counseling in high prevalence countries is, due to projects and policy changes, increasing rapidly. This resulted in a testing and counseling rate of 60% in 2007 (Fig. 7)

Conclusion

There has been done extensive research into the mechanisms, risks and prevention of MTCT of HIV and most of the mechanisms behind it are uncovered today. Besides the progress in fundamental research on MTCT of HIV, prevention and risk avoidance of HIV infections is increasingly efficient. In part thanks to prevention of MTCT, recent numbers of the WHO show that HIV prevalence is leveling off. While in past years, the prevalence was rising steadily each year. Furthermore the number of newly infected people is declining. This is also partly due to the prevention of MTCT of HIV. Unfortunately there are still infants born with HIV primarily in low-income sub-Saharan Africa. Therefore there is still more research to be done and actions to be taken to prevent HIV from infecting more newborns.

To reach the goal of less MTCT of HIV, more counseling and HIV testing should be available, because in high prevalence areas only 60% of the pregnant woman received an HIV test. Therefore not all HIV positive pregnant woman are identified and get treatment. Numbers of the WHO show that in sub-Saharan Africa, only 45% of the pregnant woman in need of anti-retroviral drugs received them. So if counseling, testing and treatment accessibility can be globally upgraded MTCT of HIV can be stopped some day.

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