# Chapter 18
# Bloodborne and Sexual Transmission: HIV/AIDS

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## 18.1 HIV-1 Pandemic

In 2007, approximately 33 million people were estimated to be living with human immunodeficiency virus (HIV)-1 worldwide. An estimated 2.5 million became newly infected with HIV-1 that year, while an estimated 2.1 million died of AIDS. This means that everyday almost 6,850 people are newly infected with HIV-1, and over 5,750 die from AIDS, mostly because of inadequate access to HIV-1 prevention and treatment services. In the 27 years since the first cases of AIDS were described, approximately 20 million people have died from AIDS.

HIV-1 infection predominantly strikes young, sexually active adults, and children. This has an important impact on the social and economical situation in countries with a high HIV-1-prevalence, because this way the people who can make the largest contribution to the social structures and economical vitality in a region are lost through illness or death.

Worldwide most new HIV-1 infections are transmitted heterosexually or from mother to child. Depending on the geographic region, a sizeable proportion of new HIV-1 infections are attributable to other risk factors like male homosexual contact or injecting drug use.

### *18.1.1 Sub-Saharan Africa*

Sub-Saharan Africa is the region with the largest burden of the AIDS epidemic, more than two thirds of all HIV-1-positive people live in this region and about three quarters of all AIDS deaths in 2007 occurred in sub-Saharan Africa. Approximately 1.7 million people were newly infected with HIV-1 in 2007, bringing the total number of HIV-1-infected individuals in the region to 22.5 million. The HIV-1 epidemic

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in sub-Saharan Africa is mainly driven by heterosexually transmitted infections. Therefore, and unlike HIV-1 epidemics in other parts of the world, the majority of people living with HIV-1 in sub-Saharan Africa (61%) are women.

Southern Africa is the most gravely affected region of sub-Saharan Africa. In 2005, national adult HIV-1 prevalence exceeded 15% in 8 countries (Botswana, Lesotho, Mozambique, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe). In studies among women attending antenatal care in South Africa, prevalences as high as 30% have been reported. In most countries in southern Africa the epidemics seem to be plateauing (UNAIDS 2008).

### *18.1.2 Europe and North America*

The World Health Organization (WHO) calculated that in 2007 there were an estimated 740,000 people living with HIV-1 or AIDS in Western and Central Europe. The largest proportion of new HIV-1 diagnoses is heterosexually acquired, mainly in migrants and immigrants from high endemic countries. In Western Europe in 2007, approximately 30% of new HIV-1 diagnoses were among men having sex with men (MSM). Only 6% was attributable to injecting drug use. Between 1999 and 2006 the number of new HIV-1 diagnoses attributed to unsafe sex between men nearly doubled, while those attributed to injecting drug use declined in the same period. In Spain and Portugal, countries where injecting drug use is more prevalent than in the rest of Western Europe, the majority of new HIV-1 infections occurs through the use of contaminated equipment by injecting drug users (IDU). There has been an increase in the number of new HIV-1 diagnoses in Western Europe since 2002, opposed to a relatively stable number of new HIV-1 infections each year in North America. This discrepancy is probably partly explained by an increase in HIV-1 testing resulting from a change in HIV-1 testing policy in Europe. As many as 30% of people infected with HIV-1 in Europe may be unaware of their HIV-1-status. People who are unaware of their HIV-1-status cannot benefit from treatment and care and may transmit HIV-1 to others. Almost universal access to effective antiretroviral treatment (ART) has helped to keep the number of AIDS-related deaths in these regions comparatively low.

Like in Western Europe, the most important risk factor for HIV-1 is unsafe sex between men in the United States and Canada. Furthermore, racial and ethnic minorities have a higher HIV-1 prevalence (UNAIDS 2008; EuroHIV 2007).

### *18.1.3 Former Soviet Union and Central Asia*

Approximately 150,000 people were newly infected with HIV-1 in 2007, bringing the number of people living with HIV-1 in Eastern Europe and Central Asia to approximately 1.6 million people. This is a 1.5-fold increase compared to the situation in 2001. The majority (90%) of the new infections were in two countries: the Russian Federation and Ukraine. Also in Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, the Republic of Moldova, Tajikistan, and Uzbekistan the annual numbers of newly reported HIV-1 diagnoses are rising. The driving force behind the

epidemic in Eastern Europe and Central Asia is injecting drug use; nearly two thirds of the new HIV-1 infections could be attributed to this route of transmission. In the Baltic States (Estonia, Latvia, and Lithuania), where the epidemics appear to have stabilized, injecting drug use is also the most-reported mode of HIV-1 transmission (UNAIDS 2008).

### *18.1.4 Southeast Asia*

In Southeast Asia the HIV-1 epidemic is widespread and behaves differently in different countries. In some countries HIV-1 prevalence is declining (i.e., Cambodia, Myanmar, and Thailand), while in others (e.g., Indonesia) the epidemic is increasing.

In China, injecting drug use has been the most important driving force behind the HIV-1 epidemic; however, heterosexual transmission is an increasingly important issue. The Chinese Ministry of Health and UNAIDS estimated that half of new HIV-1 infections were due to injecting drug use, and half to unprotected sex. One of the problems China is facing is the overlap between injecting drug use and commercial sex work, with many female IDUs selling sex and many male IDUs buying sex, often without using condoms. In the larger Chinese cities, the HIV-1 epidemic among MSM is also rising, with some studies reporting a HIV-1 prevalence of 1.5–4.6% (UNAIDS 2008; Liu et al. 2006).

### *18.1.5 Other Areas of the World*

No region of the world has remained untouched by the HIV pandemic. In Asia, besides Southeast Asia, the main mode of acquisition is through injecting drug use, and the prevalence in the general population remains low. The available epidemiological data for the Middle Eastern and North-African region is limited. It is estimated that there are 380,000 people living with HIV-1 in this region.

In the Caribbean the prevalence of HIV-1 in adults is estimated to be 1.0%; the main mode of transmission is through unprotected sexual intercourse. In Central and South America the HIV-1 epidemic remained stable in the past years with higher HIV-1 prevalence in high-risk populations, i.e., MSM and commercial sex workers.

About three quarters of the people living with HIV/AIDS in Oceania live in Papua New Guinea, where the HIV-1 prevalence in adults is 1.8%. In Australia and New Zealand the most new HIV-1 infections occur in MSM (UNAIDS 2008).

## 18.2 HIV Pathogenesis

### *18.2.1 Virology*

#### 18.2.1.1 HIV-1

The probable origin of HIV-1 in humans is the introduction of simian immunodeficiency virus (SIVcpz) from chimpanzees (*Pan troglodytes*) in the human population,

while HIV-2 has originated from SIVsm in sooty mangabeys (*Cercocebus atys*). The worldwide pandemic is caused by HIV-1. Based on molecular epidemiological models it is estimated that HIV-1 was introduced in the human population in the mid-20th century. Phylogenetic analyses have shown that there must have been at least three distinct introductions of HIV-1 in the human population. These three introductions – originating from different three SIVcpz subtypes – gave rise to the three HIV-1 lineages: M-, N-, and O-group (Main, non-M-non-O, and Outlier group). Within the M-group nine subtypes exist (named A through K). HIV-1 viruses from the M-group are most widespread and have originated from a *lentivirus* found in *Pan troglodytes troglodytes*. Individuals infected with viruses from the O-group originate mainly from Cameroon, Gabon, and Equatorial Guinea and the viruses have originated from a *lentivirus* in a distinct Chimpanzee subspecies, *Pan troglodytes schweinfurthii*. Group N was most recently discovered and it has spread the least, it has been documented in individuals from Cameroon. This virus is a mosaic of SIVcpz and HIV-1-related sequences, indicating a recombination event in an ancestral chimpanzee host. The clinical course of infection with diverse subtypes is similar.

#### 18.2.1.2 HIV-1 Lifecycle

When a cell is infected with two different HIV-1 subtypes, the viruses can swap parts of their genetic material (i.e., recombination). When the resultant virus recombinant is found in one individual, this new virus is called a unique recombinant form. When recombinant forms are found in at least three individuals that cannot be epidemiologically linked to each other, this recombinant form is called a circulating recombinant form (CRF). In some parts of the world, these CRF contribute substantially to the epidemic (e.g., in Thailand AE-CRF).

HIV-1 infected individuals can be infected with another HIV-1 virus after their initial infection, so-called superinfection.

HIV-1 is a retrovirus and belongs to the family of lentiviruses. When HIV-1 enters the human body via mucosal membranes (e.g., sexual transmission) or via direct injection in the bloodstream (e.g., injecting drug use, blood transfusion), it binds to a CD4 receptor and a coreceptor on the cell surface. The virus undergoes a conformational change and fuses with the cell membrane. The HIV-1 RNA is released into the cell. Next, HIV-1 reverse transcriptase transcribes single-stranded HIV-1 RNA into double-stranded HIV-1 DNA. This HIV-1 DNA is then transported to the cell nucleus, where it is integrated in the host DNA, this is called a provirus. The provirus can remain inactive in the host DNA for years without producing new HIV-1 copies. The formation of new HIV-1 copies starts when (host) RNA polymerase transcribes the provirus into HIV-1 RNA and messenger RNA (mRNA). The HIV-1 enzyme protease cuts the long chains of HIV-1 proteins into smaller individual proteins. Once these proteins and HIV-1 RNA come together, new HIV-1 particles are formed. These newly formed HIV-1 particles bud out of the cell, and while doing that they also use some of the cell membrane as their envelope. This envelope is heavily covered with so-called glycoproteins, necessary for binding to CD4 and

other cell surface receptors. The newly formed viruses can now move further and infect other cells (Geretti 2006; Coakley et al. 2005; Kanki et al. 1997).

#### 18.2.1.3 HIV-2

HIV-2 has approximately 60% genetic homology with HIV-1, but is transmitted at a lower rate and the clinical course is much more benign. However, progression to AIDS does occur and some patients will require therapy. HIV-2 is more or less geographically restricted to West Africa, and HIV-2 infected people in other regions of the world are mostly epidemiologically linked to this region. The genomic arrangement of HIV-2 is indistinguishable from SIVsm, the two viruses are phylogenetically closely related and the sooty mangabey natural habitat coincides with the epicenter of the HIV-2 epidemic. The prevalence of SIVsm is high in wild-living sooty mangabeys. Close contact between humans and sooty mangabeys is common because the monkeys are hunted for food and they are kept as pets. It has been proposed that at least six independent transmissions of SIVsm to humans have taken place (Myers et al. 1992; Stebbing and Moyle 2003; AIDSinfo 2008; Peeters 2000).

### *18.2.2 Immunology*

HIV-1 uses two different types of receptors for attachment to target cells and viral entry. First the envelope protein gp120 attaches to the CD4 molecule expressed mainly on the surface of helper T lymphocytes and macrophages. Viral binding to CD4 is crucial, but for viral entry also coreceptors are needed. Interaction between CD4 and gp120 increases the affinity of virus for coreceptor molecules. The two most important HIV-1 coreceptors, CCR5 and CXCR4, are differentially expressed on subpopulations of CD4-expressing cells. Viruses differ in ability to attach to different coreceptors and can be defined by coreceptor use. The coreceptor usage of a HIV-1 virus is determined by genetic variation in HIV-1 envelope domains. Host genetic polymorphisms or deletions within the gene coding for CCR5 diminish or abrogate viral binding to the coreceptor, which leads to a lower susceptibility to infection and slower disease progression in such persons (e.g., CCR5$\Delta$32 deletion) (Coakley et al. 2005).

In the first weeks after HIV-1 infection, there is a massive depletion of $CD4^+/CCR5^+$ memory T cells in all mucosal surfaces. Normally, the largest pool of memory $CD4^+$ T cells in the body resides in submucosal areas. This depletion is caused by target cell infection and virus-induced apoptosis. In the acute phase of HIV-1 infection, HIV-1 viremia can reach very high levels of more than $1 \times 10^6$ HIV-1-RNA copies/mL.

After approximately 6 months the plasma HIV-1-RNA concentration stabilizes, and this more or less stable level is called the viral setpoint. This viral setpoint is one of the strongest predictors of the time of progression to AIDS, independent of age at time of infection. Although the rate of progression from infection to AIDS is multifactorially determined, individuals with a higher viral setpoint typically have

a faster progression to AIDS than individuals with a lower viral setpoint. There is a strong correlation between the height of the viral setpoint and the amount of immune activation, as measured by immune activation markers like CD38 and HLA-DR or proliferation markers like Ki67. Individuals with a high viral load have higher levels of immune activation.

The CD4 decline eventually leading to AIDS is attributed to the chronic immune activation that is caused by the high amount of virus present in the blood. This idea is supported by studies showing that in patients that are treated with highly active antiretroviral therapy (HAART) the activation status of $CD4^+$ T cells normalizes while the CD4 count has not yet returned to normal levels.

## 18.3 HIV-1 Transmission

### *18.3.1 Sexual Transmission*

Although HIV-1 has been isolated from many body fluids of HIV-1 infected individuals, the virus is only transmitted through contaminated blood and blood products, semen, vaginal fluids, and breast milk. Worldwide, most HIV-1 infections are transmitted sexually. The probability of sexual transmission is a function of infectivity, susceptibility, and type of sexual practice. These factors are closely interconnected, with each individual factor influenced by several aspects. HIV-1 blood plasma viral load (BPVL) is the strongest predictor of sexual HIV-1 transmission with higher BPVL associated with an increased infectivity, probably through increased genital HIV-1 viral loads (Chan 2006). High BPVL is observed during primary HIV-1 infection and advanced HIV-1 disease. The risk for HIV-1 transmission is calculated to increase by 8–10 times during primary HIV-1 infection (Wawer et al. 2005).

In Table 18.1, risks of HIV-1 transmission per exposure to a known HIV-1 positive source are presented (Eurosurveillance 2004). For sexual transmission, receptive partners are at greater risk for HIV-1 acquisition through unprotected sex compared with insertive partners. The odds ratio (OR) for male to female HIV-1 transmission is 2–3 times higher than the OR for female to male transmission. The

**Table 18.1** HIV-1 transmission risk per exposure to a known HIV-1 positive source (Almeda et al. 2004)

| Type of exposure | Risk of HIV-1 transmission per exposure (%) |
|---|---|
| Receptive oral sex | 0– 0.04 |
| Insertive vaginal sex | $\leq 0.1$ |
| Insertive anal sex | $\leq 0.1$ |
| Receptive vaginal sex | 0.01– 0.15 |
| Receptive anal sex | $\leq 3$ |
| Accidental needlestick | 0.2–0.4 |
| IDU sharing needle | 0.7 |
| Transfusion | 90–100 |

larger anatomical surface area of the vagina, with a higher number of HIV-1 susceptible cells, might be a biological explanation for this difference. Unprotected receptive anal intercourse with a known HIV-1 positive partner is associated with the highest sexual transmission risk. Rectal mucosa is easily ruptured, providing an entry point for HIV-1 and the lymphoid tissue of the gut wall contains many lymphocytes which are targets for HIV-1. Risk for HIV-1 transmission for women during unsafe receptive vaginal intercourse varies between 0.01 and 0.2% per coitus for serodiscordant couples. For oral-genital sexual contacts the risk of HIV-1 transmission is thought to be very low. Transmission risks are shown in Table 18.1 and discussed in Chapter 7.

Sexually transmitted infections (STI) increase both the infectiousness of HIV-1 infected individuals as well the susceptibility for HIV-1 acquisition of those uninfected. Genital tract inflammation increases the genital shedding of HIV-1, most likely as the result of locally released cytokines as well as leakage of HIV-1 from the blood plasma. The number of activated target cells for HIV-1 ($CD4^+$ T cells and macrophages) may be increased by several bacterial and viral STI, leading to an increased susceptibility. In addition, STI can cause (micro) ulcerations that may bleed, thereby increasing both the infectiousness of and the susceptibility to HIV-1.

The most common ulcerative genital disease worldwide, caused by Herpes simplex virus type 2 (HSV-2), is associated with 4.5 times increased infectivity and susceptibility for HIV-1 infection (Wald and Link 2002; Corey et al. 2004). Recent acquisition of HSV-2, compared with prevalent HSV-2 infection, carries a higher risk of HIV-1 transmission, while asymptomatic and symptomatic HSV-2 infection carry almost the same probability of acquiring HIV-1 per coital act. Most HSV-2 reactivations are subclinical, but mucosal damage and lymphocytosis occur during this phase as shown by microscopy. HIV-1 is associated with an increased rate of reactivation of HSV-2, with the rate of reactivation correlated to CD4+ T-cell count and HIV-1 BPVL (Schacker et al. 1998). Non-ulcerative STI, like gonorrhea and *Chlamydia trachomatis* infection can increase both infectivity and susceptibility to HIV transmission. Additionally, several other factors influence sexual HIV-1 transmission. Systemic illnesses, opportunistic infections, as well as recent vaccinations may increase the HIV-1 BPVL, increasing HIV-1 infectivity (Chan 2006). Nonspecific urethritis is associated with increased susceptibility for HIV-1. Cervicitis, pelvic inflammatory disease, and bacterial vaginosis, associated with low concentrations of hydrogen peroxide-producing lactobacilli, appear to increase the risk of HIV-1 acquisition (Fig. 18.1).

### *18.3.2 Blood and Blood Products*

IDU are at risk for HIV-1 infection through sharing of needles and syringes and borrowing and lending of other paraphernalia. The risk for HIV-1 transmission through the sharing of needles and syringes is approximately 0.7% (Eurosurveillance 2004)

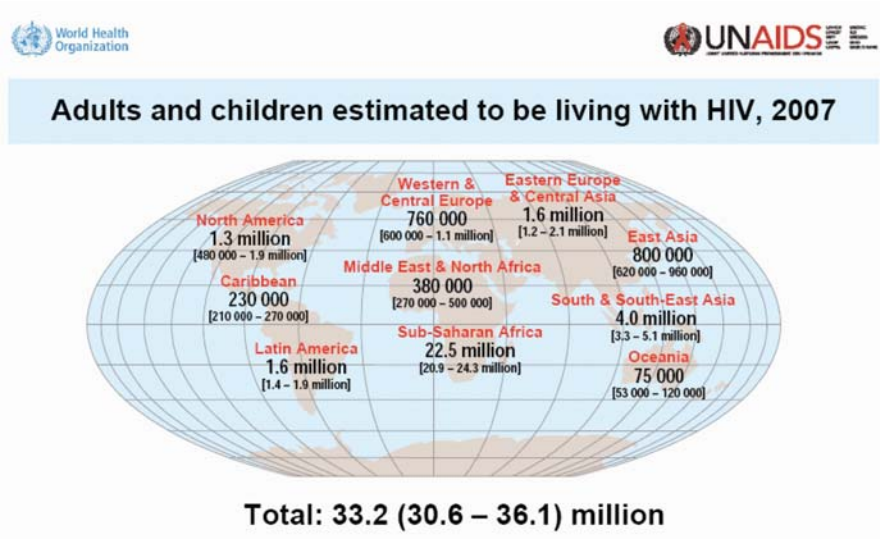


**Fig. 18.1** Worldwide distribution of HIV-1 infections. Reproduced with kind permission from UNAIDS (www.unaids.org)

per act. Increased inoculum size is associated with an increased risk of HIV-1 transmission.

Transfusion of HIV-1 infected blood and blood products carries a 90–100% chance of HIV-1 transmission. In the early 1980s, before the implementation of safe methods to make blood products, many hemophiliacs were infected with HIV-1.

### *18.3.3 Mother-to-Child Transmission*

Worldwide, mother-to-child transmission (MTCT) is the primary mode of HIV-1 acquisition among children. HIV-1 transmission can occur during pregnancy, labor, or breast-feeding. In non-breast-feeding women, the estimated risk of HIV-1 MTCT is between 15 and 25%, while this risk varies between 25 and 40% in breast-feeding populations (Dao et al. 2007). High maternal HIV-1 BPVL and preterm delivery are risk factors for HIV-1 transmission. Vaginal delivery carries an increased risk of MTCT, compared to elective caesarean section (before labor and before ruptured membranes). HIV-1 transmission through breast-feeding accounts for about 33–50% of all HIV-1 MTCT in resource-limited settings where breast-feeding into the second year of life is the norm. Some studies have suggested that the highest risk of breast milk transmission is in the immediate neonatal period but it is difficult to differentiate between early breast milk transmission and intrapartum transmission. However, two studies showed a high risk of HIV-1 transmission in the first weeks of life through breast-feeding, compared to those who gave formula from birth. In breast milk of infected women HIV-1 viral load was found to be highest

immediately after delivery. The risk of HIV-1 transmission per month of breast-feeding was calculated to be 0.6–0.7% in the first year of life and 0.3% in the second year in a study in Malawi. However, a recent meta-analysis showed a more constant risk of about 0.9% per month after the first month of life. Risk factors associated with postnatal HIV-1 transmission include higher HIV-1 viral load in plasma and in milk, decreased maternal $CD4^+$ T-cell count, mastitis or breast milk stasis, oral thrush of the baby, and longer duration of breast-feeding. Additionally, breast- and formula-feeding combined, versus exclusive breast-feeding, is associated with a higher HIV-1 transmission. This might be explained by intestinal mucosal damage or immune activation, providing a port of entry for HIV-1.

## 18.4 HIV-1 Disease Progression

### *18.4.1 Natural History*

HIV-1 infects $CD4^+$ T lymphocytes, thereby destroying and harming important players in the immune reaction against foreign pathogens. The natural history of HIV-1 infection can be divided in three phases: acute 'primary' HIV-1 infection, the chronic phase of infection, and the last stage: AIDS (acquired immunodeficiency syndrome).

The primary HIV-1 infection can take up to 6 months. During this phase, most patients remain asymptomatic, approximately one-third of patients suffer from a-specific flu-like symptoms. During acute HIV-1 infection, the number of HIV-1 copies in plasma is usually very high and there is frequently a simultaneous drop in $CD4^+$ T-cell count.

After acute infection, infected persons remain asymptomatic for years during chronic infection. During this period however, the $CD4^+$ T-cell count continues to decrease gradually. The median time without treatment from acute infection to the AIDS is 8–10 years, but this varies widely between individuals (Collaborative Group on AIDS incubation and HIV survival 2000).

Host genetic factors play a role in susceptibility to HIV-1 infection and are the main determinants of the time from infection to development of AIDS. Since HIV-1 uses CCR5 as coreceptor for host cell entry, a normal structure of this molecule is required for infection. People with a certain genetic variation of their CCR5-molecule have a truncated form of this molecule ( CCR5$\Delta$32), and are less vulnerable to infection after exposure. While some individuals develop AIDS fast, approximately 5% of HIV-1 infected individuals are so-called long-term non-progressors and can take more than 20 years to progress to AIDS. One of the major host genetic factors associated with long-term non-progression are the human leukocyte antigens (HLA) B27 and HLA B57, molecules involved in presenting antigens to the immune system.

It has been suggested that geographic factors and behavior influences the rate of progression to AIDS. However, the overall time span is the same for all individuals and is not dependent on demographic factors (e.g., where one lives: tropics or

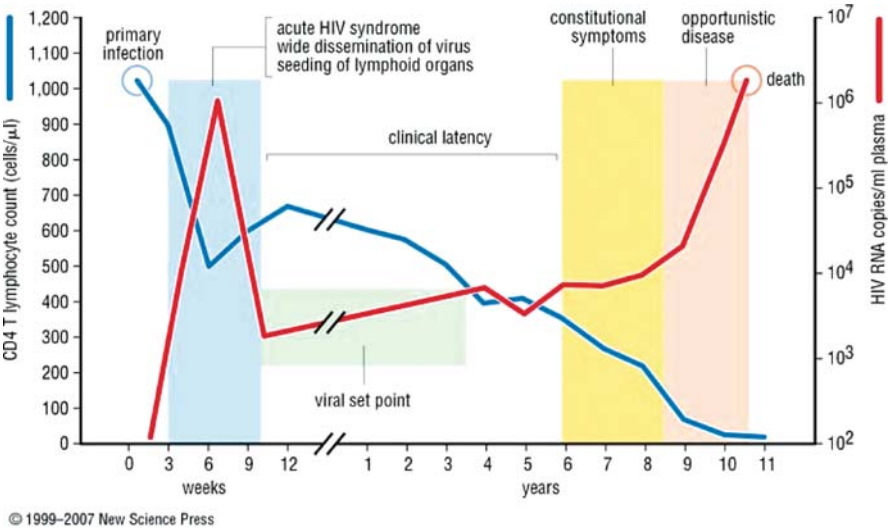


**Fig. 18.2** The natural history of HIV [(reproduced with permission from Immunity by AL DeFranco, RM Locksley and M Robertson (New Science Press, London, 2007)]

western world) or on acquisition route (e.g., how one contracted HIV-1: injecting drug use, unsafe homosexual, or heterosexual contact). Age does influence the rate of progression to AIDS, older individuals progress faster to AIDS than do younger individuals (Pezzotti et al. 1996) (Fig. 18.2).

## *18.4.2 Opportunistic Infections and Coinfections*

As the immune system deteriorates during the course of HIV-1 infection, infections with other micro-organisms or viruses that do not necessarily cause illness in immunocompetent hosts, can cause severe morbidity and mortality. Opportunistic and coinfections with other micro-organisms or viruses in HIV-1 infected individuals cause a great increase of HIV-1-related morbidity and mortality. Some micro-organisms share geographic regions or routes of transmission. When the $CD4^+$ T-cell count drops below 200 $CD4^+$ T cells/mL, the risk of opportunistic infections increases dramatically. Also cancers in which a viral pathogenesis is involved (e.g., human herpes virus 8 (HHV-8) in Kaposi's sarcoma, Epstein–Barr virus in Burkitt lymphoma) have a higher incidence in HIV-1 infected individuals.

### 18.4.2.1 Tuberculosis

Tuberculosis (TB) is caused by infection with *Mycobacterium tuberculosis*. After infection with *M. tuberculosis* some persons develop disease early, while in others it causes latent infection and is not infectious for the surrounding. When active TB

develops, the mycobacterium can be transmitted to other people. HIV-1 infection is the strongest risk factor for the development of active TB. TB is an aggressive opportunistic infection that arises at higher median CD4 counts than other opportunistic infections. HIV-1 also increases the risk of rapid TB progression after infection or re-infection with TB. TB is the leading cause of death among HIV-1-infected persons and may accelerate the course of HIV-1 infection, increasing the HIV-1 load in some patients (Corbett et al. 2003; Corbett et al. 2006).

#### 18.4.2.2 Hepatitis C Virus

Hepatitis C virus (HCV) was first identified in 1989. HCV is mainly transmitted parenterally, and therefore HIV-1-HCV coinfection is common in individuals that are exposed to infected blood (e.g., IDU, recipients of blood transfusion before screening was introduced). Acute HCV is usually asymptomatic and progresses to chronic HCV viremia in 60–80% of individuals. After decades of chronic HCV infection liver cirrhosis develops in a third of individuals. Of these 1–5% per year develop hepatocellular carcinoma (primary liver cell cancer). There is no prophylactic or therapeutic vaccination against HCV available.

HIV-1/HCV coinfection is associated with a faster progression to liver cirrhosis and with lower success rates of anti-HCV treatment. Furthermore, HIV-1/HCV coinfection leads to higher mortality, even if HIV-1 is treated with HAART. The effect of HCV coinfection on HIV-1 disease progression is not clear (Shepard et al. 2005; Alter 2006; Koziel and Peters 2007).

#### 18.4.2.3 Hepatitis B Virus

Hepatitis B virus (HBV) accounts for an estimated 370 million chronic infection worldwide, an estimated 2–4 million HIV-1-infected persons have chronic HBV coinfection. Vaccination against HBV is possible. The rate of HBV viral persistence after acute infection depends on the age at HBV infection. Immunocompetent adults clear HBV in more than 90% of infections, while children infected in the perinatal period or during childhood clear only in approximately 10% of infections. In adult HIV-1 infected individuals that are acutely infected with HBV, 20% develop chronic HBV infection. As with HCV infection, HIV-1/HBV coinfection increases the progression to cirrhosis, and death from liver disease, especially in patients with a low $CD4^+$ cell count or concomitant alcohol use (Alter 2006; Koziel and Peters 2007).

## 18.5 Prevention

Models have predicted that strong global commitment for the expansion of HIV-1 prevention programs might avert 28 million new HIV-1 infections through 2015 (Stover et al. 2006). Prevention methods are focused on decreasing risk behavior, infectivity, and susceptibility for HIV-1.

### 18.5.1 Behavioral Interventions

Behavioral interventions aim to reduce sexual and drug use-related risk behavior. Male condoms are cheap and effective in preventing HIV-1 and other STI. Female condoms have these same features, but are hardly used because of impracticalities. Many countries have adopted the ABC approach, sequentially advising sexual abstinence, being faithful, and Condom use. Reduction of the presence of STI on population level might affect the HIV-1 epidemic but its effectiveness on population levels depends on factors like the stage of the HIV-1 epidemic and sexual networks. Many approaches to prevent STI have been implemented and have proven to effectively lower the prevalence of some major STI in many parts of the world. However, the effectiveness of these programs to reduce HIV-1 incidence remains unproven.

Needle exchange and methadone maintenance programs have been found to decrease drug use-related risk behavior. However, the coverage of such programs for drug users is still very low.

### 18.5.2 Prophylactic Antiretroviral Interventions to Prevent MTCT

In their landmark study, the Paediatric AIDS Clinical Trial Group found that by treating women and their infants with the antiretroviral agent zidovudine, the HIV-1 transmission risk was reduced from 25 to 8% (Ellerbrock et al. 1991). Additionally, several trials were conducted to evaluate the effect of short-course antiretroviral therapy (ART) regimens on MTCT, comparing different agents and regimens. Overall, combining several ART agents proved to be more effective as did longer duration of prophylactic ART. In developed countries where women have access to HAART the risk of HIV-1 transmission from mother to child can be reduced to 1–2%.

An important clinical study, the HIV-1 NET 012 trial showed that, in breast-feeding populations, a single dose of nevirapine (NVP) at labor onset and a single dose of NVP to newborns reduced the risk of HIV-1 transmission by nearly 50% at approximately 6–8 weeks after birth compared to a short course of zidovudine. In Africa, this shortest possible ART regimen has greatly reduced the risk of intrapartum HIV-1 transmission (Guay et al. 1999). However, the efficacy of prophylaxis against MTCT diminishes gradually with continued breast-feeding after the prophylaxis has stopped. The long half-life of NVP might have a protective effect on early breast milk HIV-1-transmission, thereby possibly preventing MTCT during the first weeks of life (Fowler and Newell 2002). On the other hand, the prolonged presence of this single drug promotes the development of drug resistance by HIV-1. This risk is strongly related to higher maternal plasma RNA levels and lower CD4 counts at the time of exposure (Eshleman et al. 2001). The proportion of viral variants with NVP resistance declines over time, but low levels of resistant virus can be detected for more than 1 year after exposure (Dao et al. 2007). The clinical significance

of this resistance remains unclear. Studies have shown that previous exposure to a single-dose NVP (SD-NVP) did not reduce the efficacy of SD-NVP in subsequent pregnancies. In addition, studies did not find a significant difference in virological response to NVP-based regimens among women who began treatment more than 6 months after SD-NVP, while initiating treatment less than 6 months after SD-NVP was associated with worse virological response in two studies.

The 2006 WHO guidelines regarding the use of ART for prevention of MTCT in resource-limited countries aim to optimize access to high-quality services. It calls for the best MTCT interventions where feasible, at least some effective MTCT interventions at all levels of the health system, and worldwide maximization of populations reached. The key principle in the 2006 WHO guidelines is the evaluation of pregnant women for their personal ART need; ART should be provided if necessary and continued indefinitely after delivery. This requires adequate infrastructure and manpower for CD4+ T-cell testing. While choosing ART regimens maternal health status and possible detrimental effects of drug exposure to fetal organ development should be evaluated. For women who are not eligible for ART, the WHO recommends AZT starting at 28 weeks of gestation (or as soon as feasible thereafter), intrapartum SD-NVP, and a single dose of NVP combined with 1 week of AZT for the infant. Where access to ART is limited, at least the SD-NVP should be made available to mothers and infants. However, this most simple regime is not widely accessible. It is estimated that currently <10% of HIV-1-infected women in sub-Saharan Africa receive ART during pregnancy or delivery. Even in settings where SD-NVP is available, uptake has been limited due to infrequent HIV-1 testing (not offered or not accepted), inconsistent supplies, inadequate numbers of staff, and reluctance of women to disclose their status. As a result, only half of eligible women receive NVP in settings where PMTCT programs are in place. In contrast, in developed countries, with the implementation of universal prenatal HIV-1 testing, using a combination of several ART agents and elective caesarean delivery when indicated, overall MTCT rates have dropped to about 1–2% (Dao et al. 2007; Fowler et al. 2007; Cooper et al. 2002; Luzuriaga and Sullivan 2005).

A key factor limiting the scaling up of MTCT programs is the lack of knowledge of HIV-1 serostatus. For that reason, several countries have recently adopted the opting-out approach in which certain risk groups attending health facilities are informed that a HIV-1 test is routinely performed, unless individuals specifically refuse.

### *18.5.3 Formula Feeding*

The WHO recommends exclusive breast-feeding for HIV-1-infected women for the first 6 months of their baby's life, unless replacement feeding is 'acceptable, feasible, affordable, sustainable, and safe for mother and child.' In many parts of the world these criteria cannot be met, but if so, avoidance of all breast-feeding by HIV-1-infected women is recommended. The benefits of breast-feeding in settings with poor hygiene, unsafe water and lack of affordable substitutes for breast milk, and

the related child morbidity and mortality thereof, have to be balanced against the risk of postnatal HIV-1 transmission.

### *18.5.4 Caesarean Deliveries*

Early observational studies showed conflicting results on the preventive effect of caesarean delivery, through which exposure to blood and genital secretions in the birth canal is reduced, on MTCT. In 1998, elective caesarean delivery was demonstrated to reduce HIV-1 transmission by 50–80% in both a European randomized trial, dependent on the timing of the procedure, as well as on a meta-analysis (Fowler et al. 2007). In the USA this led to the recommendation that all women with HIV-1 viral loads >1000 copies/mL should be counseled on the benefits of elective caesarean delivery, which should be performed at 38 completed weeks of gestation. In America and Europe this has led to an increase in the proportion of HIV-1-infected women having caesarean deliveries. In developing countries there are limited data suggesting that the risks of postpartum morbidity or mortality among HIV-1-infected women who have caesarean deliveries are increased (Jamieson et al. 2007). The benefits of caesarean delivery in these settings need to be weighed against potential increases in maternal and infant morbidity and mortality and the costs related to this procedure. Whether caesarean delivery is beneficial in the era of HAART among women with undetectable viral load, remains unanswered; a report from the European Collaborative Study did not find a statistically significant protective effect of caesarean delivery in multivariate analyses (Luzuriaga and Sullivan 2005).

### *18.5.5 Male Circumcision*

Over the years, several epidemiological studies have suggested the protective effect of male circumcision on HIV-1-acquisition. However, early studies could not control for potential confounding factors and results were conflicting. Since 2005, three randomized controlled field trials have been stopped after interim analyses on the recommendation of the Data Safety and Monitoring Boards (DSMB), when strong reductions (51–60%) in HIV-1-acquisition were observed among those circumcised (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007). This reduction might be explained by several biological mechanisms. The inner mucosa of the foreskin is less keratinized and has a higher density of HIV-1 target cells (Langerhans cells and dendritic cells) than external skin mucosa, rendering the foreskin more susceptible for HIV-1 infection. The foreskin may be damaged by epithelial lesions during sexual intercourse, providing an entry point for HIV-1. Whether male circumcision will be implemented on larger scales will be influenced by social factors, and cultural and religious acceptability of this prevention method relative to the availability and acceptance of other prevention methods. Increased sexual high-risk behavior by circumcised men may negatively influence HIV-1-incidence and prevention messages

should focus on this aspect. Studies are currently undertaken to look into the long-term effects of male circumcision, measuring HIV-1-incidence and post-intervention risk behavior.

### *18.5.6 Microbicides*

Women are at risk for HIV-1 infection mainly through heterosexual transmission and often have no control over condom use by their sexual partners based on cultural, social, or economic inequalities. The development of topical agents which could be applied vaginally or rectally, aiming to prevent transmission of HIV-1 and/or other STI, so-called microbicides, could empower women and influence the HIV-1 epidemic. Over the years, advances in investment and product development have occurred. A major obstacle in the development of effective microbicides is the absence of an in vivo biomarker associated with protection. Agents in development focus on direct inactivation of HIV-1 through HIV-1 membrane disruption or the decrease of vaginal acidity, which has been associated with limited HIV-1 viral proliferation. Others agents target HIV-1 viral replication and HIV-1 or host-cell structures, thereby inhibiting HIV-1 entry. Several drugs that are currently used for systemic HIV-1 treatment might qualify for microbicidal use. However, issues on the possible development and transmission of drug resistant virus need to be resolved. Effective microbicides will probably contain several agents, targeting different steps of HIV-1 replication and entry. Ideally, microbicides should be non-immunogenic, provide long-lasting and broad protection through simple dosing regimens while being easily manufactured and distributed. Safety in microbicide development is of great concern with one of the first microbicides (cellulose sulfate) tested showing increased HIV-1 transmission through the induction of local inflammation. For this reason, two phase III trials with cellulose sulfate were ended prematurely. A recently completed phase III trial testing the efficacy of Carraguard found this product to be safe for vaginal use. However, Carraguard was not shown to be effective against HIV-1 transmission. Results from additional phase III trials are expected in 2009 (http://www.microbicide.org). Whether effective microbicides can be developed remains a topic of scientific debate.

### *18.5.7 HIV-1 Vaccines*

The only solution to halt the HIV-1 pandemic may be a safe, broadly protective vaccine. Development is hindered by the lack of a good animal model for HIV-1, the great genetic variability of HIV-1, and the lack of clear correlates of protection against HIV-1 infection. Additionally, HIV-1 epitopes are hidden by protective structural carbohydrates that cover the antigens on the virus′s surface and specific molecule configurations. Prophylactic vaccines are aimed at preventing HIV-1 infection. In contrast, therapeutic vaccines are designed to alter HIV-1 disease progression by lowering the level of viral replication and immune deterioration. Partially effective vaccines might render individuals less infectious which

could reduce transmission probabilities. Overall, scientists believe that a vaccine that induces both strong humoral and cellular immune responses might provide the most promising agent to prevent or control HIV-1 infection. Several types of vaccines have been studied: envelope-based subunit vaccines, containing recombinant parts of HIV-1 envelope proteins; DNA vaccines; and recombinant vector vaccines, where HIV-1 genetic material is placed into harmless viruses expressing these genes to present pieces of HIV-1 to the immune system. Live attenuated HIV-1 vaccines are currently not being investigated for use in humans because of safety concerns. Since 1987 numerous HIV-1 vaccine products have entered clinical trials, including four phase III trials. Major setbacks in HIV-1 vaccine development occurred when the first phase III trial with Aidsvax, a single subunit vaccine, proved to be ineffective. Currently ongoing phase III vaccine trials consist of a prime-boost combination including a recombinant vector vaccine and a subunit, aiming to provoke both cellular and humoral immune responses (www.iavi.org). Disappointing results with clinical trials using the recombinant adenovirus type 5 (rAd5) vector developed by Merck were observed. Despite the potential of this vaccine to induce robust and durable cell mediated HIV-1 immune response no evidence of protection was found. Disturbingly, persons with high preexisting antibodies against adenovirus 5 were found to have an increased HIV incidence. These findings raise doubts about the possible future development of an effective HIV-1 vaccine.

### *18.5.8 PEP*

Post-exposure prophylaxis (PEP), the provision of ART to prevent HIV-1 infection after risk situations have occurred, has become the standard of care in many developed countries for health-care workers who are accidentally exposed to an HIV-1 infected source. When the HIV-1 serostatus of the source is unknown, an individual risk assessment should be made when considering PEP, including evaluation of the risk group of the source and the type of exposure. PEP should be initiated within 72 hours after the incident and consists of 1 month of HAART. Over the years, only small observational studies have found PEP use to be protective and cost-effective for occupational exposure with a high risk of HIV-1 transmission (Pinkerton et al. 1997). However, a randomized controlled clinical trial to study PEP is neither feasible nor ethical. Guidelines for PEP after non-occupational exposure, like unprotected sex and unsafe drug use are of more recent date (European and American guidelines). Like for occupational accidents, PEP should be prescribed when the source is known to be HIV-1-infected and/or the type of exposure contains a high risk for transmission, i.e., receptive anal sex and deep injuries with fresh blood during needle stick exposures, and otherwise considered on a case-by-case basis. The efficacy of PEP for non-occupational exposure has not been shown. Subjects receiving PEP should be followed up for 6 months and checked for other infectious diseases like hepatitis B and hepatitis C.

### *18.5.9 PREP*

Pre-exposure prophylaxis (PREP) is the use of ART before HIV-1 exposure, aiming to prevent infection in HIV-1 negative individuals. Animal studies have shown some protection through PREP. For years, PREP was thought to be unfeasible since no drug was available for the long-term use in healthy individuals, but the licensing of tenofovir (TDF) changed that situation. The only completed study to date, performed in Ghana, showed that TDF was safe but did not find a statistically significant protective effect. Currently, four clinical trials are conducted worldwide, evaluating the safety and efficacy of PREP regimens and results are expected in 2008. Three additional studies are planned (www.prepwatch.org). The effects of future (partially) protective PREP regimens might be counteracted, however, by simultaneous increases in sexual risk behavior.

## 18.6 Highly Active Antiretroviral Therapy

### *18.6.1 ART Classes*

The HIV-1 replicative life cycle has different phases which form the potential targets for antiretroviral therapy (ART). ART can be divided into five main classes and the US Food and Drug Administration (FDA) had approved 31 compounds, including 6 combination products, by the end of 2007. The nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) limit the effect of the viral reverse transcriptase, blocking the transcription of viral RNA into DNA. Protease inhibitors (PI) block the enzyme protease and prevent new infectious particles from being formed. The first fusion inhibitor was marketed in 2003, a new ART class that prevents merging of the viral membrane with the membrane of $CD4^+$ T cells, thus preventing HIV-1 entry. In 2007, products of two new classes of ART received approval by the FDA. First, an entry inhibitor, which blocks the chemokine receptor CCR5 which HIV-1 uses as a coreceptor to bind and enter $CD4^+$ T cells. This product needs to be injected twice daily and is reserved for treatment of drug-experienced patients since it can help overcome drug resistance. Second, an integrase inhibitor, which prevents viral DNA to be integrated into the DNA of host cell. Currently, there is one multi-class combination product on the market, combining an NNRTI with two NRTIs.

### *18.6.2 HAART*

The goal of ART is to decrease HIV-1-related morbidity and mortality. The clinical effectiveness of ART has improved markedly with the introduction of HAART in 1996. HAART combines three ART agents, generally including at least one NNRTI or PI. The rationale for combining several agents is provided by the high genetic variability of HIV-1. The virus has an extremely high rate of viral turnover. During transcription, the viral enzyme reverse transcriptase has a high mutation rate and

HIV-1 has the capacity to recombine. These factors lead to a great diversity of HIV-1 (quasi) species in chronically infected individuals.

HAART aims to reduce and sustain HIV-1 plasma viral load below levels of detectability of current ultra sensitive viral load assays (<50 copies/mL). The likelihood of accumulation of drug-resistance mutations is thus minimalized. The inhibition of viral replication results in a partial reconstitution of the immune system in most patients, thereby reducing the risk of clinical disease progression and death. Even those with more advanced HIV-1 disease and low $CD4^+$ T-cell counts who initiate HAART can achieve substantial increases in $CD4^+$ T-cell counts, leading to clinical benefit (Weller and Williams 2001). However, current HAART regimens do not clear HIV-1 infection and HIV-1 establishes latent infection in resting memory CD4+ T cells, monocytes, macrophages, and perhaps other cells. These cells can harbor infectious HIV-1 for decades. Therefore, lifelong treatment is needed.

Limited data are available, but treatment for HIV-2 mirrors treatment approaches of HIV-1. However, currently available NNRTIs are ineffective in treating HIV-2, therefore the use of a protease inhibitor with two NRTIs to treat HIV-2 infection is recommended.

### *18.6.3 Side Effects*

Between 25 and 50% of patients discontinue their initial HAART regimen because of treatment failure or non-compliance within the first year of therapy. All ART can have a wide range of both short-term and long-term adverse effects. Gastrointestinal side effects like nausea and diarrhea, occurring early on and sometimes continuously throughout the use of many ARTs can negatively effect adherence. Other frequently observed effects are fatigue, headaches, nightmares, and more serious adverse events like anemia, peripheral neuropathy, hepatotoxicity, and hypersensitivity reactions. NRTIs can disrupt mitochondrial function causing hyperlactatemia, hepatic steatosis, and lactic acidosis, which may lead to death. PI-based regimens sometimes cause diabetes mellitus type 2 and insulin resistance. Lipodystrophy, defined as a metabolic syndrome including fat redistribution, hyperlipidemia, and insulin resistance or diabetes mellitus, is caused by PIs and some NRTIs. Lipodystrophy includes fat loss in face, limbs and buttocks, together with fat accumulation in abdomen, breasts, and over the dorsocervical spine. ART is associated with dyslipidemia and especially in the presence of other risk factors, like smoking, the risk for cardiovascular disease in HAART receiving subjects might be increased. The pathogenesis of lipodystrophy, insulin resistance, and dyslipidemia are still unclear. Treatment for dyslipidemia, diabetes, and insulin resistance should be prescribed according to national guidelines.

Individuals initiating HAART may experience a worsening of preexisting medical conditions through the restoration of antigen specific immune response through HAART. This immune reconstitution syndrome is more often seen among individuals initiating therapy with a low $CD4^+$ T-cell count (Montessori et al. 2004; French 2007).

### 18.6.4 Adherence

Inadequate adherence remains an important reason for poor treatment outcome in HIV-1 disease. Adherence is influenced by several factors among which are the frequently observed side effects during HAART regimens, pill burden, dosing frequency, food requirements, mental health, substance abuse, and social or psychological barriers to adherence. In the past several years, progress has been made in that convenient regimens with few or no food restrictions, decreased pill burden and dosing, and one-pill once-daily regimens have become available, which may improve adherence. It is suggested that very high adherence rates (defined as the number of doses taken divided by the number of doses prescribed) of >95% to PI-based regimens are needed to prevent treatment failure (Paterson et al. 2000). Some studies have demonstrated that adherence in resource-limited countries is as high as in the industrialized world. Whether population-based introduction of (HA)ART will confirm these results remains to be proven.

### 18.6.5 Drug Resistance

The most common reason for treatment failure is the emergence of drug resistance, limiting future treatment options. Drug-resistant HIV-1 is transmissible and in developed countries with broad access to HAART, HIV-1 resistance can be found in up to 10–20% of newly infected individuals. Several western world guidelines recommend resistance testing before the initiation of the first HAART regimen. In resource-limited countries with low access to (HA)ART the prevalence of drug resistance remains low (Gilks et al. 2006).

### 18.6.6 Structured Treatment Interruptions

The rationale for structured treatment interruptions during the course of HAART is that the immune system, if exposed to low levels of viral replication, might be stimulated to control HIV-1. Besides, structured treatment interruptions might add to the quality of life of HIV-1-infected individuals, reduce treatment costs, and reduce (long-term) side effects. The largest structured treatment interruptions study so far was closed early because of both increased HIV-1 and non-HIV-1-related illnesses in the treatment interruption arm. At this point, except for reasons of treatment intolerance, structured treatment interruptions are discouraged (el-Sadr et al. 2006).

### 18.6.7 Global Perspectives of HAART

Combination therapy is becoming more widely available throughout the world, including in resource-limited countries. Over the years, several international organizations provoked price reductions through the adaptation of international laws on patents, the introduction of generic products, and the creation of relief funds. Depending on the regimen, prices of most first-line ART products dropped between

37 and 53% between 2003 and 2006 in low and middle-income countries. Currently, the cheapest form of HAART is between 132 and 148 dollars/person/per year. However, this exceeds the health-care budget per person in many developing countries. In 2003, the WHO issued their '3 by 5'-slogan aiming to provide 3 million persons with ART in 2005. In 2006 a campaign for universal access to ART by 2010 was launched. However, UNAIDS reported that globally only 24% of people who needed HIV-1 treatment had access to it by mid-2006. HIV-1-diagnostic and treatment evaluation assays are often not available in resource-limited countries and the WHO has created guidelines for simplified treatment initiation and follow-up centered around the four 'S-es': when to Start drug treatment, Substitute for toxicity, Switch after treatment failure, and Stop criteria (Gilks et al. 2006).

In 2006, almost 700,000 people received ART for the first time. By December 2006 it was estimated that approximately 2 million people living with HIV-1/AIDS in low- and middle-income countries were receiving treatment, this being approximately 28% of the close to 7 million people in need (www.who.com). In sub-Saharan Africa an estimated 1.3 million persons are taking ART while this number was 100,000 three years earlier.

## 18.7 Conclusion

In the 28 years that have passed since the start of the HIV-1 epidemic, HIV-1 has had a devastating effect on global morbidity and mortality. This has greatly impacted the socio-economical situation in many parts of the world. So far, despite many efforts and attempts to develop effective prevention methods (e.g., vaccination, risk behavior reduction strategies, microbicides), these have not been shown to be successful. Recently, studies on the effect of circumcision have demonstrated promising results in decreasing HIV-1 transmission. However, population-wide implementation of this prevention method might have unforeseen counteractive effects, when risk behavior or HIV-1 infectivity is increased.

Alarmingly, in recent years most industrialized countries have reported increased sexual risk behavior and HIV-1 incidence especially among MSM. This trend could fuel the HIV-1 transmission in regions where the HIV-1 epidemic was thought to be under control.

Through effective HAART regimens and subsequently lowered mortality, the total pool of HIV-1 infected individuals will grow. Extended survival in combination with the fact that prevention methods do not seem to have the desired impact on the spread of HIV-1 suggest that the HIV-1 pandemic is likely to increase worldwide, despite the progress that has been made in raising international funds and making HAART available for more people, especially in sub-Saharan Africa.

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