HETEROGENEITY IN SUSCEPTIBILITY TO AND INFECTIVITY OF HIV

Evy LENAERTS

Promoter: Prof. Dr. M. Temmerman
Co-promoter: Dr. W. Delva

Thesis presented in the 2nd Master year in the context of obtaining the degree of MEDICAL DOCTOR
HETEROGENEITY IN SUSCEPTIBILITY TO AND INFECTIVITY OF HIV

Evy LENAERTS

Promoter: Prof. Dr. M. Temmerman
Co-promoter: Dr. W. Delva

Thesis presented in the 2nd Master year in the context of obtaining the degree of MEDICAL DOCTOR
“The author and the promoter grant the permission to consult and copy parts of this work for personal use only. Every other unauthorised use is subject to the copyright laws and will constitute an infringement of copyright, more specifically in relation to the obligation to specify the source extensively when referring to results of this thesis. Permission to reproduce any material contained in this work in any other way should be obtained from the author.”

Date,

Signature student, Signature promoter,

Evy Lenaerts Prof. Dr. M. Temmerman
‘AIDS is no longer just a disease, it is a human rights issue.’

Nelson Mandela at the first 46664 Concert, Cape Town, 2003
ACKNOWLEDGEMENTS

First of all, I would like to take the opportunity to thank my supervisors Prof. Dr. Marleen Temmerman and Dr. Wim Delva for taking time out of their busy schedules to get me started with this literature study. They deserve my deepest respect for their efforts, achievements and expertise in the field of reproductive health and HIV/AIDS.

The all-known words ‘thank you’ cannot describe the gratitude I feel towards my parents who gave me the possibility to study and the freedom to explore my own interests and passions, who kept believing in my capacities and who assisted me considerably in my struggle against a disease that has accompanied me throughout most of my life so far. The same words of thankfulness equally apply to my grandmother, who passed away two years ago, but who left me with a strong sense of justice and equality from ever since I was a little child. Furthermore, I would like to express my sincere gratefulness towards my sisters for their belief in my will to fight back, and their numerous words of comfort and support in times when I had given up on my future. And of course, I am very thankful to all of my friends who have brightened up my life, and with whom I have had many unforgettable moments: moments of tears and despair, but most of all, moments of regained hope, fun and true friendship. Of my list of best friends, Pieter Heye merits a special mention for taking on the role of external reader and for subjecting this work to rigorous scrutiny.

Special appreciation also goes out to Prof. Dr. Robert Woollard, whose precious advice made me gain additional insights about myself and whose encouragements have made me even more determined to keep pursuing my dreams and passions in life. And last, but not least, I would like to acknowledge Aina Olujimi Olusola for his efforts to give HIV/AIDS names and faces and for supplementing this work with a touch of reality by providing me with a number of testimonies from seropositive people in Nigeria.

These acknowledgements would not be complete without dedicating a few words to the millions of HIV infected people who bear the daily burden of the consequences this stigmatizing disease brings along. Without their co-operation, most of the progress in HIV research would not have been possible, although they are often the least to benefit from these advances.

Finally, I wish all the best to the lovely people I have met during my visits to and participation in volunteering projects in several developing countries. Their courage, perspectives on life and optimism, despite their often bothersome situation, have touched me deeply, and partly inspired me to become the person I am now. Xie xie! Shukran! Merci! Istut! Terima Kasih! Djere dief! Gracias! Nandri! Thank you!
"They all left me to die. Please, help me, I do not want to die."  
These were the words of Itohan a few hours before she died of AIDS.  
As her family and friends had abandoned her because of her HIV status, she died alone.

After almost thirty years of continuous spread, the Human Immunodeficiency Virus (HIV) – the causative agent of the Acquired Immunodeficiency Syndrome (AIDS) – has turned itself into a global health problem of unprecedented dimensions. Since the first case was reported in 1981, AIDS has already killed more than 25 million people worldwide, thereby generating profound demographic changes in the most heavily affected countries (UNAIDS, 2008). But despite its staggering prevalence and incidence figures and the undeniable evidence of its impact on all levels of society, HIV is still considered as a mythical virus by some individuals and communities, and AIDS is sometimes even referred to as an 'American Invention to Discourage Sex'.

Although HIV was generally associated with homosexual, poor and black people in earlier days, we have come to realize that everyone can be affected by the HIV pandemic, regardless of age, sex, ethnicity, wealth status or sexual orientation. But even more than others, this epidemic carries the face of women. Or like Nelson Mandela formulated it in his speech at the 46664 Concert in George, South Africa, in 2005: ‘For every woman and girl violently attacked, we reduce our humanity. For every woman forced into unprotected sex because men demand this, we destroy dignity and pride. Every woman who has to sell her life for sex, we condemn to a lifetime in prison. For every moment we remain silent, we conspire against women. For every woman infected by HIV, we destroy an entire generation.’

In the meantime, HIV/AIDS is eroding decades of hard-won development gains, increasing poverty and undermining the foundations of society in the worst affected countries (UNAIDS, 2008). Moreover, stigmatization, violations of human rights and negligence of political leaders have substantially fuelled the further spread of the epidemic. Despite some small victories and success stories mainly resulting from efforts in prevention campaigns and increased availability of antiretroviral therapy, the balance after a difficult global battle of more than twenty years is still very sad. It becomes much more obvious that other strategies will need to be explored to stop this virus from ravaging millions of people’s lives worldwide. But despite tremendous progress in HIV research in recent years, attempts to develop a highly effective vaccine have not been successful so far. However, these unrewarded efforts may not endanger the will to tackle one of the biggest challenges in medical history, so the words ‘the one you love, can kill you’ will no longer be applicable.
# TABLE OF CONTENTS

## ABSTRACT

1

## 1 INTRODUCTION

1.1 Epidemiology in a nutshell 3

1.2 Pathogenesis of HIV 3

## 2 METHODOLOGY

7

## 3 RESULTS

3.1 Viral load and genital shedding 9

3.2 Antiretroviral therapy 10

3.3 Stage of disease 12

3.4 Sexually transmitted diseases 14

3.5 Menstrual cycle 19

3.6 Hormonal contraceptive use 21

3.7 Cervical ectopy 23

3.8 Genetic polymorphisms 23

3.9 Physical and chemical barrier methods 26

3.10 Demographic, socio-cultural and behavioural variables 28

3.10.1 Age 29

3.10.2 Marriage 29

3.10.3 Level of education 30

3.10.4 Level of income 33

3.10.5 Gender inequality 36

3.10.6 Vaginal practices 37

3.10.7 Male circumcision 38

3.10.8 Sexual risk behaviour 41

## 4 DISCUSSION

44

4.1 Limitations 44

4.2 Considerations 44

## BIBLIOGRAPHY

49

## APPENDICES
ABSTRACT

English version

Background: Since there is not an HIV vaccine available yet, and the existing preventive strategies have shown to be insufficient to call a halt to the spread of the HIV pandemic, additional explanations for intra- and interindividual differences in both susceptibility to and infectivity of HIV-1 could be an important leverage point for interventions in the worldwide battle against HIV/AIDS.

Objective: To identify those variables of which research has shown that they might contribute to the heterogeneity in susceptibility to and infectivity of HIV-1, and to estimate the extent in which they are associated with a higher risk of HIV-1 acquisition.

Methods: A literature study was carried out by using PubMed, Popline and the Official Journal of the International AIDS Society to search for articles published from January 1997 up to April 2009.

Results: Infectivity of HIV-1 was found to be directly determined by plasma viral load and genital shedding, both of which are influenced by antiretroviral therapy and stage of disease. The presence of concomitant sexually transmitted diseases, hormonal changes during the menstrual cycle and hormonal contraceptive use could influence both infectivity of and susceptibility to HIV-1 by inducing changes in the level of HIV-1 in genital tract secretions and by increasing the risk of epithelial disruption and immune activation of host cells, respectively. Other identified determinants of susceptibility to HIV-1 include genetic polymorphisms, male circumcision, cervical ectopy and vaginal practices. Individuals with certain protective genetic polymorphisms and circumcised males appear to have a lower risk of contracting HIV-1, whereas cervical ectopy may be associated with a higher probability of infection with HIV-1. Finally, evidence also points towards significant associations between specific demographic, socio-cultural and behavioural variables and vulnerability to HIV-1 infection.

Conclusions: This review has shown that our precise knowledge concerning factors influencing susceptibility to and infectivity of HIV-1 infection is still limited. For the same variable studied, much of the literature showed inconsistent results, ranging from no associations to statistically significant associations. This inconsistency in results suggests that more research is needed in order to get more consensus and to implement prevention strategies of which both effectiveness and efficiency are proven by hard evidence.
Nederlandse versie

Achtergrond: Aangezien er nog geen vaccin beschikbaar is en de huidige preventiestrategieën onvoldoende zijn gebleken om de verspreiding van de HIV-epidemie tegen te gaan, kunnen bijkomende verklaringen voor intra- en interindividuele verschillen in vatbaarheid voor en besmettelijkheid van HIV-1 een belangrijke hefboom zijn voor interventies in de wereldwijde strijd tegen HIV/AIDS.

Doel: Identificatie van variabelen waarvan onderzoek heeft aangetoond dat ze mogelijk bijdragen tot de heterogeniteit in vatbaarheid voor en besmettelijkheid van HIV-1, gevolgd door een numerieke schatting van de mate waarin deze variabelen geassocieerd zijn met een hogere kans op HIV-1 infectie.


Resultaten: Besmettelijkheid van HIV-1 wordt rechtstreeks bepaald door de virale lading in het bloedplasma en in het genitale stelsel, waarbij beide parameters op hun beurt beïnvloed worden door antiretrovirale therapie en ziektestadium. Aanwezigheid van concomitante seksueel overdraagbare aandoeningen, hormonale veranderingen tijdens de menstruele cyclus en gebruik van hormonale contraceptiva kunnen zowel besmettelijkheid van als vatbaarheid voor HIV-1 beïnvloeden door respectievelijk veranderingen te induceren in de concentratie van HIV-1 in genitale secreties en het risico op epitheliale onderbreking en immuunactivering van gastheercellen te verhogen. Tot de overige geïdentificeerde determinanten van vatbaarheid voor HIV-1 behoren genetische polymorfismen, mannenbesnijdenis, cervicale ectopie en vaginale praktijken. Individuen met zekere protectieve genetische polymorfismen en besneden mannen vertonen een lager risico op infectie met HIV-1, terwijl cervicale ectopie geassocieerd zou kunnen zijn met een verhoogde vatbaarheid voor HIV-1. Tenslotte heeft onderzoek ook significante associaties aangetoond tussen specifieke demografische, socia-culturele en gedragsmatige variabelen en kwetsbaarheid voor HIV-1 infectie.

Besluit: Deze literatuurstudie heeft aangetoond dat onze precieze kennis betreffende factoren die invloed uitoefenen op vatbaarheid voor en besmettelijkheid van HIV-1 infectie nog steeds beperkt is. Voor eenzelfde variabele werden inconsistente resultaten gevonden, gaande van afwezige associaties tot statistisch significante correlaties. Deze inconsistentie in resultaten suggereert dat meer onderzoek vereist is om meer consensus te bekomen en preventieve strategieën te implementeren waarvan zowel effectiviteit als efficiëntie duidelijk aangetoond zijn.
1 INTRODUCTION

1.1 Epidemiology in a nutshell

According to the ‘Report on the Global AIDS Epidemic’ published by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2008, an estimated 33 million people were living with the deadly Human Immunodeficiency Virus (HIV) and 2 million people had died as a consequence of the Acquired Immunodeficiency Syndrome (AIDS) all over the globe in 2007 (see appendix 1). Moreover, there were 2.7 million new HIV infections worldwide, with a significant burden of 1.9 million people newly infected in sub-Saharan Africa. This region also accounted for 67 percent of all people living with HIV and for 75 percent of AIDS deaths in the year preceding publication of the report. Based upon these facts, it is indisputable that sub-Saharan Africa bears a disproportionate share of the global burden of HIV/AIDS and it will most likely continue to do so in the future.

1.2 Pathogenesis of HIV

HIV belongs to the lentivirus group of retroviruses, enveloped viruses whose genetic material consists of two single strands of ribonucleic acid (RNA) (see figure 1). Both molecules of single-stranded RNA are enclosed by a conical capsid comprising the viral core protein p24, which on its turn is surrounded by the viral matrix protein p17. Enclosed within the virion particle are enzymes that are indispensable for the development of the virion, such as reverse transcriptase, integrase and protease. The envelope glycoprotein gp160 contains an outer envelope glycoprotein (gp120) and a transmembrane protein (gp41) and mediates the membrane fusion activity of the virus (Finch et al., 2005).

![Figure 1: Structure of HIV](image)

Two molecules of single-stranded RNA are enclosed by the viral core protein p24, which is surrounded by the viral matrix protein p17. The enzymes reverse transcriptase, integrase and protease are essential for the development of an infectious virion. The envelope glycoprotein gp160 consists of gp120 (outer envelope glycoprotein) and gp41 (transmembrane protein) and mediates fusion between the viral envelope and the host cell membrane. Source: FINCH R.G., MOSS P., JEFFRIES D.J., ANDERSON J. : Infectious diseases, tropical medicine and sexually transmitted diseases. In : Clinical Medicine, 6th edition. P. Kumar, M. Clark, Elsevier Saunders, Philadelphia, 2005, 131.
HIV mainly infects CD4-receptor bearing cells, primarily T lymphocytes, which act as high affinity binding sites for the viral gp120 envelope glycoprotein (see figure 2). HIV particles are able to invade host cells by attaching the viral surface glycoprotein gp120 to the CD4 receptor and to a chemokine co-receptor on the host cell surface, typically either CCR5 or CXCR4 (Mims et al., 2004). Subsequent conformational changes in gp120 lead to membrane fusion mediated by the transmembrane subunit gp41.

**Figure 2: HIV entry and replication in CD4 T lymphocytes.**

Binding of free virus to a CD4 molecule and one of two co-receptors (either CXCR4 or CCR5), followed by fusion of the virus with the cell and consequently, entry of the virus into the cell. After entry into the cell, the virus is uncoated, and the enzyme reverse transcriptase converts single strands of viral RNA into double-stranded DNA. Viral DNA is combined with the cell’s own DNA by the integrase enzyme. When the infected cell divides, the viral DNA is ‘read’ and long chains of proteins are made (transcription). During assembly, sets of viral protein chains come together. The immature virus then pushes out of the cell, taking some cell membrane with it (budding). Immature virus breaks free of the infected cell and protein chains in the new viral particle are cut by the protease enzyme into individual proteins that combine to make a working virus (maturation). Source: FINCH R.G., MOSS P., JEFFRIES D.J., ANDERSON J.: Infectious diseases, tropical medicine and sexually transmitted diseases. In: Clinical Medicine, 6th edition. P. Kumar, M. Clark, Elsevier Saunders, Philadelphia, 2005, 131.

After entry into host cells, the viral enzyme reverse transcriptase allows viral RNA to be transcribed into DNA, which is then incorporated into the host cell genome by the enzyme integrase and causes the DNA in the host cell to make copies of HIV (Mims et al., 2004; Finch et al., 2005). Reverse transcription is an error-prone process with a striking rate of misincorporation of bases. This, combined with a high rate of viral turnover, leads to a considerable degree of genetic variation (Finch et al., 2005), which is one of the challenges that needs to be overcome in the quest for a successful HIV vaccine. Another enzyme, protease, facilitates the production of new virus particles by cleaving newly synthesized polyproteins at the appropriate places to create the mature protein components of infectious HIV virions, which then ‘bud’ off the infected cells into the body, where they will infect more CD4 positive T-cells (Mims et al.,
Acute or primary HIV infection is characterized by a considerable increase in viral load, accompanied by an abrupt decrease in CD4 positive T-cells (see figure 3). During the following months, an immune response to HIV ensues, with virus-specific CD8 positive T-cells being produced, which attack and kill infected virus-producing cells and antibodies produced by B lymphocytes, resulting in a decrease in viral load. Clinical latency then follows, despite low-level replication of HIV and ongoing destruction of the immune system. As HIV infection progresses, the viral load rises and the CD4 count falls below a critical level, eventually overwhelming the immune system’s regenerative capacity. In this final stage, the infected individual develops an array of symptoms, also known as AIDS, as a result of direct HIV effects and of the associated immunosuppression (Mims et al., 2004; Finch et al., 2005) (see also appendix 2).

Figure 3: The immune response to HIV
Primary or acute HIV infection (1) refers to the period of time immediately after initial infection, which is characterized by a prolific phase in viral replication, and an acute drop in the number of CD4 positive T-cells. The acute infection is followed by a chronic asymptomatic stage (clinical latency) (2) in which viral replication is reduced in line with the immune response. As HIV infection progresses, the viral load rises, the number of CD4 positive T-cells falls below a critical level and the infected individual becomes symptomatic (AIDS) (3). Source: Amhara HIV/AIDS Prevention and Control Secretariat (http://www.etharc.org).

To date, two viral types could be identified, including HIV-1 and the closely related but antigenically distinct HIV-2, which is less virulent than HIV-1 and predominantly confined to West Africa. Furthermore, HIV-1 is divided into three groups, namely M (major), N (new) and O (outlier), with the latter two being focused in western central Africa. The M group comprises the HIV-1 subtypes A to J, with subtype B being most common in Europe and North America, while subtypes A and C are predominantly found in Africa (Mims et al., 2004).
The majority of HIV infections are transmitted via semen, cervical secretions and blood (Finch et al., 2005). Therefore, vaginal and anal sexual intercourse, contact with contaminated blood, blood products and needles, and vertical transmission from mother to child – which can occur in utero, intrapartum or postnatally through breastfeeding – are considered to be the main HIV transmission routes. From a global perspective, heterosexual intercourse remains the epidemic’s driving force, and this statement particularly applies to sub-Saharan Africa (UNAIDS, 2008).

It follows from the above that the risk of HIV transmission is determined by a complex interaction between host factors and viral characteristics, although the precise components of this interaction, the extent to and causal direction in which they influence viral transmission have not been fully elucidated yet. The objective of this study is to identify those host variables of which studies have suggested that they modulate the transmission risk of HIV-1 infection. Furthermore, estimates on the contribution of each variable to the transmission risk of HIV-1 infection will be presented on the basis of previous research. This study forms part of a larger research project that aims to integrate the main risk factors for the HIV-1 epidemic in a statistical predictive model for estimating the probability of HIV-1 infection in the presence of these identified risk factors. Such estimates could be useful for resource allocation and enhanced targeting of community-based interventions for primary and secondary HIV prevention.
2 METHODOLOGY

Before starting to search through the elaborate existing literature on the HIV epidemic, inclusion criteria were defined in order to restrict the amount of publications specifically applicable to this literature study. Only studies on HIV-1 infection in adolescent and adult populations in sub-Saharan Africa were included. Viral characteristics and variables influencing mother-to-child, homosexual and non-sexual transmission of HIV-1 were beyond the scope of this study, as were also study results based on penile-anal heterosexual contacts. Study designs eligible for inclusion comprised cohort, case-control, cross-sectional studies and randomized controlled trials as well as systematic reviews and meta-analyses. However, when the latter two were based on studies from regions other than sub-Saharan Africa, instead of using the combined results, only the publications conducted in sub-Saharan Africa to which the authors referred were included.

Studies were eligible if HIV status was actually measured in the study participants by means of standard diagnostic HIV tests, including enzyme-linked immune-sorbent assay (ELISA) and Western blot tests. No restrictions were put on language, but as English is still the main working language in the field of medical and health sciences, only abstracts and articles in English were used.

Originally, this review aimed at using studies providing an estimate of transmission probabilities per heterosexual act as outcome measures. As relatively few such estimates have been published to date, studies providing estimates for risk, hazard or odds ratios were also included, preferably after adjustment for confounding variables. Furthermore, it was important that studies mentioned their precise methodology in order to classify them as meeting the inclusion criteria.

The search for literature upon which this study is based could be divided into three main parts. First, PubMed, Web of Science, Popline and the Official Journal of the International AIDS Society were used to search for articles published during the last decade at the time of the start of this study (from January 1997 until October 2007). Combinations of thesaurus terms were used, in which the fixed search term ‘human immunodeficiency virus’ was followed by ‘heterogeneity’, ‘susceptibility’, ‘infectiousness’, ‘infectivity’, ‘risk factors’ and ‘risk behaviour’, respectively. In this way, potential factors explaining differences in susceptibility to and infectivity of HIV could be identified.

Subsequently, the same databases were used to explore each of the identified variables more in detail, although another, more specific combination of search terms was used, with the fixed thesaurus term ‘human immunodeficiency virus’ or ‘HIV’ being followed by ‘viral load’, ‘genital shedding’, ‘antiretroviral

To make sure that only studies carried out in sub-Saharan Africa were identified, the terms ‘Africa’ or ‘sub-Saharan Africa’ were added to each search strategy.

Next, all identified abstracts were scanned and those clearly not meeting inclusion criteria were eliminated at this point. Full-length articles of the remaining abstracts were then retrieved if possible, otherwise only abstracts were used if the methodology and results were clearly described. Finally, reference lists of the included articles were examined for other pertinent studies, which were also scanned for fulfilling the inclusion criteria.

The PubMed search as well as the search through the archives of the Official Journal of the International AIDS Society were regularly updated up to April 2009 in order to include the most recent publications into this literature study.

While this review is not fully comprehensive, it includes a large body of literature which I believe is useful in disentangling the most important determinants of susceptibility to and infectivity of HIV-1, and in creating a better understanding of the complexity of the HIV puzzle.
3 RESULTS

Defining the key concepts ‘susceptibility’ and ‘infectivity’ is necessary in order to appreciate the factors that drive the HIV/AIDS epidemic. Susceptibility in this context refers to the likelihood of becoming infected following exposure to the infective agent. Infectivity is defined as the probability of transmission between an infected individual and a susceptible individual in a single sexual contact. Transmission of HIV depends upon the infectivity of the index case and the susceptibility of the person exposed to the virus, and both infectivity and susceptibility can vary significantly over time.

After a thorough search through the existing literature, a variety of determinants were identified that may explain the differences in susceptibility to and infectivity of HIV-1 between individual subjects. These determining factors will each be explored in this section, while taking their protective or enhancing contribution to the transmission risk of HIV-1 into account. The ‘beaten’ medical track will be left behind as well, when scrutinizing demographic, socio-cultural and behavioural risk variables, as they are as equally important as purely medical parameters concerning the spread of HIV-1 infection.

3.1 Viral load and genital shedding

Quinn et al. (2000) identified viral load as the chief predictor of the risk of heterosexual transmission of HIV-1. They found transmission of HIV-1 to be rare among individuals with levels of less than 1,500 copies of HIV-1 RNA per millilitre (ml). A significant dose-response association of increased transmission with increasing viral load was observed. In multivariate analyses of log-transformed HIV-1 RNA levels, each log increase in viral load was associated with an increase by a factor 2.45 in the risk of HIV-1 transmission (95% confidence interval (CI), 1.85 – 3.26). Increasing plasma HIV-1 RNA concentrations were also found to be associated with viral transmission in a study conducted in Zambia (Fideli et al., 2001), although the observed association was more predictive for female-to-male transmission than for male-to-female transmission. The adjusted risk ratio for female-to-male transmission was 7.6 (95% CI, 2.3 – 25.5) for viral loads more than 100,000 copies per ml, and 4.1 (95% CI, 1.2 – 14.1) for viral loads between 10,000 and 100,000 copies per ml compared with the reference group of less than 10,000 copies per ml. Corresponding risk ratios for male-to-female transmission were 2.1 (95% CI, 0.8 – 5.6) and 1.2 (95% CI, 0.5 – 3.4), respectively.

Auvert et al. (2004) calculated the annual risk of HIV-1 transmission as a function of plasma HIV-1 RNA loads, and also concluded that the higher the plasma viral load, the higher the risk of HIV-1 transmission (less than 399, 400 to 3499, 3500 to 49,999 and more than 49,999 copies per ml corresponded to an
annual risk of HIV-1 transmission in person per year of 0, 0.04, 0.12, 0.14 and 0.23, respectively). Finally, probabilities of HIV-1 transmission per coital act were also calculated in monogamous, heterosexual, serodiscordant couples in Rakai, Uganda (Gray et al., 2001a). In this study, transmission probabilities increased from 0.0001 per act at low serum viral loads (less than 1,700 copies per ml) to 0.0013 or 0.0014 per act at medium serum viral loads (1,700 to 12,499 or 12,500 to 38,499 copies per ml) to 0.0023 per act at high serum viral loads (more than 38,500 copies per ml), also suggesting a dose-response association of increased transmission with increasing viral load.

Plasma viral load on its turn was found to be strongly correlated with genital viral load. In a study by Hart et al. (1999), the amount of cell-free HIV-1 RNA in blood plasma was correlated with that in vaginal secretions (Spearman’s rank correlation coefficient \( r = 0.64; P < 0.001 \). Genital HIV-1 shedding was also associated with a high plasma viral load in a study among sex workers in rural Zimbabwe (Cowan et al., 2006). These findings were confirmed by another study (Hawes et al., 2008), in which genital shedding strongly correlated with plasma viral load (odds ratio (OR), 1.9; 95% CI, 1.3 – 2.8 for each log\(_{10}\) increase in HIV-1 RNA).

In the following sections, it will become clear that viral load and genital shedding both are affected by antiretroviral therapy, stage of disease, concomitant sexually transmitted diseases, menstrual cycle and hormonal contraceptive use.

### 3.2 Antiretroviral therapy

Since the introduction of antiretroviral therapy (ART) as a life-prolonging treatment of HIV, many questions have been raised about the possible impact of this therapy on the HIV epidemic. ART has the potential to decrease the risk of sexual transmission of HIV-1 by reducing blood and genital tract HIV-1 RNA levels, strongly suggesting that it could potentially be used as a means to control the epidemic. A recent consensus statement released on behalf of the Swiss Federal Commission for HIV/AIDS even asserted that people with HIV infection receiving effective ART – those with undetectable plasma HIV viraemia (HIV RNA less than 40 copies per ml) – and without other genital infections cannot transmit HIV through sexual contact (Wilson et al., 2008).

At several levels, evidence exists to provide strong support for this statement. Lalani and Hicks (2008) found the use of ART among serodiscordant couples to be associated with reduced seroconversions in partners who are HIV negative. A study of HIV discordant couples in Uganda showed that there was a strong relation between HIV plasma viral load and heterosexual transmission rates and no transmissions
from the initially positive partners with an undetectable viral load were observed (Quinn et al., 2000). In a longitudinal follow-up study, in which HIV-discordant couples in Rwanda and Zambia were followed, the HIV incidence during ART was 0.7 percent per 100 person-years, compared to an incidence rate of 3.4 percent per 100 person-years without ART, which corresponds to a rate ratio of 0.21 (95% CI, 0.08 – 0.59), or a fivefold reduction in HIV transmission risk (Sullivan et al., 2009).

In a cross-sectional study by Auvert et al. (2004), the impact of highly active antiretroviral therapy (HAART) on the annual risk of HIV-1 transmission was estimated, using guidelines launched by the World Health Organization (WHO) and the US Department of Health and Human Services (USDHHS) (see appendix 3). This risk would be reduced by 11.9 percent if WHO guidelines were implemented (CD4 cell counts less than 200 per mm³ in clinical stage I or II disease (see appendix 2)), corresponding to a decrease in the annual risk of HIV-1 transmission from 0.171 per person per year without HAART to 0.151 per person per year with HAART. It is important to note that under WHO guidelines, many people are not eligible for ART because their CD4 cell counts are above 200 cells per mm³, even though they have high plasma viral loads, and they will continue to contribute substantially to the spread of HIV after the introduction of ART. When using USDHHS guidelines (CD4 cell counts less than 350 per mm³), the proportion of HIV-1 positive individuals eligible for ART reached higher numbers, and the impact of ART on the annual risk of HIV-1 transmission reached 71.8 percent.

If provision of ART would be systematically associated with intensive additional prevention activities, HIV transmission might be further reduced independently of the impact of ART, as was seen in an observational study in Uganda, where the risk of HIV transmission among discordant couples was reduced by 98 percent, when the HIV-1 infected partner was taking ART (Bunnell et al., 2006).

Although ART significantly reduces the frequency of genital shedding of HIV-1 in women, Nagot et al. (2008) found that HIV-1 RNA remained detectable in the genital tract of a significant proportion of individuals on ART, even when they had an undetectable viral load in their blood. It must be noted that all of the study participants in this cohort were also infected with herpes simplex virus type 2, which could enhance genital HIV-1 shedding, as will be seen later on. A small observational study also noticed continued genital shedding by some women treated with ART despite undetectable plasma viral loads (Graham et al., 2007). The same findings were reported in HIV-1 infected men on ART (Auvert et al., 2004). According to Graham et al. (2007), the observed compartmentalized replication of HIV-1 could be due to a poor penetration of some antiretroviral drugs in the genital tract, resulting in low concentrations of antiretroviral drugs in the genital compartment, which in turn raises the worrying possibility of the development of resistant HIV-1 strains.
The availability of an effective therapy could lead to an increase in demand for HIV testing and counselling, which has been shown to be effective in reducing risky sexual behaviour in heterosexual couples, and to a lessening of the stigma associated with AIDS (Auvert et al., 2004). At the same time, it could be feared that the reduced infectivity brought about by ART could be offset by increases in risky sexual behaviour (Bunnell et al., 2006).

However, a meta-analytic review by Crepaz et al. (2004) showed that the prevalence of unprotected sex was not higher among persons with HIV receiving ART versus those not receiving ART (OR, 0.92; 95% CI, 0.65 – 1.31) or among HIV-positive persons with an undetectable viral load versus those with a detectable viral load (OR, 0.99; 95% CI, 0.82 – 1.21). The prevalence of unprotected sex was only elevated (OR, 1.82; 95% CI, 1.52 – 2.17) in individuals who believed that ART or undetectable viral loads protect against transmitting HIV or who had reduced concerns about engaging in unsafe sex given the availability of ART. Bunnell et al. (2006) found that 6 months after initiating ART, risky sexual behaviour reduced by 70 percent (adjusted RR, 0.3; 95% CI, 0.2 – 0.7) among individuals in rural Uganda. The estimated risk of HIV transmission from cohort members declined by 98 percent, from 45.7 to 0.9 per 1000 person years. In a cohort of HIV discordant couples, being prescribed ART initiation was associated with lower indicators of unprotected sex as well (Sullivan et al., 2009). Couples where the infected partner was on ART were less likely to show sexual risk behaviour than couples where the infected partner was not on ART (OR, 0.87; 95% CI, 0.79 – 0.96). From these studies, it is obvious that receiving ART is not necessarily associated with an increased frequency of sexual risk behaviour.

### 3.3 Stage of disease

The concentration of HIV-1 in blood and genital secretions varies dramatically depending on the stage of disease. Epidemiological modelling generally divides HIV infection into three distinct stages with different infectivity estimates for each stage (see figure 3). The primary stage is defined as the time soon after initial infection when viral levels are typically high. Seroconversion – the response of the immune system to infection during which antibodies to the virus are produced – typically occurs before the end of the primary stage. One then enters an asymptomatic or latent period during which viral levels are relatively low, followed by a symptomatic stage during which viral loads are extremely high.

If HIV-1 infectivity is assumed to correlate with genital tract viral levels, HIV-1 transmission would be expected to be more infectious during the primary and symptomatic stages than during the asymptomatic stage. The existing literature is unanimous in concluding that the asymptomatic stage has low infectivity, but it still remains in doubt which stage primarily drives the HIV-1 epidemic.
According to results of a study of monogamous discordant couples in the Rakai district of Uganda by Wawer et al. (2005a), the risk of heterosexual HIV transmission per coital act would be highest in the months immediately after seroconversion, a time when few individuals know their HIV status or receive ART, and again during terminal AIDS. The average rate of HIV transmission was 0.0082 per coital act (95% CI, 0.0039 – 0.015) within approximately 3 months after seroconversion of the index partner. The rate declined to 0.0015 per coital act within 6 to 15 months after seroconversion of the index partner (95% CI, 0.0002 – 0.0055), then stabilized at 0.0007 per coital act (95% CI, 0.0005 – 0.0010) among HIV-prevalent index partners. The rate increased again to 0.0028 per coital act (95% CI, 0.0015 – 0.0041) at 6 to 25 months before the death of the index partner. However, the overall contribution of late-stage infection to the HIV-1 epidemic is likely to be limited, as individuals with advanced HIV infection report less sexual intercourse and have fewer partners.

As Pinkerton (2008) pointed out in his secondary analysis of data from the Rakai study, transmission rates (as used in the Rakai study) should not be confused with transmission probabilities. Transmission rates can be considered as approximations to transmission probabilities when the true transmission probability is small, but they are less accurate when the transmission probability is relatively high, as it is during the acute phase of HIV infection. When using the latter parameter, the average per-act transmission probability during acute infection equalled 0.03604 versus 0.00084 for chronic HIV infection.

Hollingsworth et al. (2008) estimated transmission hazards and durations of periods of high infectivity during primary, asymptomatic and late-stage infection for the same population of serodiscordant heterosexual couples in Rakai. They calculated that primary infection and late-stage infection were 26 and 7 times, respectively, more infectious than asymptomatic infection. High infectivity during primary infection was estimated to last for approximately 3 months after seroconversion, whereas high infectivity during late-stage infection was concentrated between 19 and 10 months before death. These findings are supported by research by Pilcher et al. (2004), who also found that sexual transmission by acutely infected individuals has a disproportionate large effect on the spread of HIV-1 infection.

In their mathematical model, Abu-Raddad and Longini (2008) estimated the role of each of the HIV progression stages in fueling HIV-1 transmission in sub-Saharan Africa by using empirical data from different studies conducted in Kisumu (Kenya) and Yaoundé (Cameroon). In both settings, they estimated that 17, 51 and 32 percent of HIV-1 transmissions in Kisumu and 25, 44 and 31 percent in Yaoundé were due to index cases in their acute, latent and late stages, respectively. These results indicate that the latent stage would contribute to about half of all HIV-1 transmissions.
On the basis of these studies can be drawn the careful conclusion that primary and – to a lesser extent – late-stage HIV-1 infection are more infectious when compared to the asymptomatic stage. However, the asymptomatic stage of infection might contribute more to the risk of HIV-1 transmission over the lifetime of an infected individual because of its longer duration.

### 3.4 Sexually transmitted diseases

A consensus has grown that other sexually transmitted diseases (STDs), especially those causing genital ulcer disease, increase the spread of HIV, a hypothesis first suggested by Piot and co-workers in 1984. Following on from this hypothesis and the early epidemiologic studies, several reviews have explored the epidemiologic synergy between STDs and HIV, concluding that the presence of either genital ulcer diseases – such as herpes, syphilis and chancroid – or non-ulcerative diseases increase the transmission probability of HIV within a partnership by increasing viral shedding in genital tract secretions (Kilmarx et al., 2001; Röttingen et al., 2001).

In HIV-1 serodiscordant couples in Rakai, Uganda, genital ulceration in the previous 10 months was shown to act as a risk factor for HIV-1 transmission, with the probability of transmission per act being 0.0041 for those with genital ulceration versus 0.0011 for those without genital ulceration (Gray et al., 2001a). This association was confirmed by Wawer et al. (2005a), who also showed that the presence of genital ulcer disease was significantly associated with a higher risk of HIV-1 transmission per coital act (adjusted rate ratio, 2.04; 95% CI, 1.04 – 3.99). In their prospective cohort study among Kenyan truck drivers, Baeten et al. (2005) found genital ulcer disease and urethritis to be associated with slightly increased per-contact infectivity estimates (0.0063 among all men versus 0.0073 among men with genital ulcer disease), but these differences were not statistically significant.

It is suggested that genital ulceration has a stronger effect on susceptibility than it has on infectivity. Gray et al. (2001b) reported an adjusted rate ratio of 3.1 (95% CI, 2.0 – 5.0) for the effect of GUDs on susceptibility, which is substantially higher than the adjusted rate ratio of 1.6 (95% CI, 0.6 – 4.2) for the effect of genital ulcer disease on infectivity. In their systematic review, Röttingen et al. (2001) also concluded that clinically diagnosed genital ulcerative and non-ulcerative diseases especially increase susceptibility to HIV-1, both in women and men, with the effect 1.6 times higher in men.

In what follows, some specific STDs and their contribution to the risk of HIV-1 infection will be discussed, including chlamydia, gonorrhoea and herpes simplex virus type 2 (HSV-2), the latter being the major cause of genital ulcer disease in both developing and developed countries. Of all the STDs, the possible
correlation between HSV-2 and HIV-1 infection is among one of the best studied to date, and there is substantial evidence that concomitant infection with HSV-2 enhances both HIV-1 susceptibility and subsequent sexual viral transmission.

In one study, using data from the Rakai cohort study, the probability of HIV-1 infection per coital act was found to be fivefold higher if the susceptible partner was HSV-2 seropositive instead of HSV-2 seronegative (0.002 versus 0.0004 per contact). In addition, subclinical HSV-2 infection tended to be almost as important as symptomatic genital ulcer disease in increasing susceptibility to HIV-1, with per-contact probabilities of HIV-1 infection of 0.0019 and 0.0031, respectively (Corey et al., 2004).

In their cohort study in Kayunga district, Uganda, Guwatudde et al. (2009) concluded that HSV-2 prevalence was strongly associated with prevalent HIV-1 infection (adjusted OR, 3.9; 95% CI, 2.50 – 6.17) as well as incident HIV-1 infection (adjusted rate ratio, 8.7; 95% CI, 1.11 – 67.2). A correlation between HSV-2 and HIV-1 was also identified in a study among male factory workers in Zimbabwe after controlling for multiple sex partners, paying for sex and history of STDs (adjusted OR, 8.0; 95% CI, 4.8 – 13.1) (Gwanzura et al., 1998). These findings are in keeping with those from a cross-sectional population-based study in four African cities. Among women, the adjusted odds ratio for the association between HSV-2 and HIV-1 ranged from 4.0 (95% CI, 2.0 – 8.0) in Kisumu to 5.5 (95% CI, 1.7 – 18) in Yaoundé, and those among men ranged from 4.6 (95% CI, 2.7 – 7.7) in Ndola to 7.9 (95% CI, 4.1 – 15) in Kisumu (Weiss et al., 2001).

However, limited causal inferences can be drawn from the associations described on the basis of cross-sectional study designs. Reversed causality might be equally true, whereby HIV infection causes genital ulcer diseases, rather than vice versa. Nonetheless, the results of a nested case-control study – which is more suitable for assessing the timing of genital ulcer disease relative to HIV seroconversion – showed that HIV acquisition remained associated with HSV-2 seropositivity (OR, 1.7; 95% CI, 1.2 – 2.4) (Serwadda et al., 2003). In another case-control study in rural Tanzania, a strong association between HSV-2 infection and HIV-1 seroconversion was once again observed in men being HSV-2 positive at baseline (adjusted OR, 6.12; 95% CI, 2.52 – 14.9) and in men acquiring HSV-2 infection during follow-up (adjusted OR, 16.8; 95% CI, 6.06 – 46.3). A weaker association was observed in women, with adjusted odds ratios of 1.32 (95% CI, 0.62 – 2.78) and 2.36 (95% CI, 0.81 – 6.84), respectively. These findings also indicate that recent acquisition of HSV-2 seems to increase the risk of HIV-1 acquisition even more than prevalent HSV-2 infection (Del Mar Pujades Rodriguez et al., 2002).

However, a study conducted among a population of Zimbabwean sex workers showed more equivocal
findings, and concluded that rate and quantity of HIV-1 genital shedding did not appear to be altered by the presence of HSV-2 genital shedding. No difference was found between HIV-1 shedding among women shedding HSV-2 and women not shedding HSV-2, which translated into an adjusted odds ratio of 0.8 (95% CI, 0.2 – 3.3) between shedders and non-shedders (Cowan et al., 2006).

In a study among clinic attenders in Kenya, McClelland et al. (2002) failed to show that women shedding cervical HSV-2 were more likely to shed HIV-1, although they did find that women shedding higher quantities of cervical HSV-2 were more likely to shed HIV-1. There was a significant Pearson correlation of 0.24 (P-value 0.05) between the quantities of HSV-2 DNA and HIV-1 RNA in the cervical secretions of HSV-2 shedding women. A tenfold increase in the quantity of cervical HSV-2 DNA was associated with 1.35-fold higher cervical HIV-1 RNA levels (95% CI, 1.00 - 1.81), and with 1.36-fold greater odds of detection of HIV-1 proviral DNA (95% CI, 1.05 - 1.75). An association between levels of HSV-2 shedding and levels of HIV-1 shedding was also noticed by Mbopi-Keou et al. (2003) in a small number of women from Bangui, Central African Republic.

Johnson and Lewis (2008) found the odds of HIV-1 detection to be increased significantly in the presence of chlamydial infection (OR, 1.8; 95% CI, 1.1 – 3.1) and gonorrhoea (OR, 1.8; 95% CI, 1.2 – 2.7). However, when combining the results of several studies, HIV-1 was not detected more frequently in the genital secretions of HIV-infected persons with chlamydia than in the genital secretions of those without chlamydia (Rotchford et al., 2000). However, chlamydial infection and gonorrhoea seem to be associated with detection of cervical interleukin 10 (IL-10), which is an enhancer of macrophage HIV-1 replication. These observations have been regarded as indicators of increased susceptibility, but they also could be markers of increased infectivity (Röttingen et al., 2001).

Although sexual risk behaviour may be one factor explaining the higher risk of HIV infection among individuals with other STDs, possible other explanations for the perceived negative synergy between HIV-1 and other STDs include disruption of the epithelial barrier, immune activation of host cells and increased levels of HIV-1 shedding in the genital tract. Genital ulcerative diseases cause physical breaches in the mucosal barrier, thereby facilitating susceptibility to and transmission of HIV-1 infection. In addition, other STDs may affect the secretion of cytokines and upregulate transcription factors, which in turn can enhance HIV-1 replication. The hypothesis that shedding of HIV-1 in the genital tract could be facilitated by STDs was confirmed by Johnson and Lewis (2008). The probability of HIV-1 detection in the genital tract in their systematic review and meta-analysis was significantly increased in the presence of urethritis (OR, 3.1; 95% CI, 1.1 – 8.6), cervicitis (OR, 2.7; 95% CI, 1.4 – 5.2), cervical discharge (OR, 1.8; 95% CI, 1.2 – 2.7), gonorrhoea (OR, 1.8; 95% CI, 1.2 – 2.7), chlamydia (OR, 1.8; 95% CI, 1.1 – 3.1)
and vulvovaginal candidiasis (OR, 1.8; 95% CI, 1.3 – 2.4).

Rebbapragada et al. (2007) tried to elucidate the negative mucosal synergy between HSV-2 and HIV in the female genital tract. Their findings suggest a vicious circle in which HSV-2 infection increases HIV target cells in the genital mucosa and subsequent HIV infection impairs HSV-2 mucosal immune control. In HIV uninfected female sexual workers, HSV-2 infection was associated with a threefold increase in cervical CD4 T-cells expressing the HIV co-receptor CCR5, which is used by R5-tropic strains to enter and infect host cells. The increase in CCR5 positive cells and chemokines during episodes of HSV-2 shedding may recruit activated CD4 positive T-cells to the genital tract, and therefore enhance local replication of HIV and consequently increase HIV transmission during sexual intercourse.

As STDs are associated with increased levels of HIV-1 and subsequent transmission of HIV-1 infection, it seems plausible that treatment of concomitant STDs could result in a substantial reduction in the genital shedding of HIV-1, thereby decreasing the infectivity of HIV-1 seropositive individuals. According to a prospective interventional study, effective treatment of cervicitis indeed resulted in significant decreases in HIV-1 infected cells in cervical secretions (OR, 2.8; 95% CI, 1.3 – 6.0) (McClelland et al., 2001). However, Wolday et al. (2004) failed to show a significant reduction in genital HIV shedding after syndromic treatment of STDs.

The evidence for vaginal infections that are not necessarily sexually transmitted as cofactors in HIV transmission is less clear than the evidence for classical STDs, but is mounting. Candidiasis and bacterial vaginosis are among the most common reproductive tract infections in women worldwide. They are not traditionally considered STDs, as the presence of both primarily depends on the microbial ecosystem of the vagina. In bacterial vaginosis (BV), the normal hydrogen peroxide producing lactobacilli of the vagina are replaced by a mixed flora of Gardnerella vaginalis and anaerobes, resulting in a raised vaginal pH and a lack of hydrogen peroxide (Finch et al., 2005). Candidiasis, on the other hand, is caused by the yeast Candida albicans, a normal inhabitant of the vaginal flora, but with the potential to become pathogenic under some circumstances, such as immunosuppression (Mims et al., 2004).

According to a population-based study in rural Uganda, women with any microbiological evidence of abnormal vaginal flora were significantly more likely to be infected with HIV-1 than those with no such evidence (OR, 1.52; 95% CI, 1.22 – 1.90) (Myer et al., 2005a). In a prospective, observational cohort study among women in Zimbabwe and Uganda, women with BV or vaginal yeast were more likely to acquire HIV, especially if the condition was present at the same visit as the new HIV infection and the visit preceding it, with corresponding hazard ratios of 2.50 (95% CI, 1.68 – 3.72) for BV and 2.97 (95%
Heterogeneity in susceptibility to and infectivity of HIV  

CI, 1.67 – 5.28) for vaginal yeast, respectively (Van de Wijgert et al., 2008). Miller et al. (2000) also observed that HIV acquisition was significantly higher in women without lactobacilli or with abnormal vaginal flora compared with those with lactobacilli in the vagina.

In a case-control study among South African women, BV was significantly associated with an increased risk of HIV-1 seroconversion (adjusted OR, 2.01; 95% CI, 1.12 – 3.62). Women with severe BV were 12 times more likely than women with normal vaginal flora to be infected with HIV-1 (OR, 2.08; 95% CI, 1.48 – 2.94) (Myer et al., 2005a). Similarly, in women attending antenatal clinics in Malawi, prevalent HIV infection was 3 times more likely in those with clinical signs of BV (OR, 3.0; 95% CI, 2.4 – 3.8) (Taha et al., 1999). In a study of Kenyan sex workers, the risk of HIV-1 seroconversion was associated with microbiological evidence of BV as well (hazard ratio, 1.9; 95% CI, 1.1 – 3.1) (Martin et al., 1999).

The above results suggest that a vaginal milieu with altered pH levels and a lack of hydrogen peroxide production might be favourable for HIV-1 transmission. Furthermore, changes in the cervicovaginal epithelial integrity, inflammation and immune activation in the female genital tract have also been postulated as possible mechanisms by which BV and vaginal yeast could increase HIV acquisition (Van de Wijgert et al., 2008). Inflammation and its accompanying immunologic changes, including the induction of higher levels of pro-inflammatory cytokines, are not only likely to enhance HIV susceptibility, but they could also increase HIV infectivity of affected women by stimulating HIV expression, and thereby raising HIV levels in the genital tract (Martin-Hilber et al., 2007). In HIV-infected women, Spinillo et al. (2005) found vulvovaginal candidiasis to be associated with increasing levels of cell-associated HIV-1 RNA (OR, 1.97; 95% CI, 1.09 – 3.57) and cell free HIV-1 RNA (OR, 2.03; 95% CI, 1.10 – 3.73) in cervicovaginal secretions. However, not all studies have identified an association between BV and candidiasis and HIV-1 (Röttingen et al., 2001; Kjetland et al., 2006), and additional data are required to help establish whether these conditions truly increases women’s risk of acquiring HIV-1 infection.

The same mechanism of immune activation might also explain the high prevalence of filariasis, tuberculosis and malaria in hyperendemic HIV regions, and vice versa. Of course, HIV affects the ability of the immune system to respond effectively to pathogens, thereby increasing the risk of concomitant infections, but the reverse could also be true. Aberrant immune activation, especially after filariasis, tuberculosis and malaria, may raise susceptibility to HIV infection (Chersich and Rees, 2008). It would lead me too far to enter into further details, but this hypothesis could indicate that HIV prevention could benefit from improved control of these infections as well.

Schistosomiasis, another non-sexually transmitted disease caused by the parasite Schistosoma
haematobium, may also contribute to the risk of HIV-1 infection in sub-Saharan Africa, as the majority of people infected with schistosomiasis are on the African continent. Urinary as well as genital schistosomiasis can cause lesions on the uterine cervix, genital sandy patches and blood vessel friability, thereby providing points of entry for viral transmission (Kjetland et al., 2006). To my knowledge, Kjetland et al. (2006) were the only one to examine this possible association among women in rural Zimbabwe and they concluded that schistosomal infection of the genital mucosa was significantly associated with HIV seropositivity (adjusted OR, 2.9; 95% CI, 1.11 – 7.5).

Finally, it is noteworthy that women might be at a higher risk of contracting HIV-1 because of their pronounced vulnerability to infection with other STDs. According to a population-based study of a village population in Tanzania, women were 5 times more likely to have a STD than men, yet women were 12 times less likely than men to be ever treated for genital discharge, partly because sexually transmitted infections are more often asymptomatic in women than in men (Klouman et al., 1997). In addition, the female genital tract offers a larger area of mucosal tissue subject to micro-injuries through which pathogens can enter the bloodstream (Chersich and Rees, 2008).

The interaction of the many STDs with HIV is quite complex, with the possibility of reciprocal influences on susceptibility and infectivity. Concomitant STDs in HIV-1 seronegative individuals might increase their susceptibility to HIV-1 infection, whereas the infectivity of HIV-1 positive individuals might be enhanced in the presence of co-existing STDs. In terms of public health, the most important interaction is the impact of STDs on HIV transmission, as this would allow the treatment of STDs to be used as a means of controlling the spread of HIV (Röttingen et al., 2001).

### 3.5 Menstrual cycle

Some studies have shown that male-to-female transmission is approximately 2 times more effective than female-to-male transmission (Mmbaga et al., 2007; Wilson et al., 2008), although this finding is inconsistent with other studies (Wawer et al., 2005a). However, considerable evidence indicates that HIV disease in women, while it progresses at the same rate, is different than in men. A potential difference between HIV in women and men is the impact of the significant hormonal changes associated with the menstrual cycle on mucosal immunity and HIV genital tract shedding (Al-Harthi et al., 2001).

Several studies have examined mucosal virus levels at different times during the menstrual cycle to evaluate the influence of endogenous hormones (estradiol and progesterone) on viral shedding. In their prospective cohort study, Money et al. (2003) observed no statistically significant difference in plasma
viral load throughout the menstrual cycle, but there was a significant decrease in genital tract viral load at the peri-ovulatory phase, when estradiol levels are typically high (see figure 4). These findings are in keeping with those from another study, in which the lowest levels of cervical HIV-1 RNA were present at the mid-cycle luteinizing hormone surge, followed by an increase in viral levels, which reached a maximum before the start of menses (Benki et al., 2004). Reichelderfer et al. (2000) also noticed a cyclic pattern of HIV-1 RNA levels in cervical secretions during the menstrual cycle. Genital tract HIV-1 RNA levels were highest during menses and in the week preceding menses and lowest immediately thereafter and gradually increased over the next two weeks until the next menses. This pattern was not seen for peripheral blood virus levels, suggesting a genital tract–specific hormonal effect on viral shedding. In contrast to these findings, some studies (Mostad et al., 1998; Villanueva et al., 2002) failed to identify a significant effect of the menstrual cycle on HIV-1 RNA levels in plasma and genital secretions.

However, there is considerable biological evidence to suggest a potential association between cyclic fluctuations in levels of endogenous hormones during the menstrual cycle and the risk of HIV transmission. One plausible explanation is the observation that the menstrual cycle is characterized by alterations in the levels of estradiol and progesterone, causing physiological changes in the genital tract mucosa, which could have an influence on the vulnerability of the epithelium and on viral concentrations (Al-Harthi et al., 2001; Benki et al., 2004).

In a hypo-estrogenic state, induced by progesterone, the vaginal mucosa may become more atrophic and susceptible to mucosal tears during intercourse, creating a route for HIV infection (Kiddugavu et al., 2003; Stephenson, 1998). Moreover, a hypo-estrogenic state is also associated with a decreased colonization of lactobacilli. Vaginal lactobacilli produce lactic acid to maintain a low vaginal pH and to ensure dominance of lactobacilli and other acidophilic bacteria in the vagina. Therefore, lower concentrations of lactobacilli result in an increased vaginal pH, which might enhance HIV transmission, as HIV particles appear to survive best at a neutral pH (Stephenson, 1998). Lactobacilli might directly kill
free virus in the vagina or might prevent bacterial vaginosis, which has been associated with an increased risk of HIV acquisition, as I have pointed out earlier. However, progesterone increases the viscosity of cervical mucus, which may inhibit HIV transmission (Stephenson, 1998).

The observed changes in HIV-1 RNA levels in genital tract secretions throughout the menstrual cycle could also be due to a sloughing off of infected cells during menses, as a result of a decline in both progesterone and estrogen levels. Other postulated mechanisms include a direct effect of steroid hormones on viral replication or less directly, through the effect of hormones on the availability or susceptibility of HIV-1 target cells to viral infection (Benki et al., 2004). Mechanisms for a hormonal effect on production of virus have been suggested by in vitro studies demonstrating regulation of the HIV-1 long-terminal repeat by steroid hormone receptors and increased surface expression of chemokine receptors on endocervical CD4 T-cells after progesterone treatment (Benki et al., 2004). Menstrual cycle patterns to genital cytokine production have been documented as well. Al-Harthi et al. (2001) found that genital cytokine levels, but not plasma cytokine levels, were significantly elevated during menses in HIV-1 seropositive women when compared to HIV-1 negative women.

These explanations support the hypothesis that alterations in steroid hormone levels during the menstrual cycle may increase HIV transmission. Susceptibility to HIV-1 could be elevated by estrogen-induced atrophic changes in the vaginal mucosa, but the most important interaction seems to be the impact of the menstrual cycle on infectivity of HIV-1. Because the highest HIV-1 RNA levels were seen before or during menses, as a result of decreased colonization of lactobacilli, increased viral replication or sloughing off of infected cells, HIV-1 infected women should be counselled that they may be at increased risk of transmitting HIV to their sexual partners during this interval (Reichelderfer et al., 2000).

3.6 Hormonal contraceptive use

If the menstrual cycle is thought to influence HIV transmission, it is a merely logical reasoning that the use of hormonal contraception might alter HIV transmission probabilities as well. But according to the current WHO Medical Eligibility Criteria for Contraceptive Use guidelines, there should be no restrictions on the use of hormonal contraception by women at risk of acquiring HIV (WHO, 2004). However, studies on the effect of hormonal contraceptive use on HIV-1 acquisition have generated conflicting results.

A meta-analysis of 28 studies found a significant association between the use of oral contraceptive pills – mostly consisting of a combination of estrogen and progestogen – and HIV-1 infection, with the strongest effect for studies conducted in Africa (OR, 1.65; 95% CI, 1.09 – 2.52) (Wang et al., 1999). In a
randomized trial among reproductive-age women in Malawi, injectable hormonal contraceptive use was significantly associated with HIV-1 seroconversion (adjusted OR, 10.42; p-value 0.03), but not with established HIV-1 infection (Kumwenda et al., 2008). Lavreys et al. (2004) conducted a prospective study among commercial sex workers in Kenya and also reported that both injectable (depot medroxyprogesterone acetate, DMPA) (hazard ratio, 1.8; 95% CI, 1.4 – 2.4) and oral contraceptive pills (hazard ratio, 1.5; 95% CI, 1.0 – 2.1) were significantly associated with an increased risk of HIV-1 acquisition. In a systematic review, in which a total of 32 studies relating to hormonal contraception and risk of HIV transmission were included, a seroconversion risk ratio of 0.30 (95% CI, 0.05-2.1) was found for women who used the oral contraceptive pill during a defined exposure period, compared with those who did not (Stephenson, 1998).

However, most of the studies that found a significant association between hormonal contraceptive use and HIV-1 acquisition were conducted among commercial sex workers, who have a higher frequency of contraceptive use, a higher turnover of sexual partners and more frequent contacts with high-risk sexual partners than the general population (Kiddugavu et al., 2003). It is thus likely that studies among high-risk women may have been affected by uncontrolled confounding.

Other studies have found no relationship between either oral or injectable contraceptive use and incident HIV-1. A study conducted in a general population in Rakai, Uganda, could not find an association between the use of hormonal contraception and HIV acquisition after adjustment for behavioural confounding. The unadjusted incidence rate ratio for hormonal contraceptive users was 1.56 (95% CI, 1.00 – 2.33) compared with non-hormonal contraceptive users. After adjustment, the incidence rate ratio associated with hormonal contraceptives was reduced to 0.94 (95% CI, 0.53 – 1.64). The adjusted estimates were 1.12 (95% CI, 0.48 – 2.56) with oral contraceptive use and 0.84 (95% CI, 0.41 – 1.72) with injectable methods, suggesting substantial behavioural confounding between hormonal contraception and higher risk behaviours (Kiddugavu et al., 2003). Kleinschmidt et al. (2007) investigated the effect of injectable progesterone contraceptive use and the risk of HIV infection in a South African family planning cohort, and they also failed to find evidence of an association between HIV infection and injectable contraceptives.

The mechanisms by which hormonal contraception might facilitate HIV infection are unknown, but it seems most likely that the explanations in the previous section equally apply to the possible association between hormonal contraceptive use and viral transmission. Several studies have shown that especially progesterone reduces the efficacy of the vaginal barrier through its anti-estrogenic effects, resulting in atrophic changes of the vaginal mucosa and a decreased colonization of lactobacilli. Hormonal
contraceptive use could also increase HIV transmission risk by altering local cell-mediated immune responses and/or by increasing recruitment of inflammatory and other target cells to the genital tract (Stephenson, 1998; Miller et al., 2000; Prakash et al., 2002; Morrison et al., 2007). Langerhans cells, antigen presenting cells that express CD4 receptors on their surface, are important target cells in the vagina and cervix for heterosexual transmission of HIV (Miller et al., 2000), but Mauck et al. (1999) found no significant change in the mean number of Langerhans cells in vaginal wall specimens after DMPA use. Alterations in cell-mediated immunity were observed in oral contraceptive pill users, who appeared to show an increased expression of CCR5 on both CD4 and CD8 T-lymphocytes, thereby increasing susceptibility to HIV infection (Prakash et al., 2002).

On the basis of these observations, it would be too soon to conclude that hormonal contraceptive use profoundly influences the risk of HIV transmission. However, we must bear in mind from the former section that significant correlations were observed between menstrual cycle-associated steroid hormones and HIV infection. As an ever increasing number of women in sub-Saharan-Africa is advised to take control of their own fertility by using hormonal contraception, more research is needed to confirm or to disprove the hypothesis that hormonal contraceptive use increases the risk of HIV transmission.

### 3.7 Cervical ectopy

Cervical ectopy refers to the condition in which columnar cells from the endocervix are present on the ectocervix. Because of its thin, vascularized epithelium, the area of ectopy is more susceptible to sexually transmitted diseases, including HIV infection. This is especially the case during adolescence, when this condition is relatively common. Although studies in earlier years have shown that the area of cervical ectopy is associated with an increased risk of HIV acquisition, not much research on this topic has been done in recent years. The only study that could be identified, was a nested case-control study among women in South Africa. In this study, ectopy extending over more than 20 percent of the cervix was associated with HIV seroconversion (adjusted OR, 2.18; 95% CI, 1.01 – 4.69) (Myer et al., 2006b).

### 3.8 Genetic polymorphisms

In recent years, more and more research has been directed towards attempts to unravel the genetic basis of a wide variety of diseases and medical conditions, including susceptibility to HIV-1. Several polymorphisms in host genes involved in modulating viral cell entry and immune responses have been identified, of which the distribution varies substantially between individuals of different racial, ethnic and high-risk groups (Gonzalez et al., 2001).
Infection by HIV-1 occurs by the binding of the viral envelope protein gp120 to two proteins on the surfaces of target cells, CD4 and a chemokine co-receptor, typically either CCR5 or CXCR4 (see figure 1). Expression of CCR5, the major co-receptor used by HIV-1 macrophage (M)-tropic strains to enter into the cells, and its ligands is widely regarded as central to the pathogenesis of HIV-1 infection (Gonzalez et al., 2001). Members of the CC chemokine receptor (CCR) family, such as CCR2 and CCR5, are bound by CC-motif chemokine ligands (CCLs), including RANTES, and macrophage inflammatory proteins (MIP-1α and MIP-1β). Members of the CXC receptor (CXCR) family, such as CXCR4, are bound by ligands such as CXCL12, which encodes stromal cell-derived factor-1 (SDF-1). The role of these molecules in HIV-1 infection was recognized more clearly when uninfected persons capable of suppressing replication of macrophage-tropic HIV-1 were found to have increased levels of RANTES, MIP-1α and MIP-1β. These chemokines are thought to diminish viral replication by competing with HIV-1 for its principal receptor by regulating receptor expression (Kaslow et al., 2005).

CCR5Δ32 homo- and heterozygosity and the CCR5-59029G allele are significant predictors of reduced expression of CCR5 chemokine receptors on CD4 cells and have been shown to affect HIV-1 transmission and disease progression (Thomas et al., 2006). Individuals homozygous for the CCR5Δ32 mutation, a naturally occurring 32-bp deletion in the gene coding for the major HIV-1 co-receptor CCR5, have no functional CCR5 receptors, and are highly protected against HIV-1 infection. Individuals heterozygous for the mutant allele have reduced receptor densities and lessened susceptibility to HIV infection (Williamson et al., 2000; Kaslow et al., 2005; Thomas et al., 2006; Agrawal et al., 2007). HIV resistance in CCR5Δ32 homozygotes may result from both genetic loss of CCR5 on the cell surface and active downregulation of CXCR4 expression by the mutant CCR5Δ32 protein. The CCR5Δ32 protein may form heterodimers with wild-type CCR5 and CXCR4 which are retained in the endoplasmatic reticulum and result in reduced cell surface expression of the co-receptors (Agrawal et al., 2007). However, HIV-1 infection in individuals homozygous for the 32-bp deletion in the CCR5 gene has been increasingly documented. This could be due to the fact that HIV-1 infection can be mediated by viruses that exclusively utilize CXCR4, and therefore cannot infect macrophages (Michael et al., 1998).

In the CCR2 receptor, a valine-to-isoleucine mutation at position 64 in the coding region (CCR2b-64I) was found to increase the AIDS-free survival in heterozygotes by several years, although the impact of this polymorphism on pathogenesis is inconsistent between study populations (Williamson et al., 2000; Kaslow et al., 2005). The role of the CCR2 single nucleotide polymorphism in preventing infection is somewhat ambiguous as well. A protective effect of the 64I-bearing genotypes, comparable to that seen for disease progression, has been observed for perinatal transmission, but evidence for a role in decreased susceptibility in the context of heterosexual transmission is mostly lacking (Kaslow et al.,
Because the CCR2-64I allele is mostly found in the presence of the CCR5-59029 AA or AG genotype, it is suggested that any effects of the CCR2 mutant allele on CCR5 expression can be attributed to its linkage to the 59029 genotype (Thomas et al., 2006).

The levels of the ligands of CCR5 (MIP-1α, MIP-1β and RANTES) were also found to be consistent and reproducible immunological parameters associated with disease progression and HIV-1 transmission. These chemokines exhibit anti-HIV-1 properties in vitro, and in vivo evidence strongly supports the notion that their expression levels may influence susceptibility to HIV-1 infection (Gonzalez et al., 2001).

Gonzalez et al. (2005) noted significant interindividual and interpopulation differences in the copy number of a segmental duplication encompassing the gene encoding CCL3L1 (MIP-1α), a potent HIV-1 suppressive chemokine, with the possession of a CCL3L1 copy number lower than the population average being associated with a markedly enhanced susceptibility to HIV-1 infection. In an earlier study, Gonzalez et al. (2001) observed that possession of the MIP-1α haplotype pair CC/TT – which is more common in African Americans compared to European Americans – was associated with a lower risk of acquiring HIV-1 compared with the ancestral haplotype CC/CC. In African Americans, possession of the TT MIP-1α haplotype was associated with a significantly lower risk of HIV-1 acquisition compared with the ancestral haplotype CC (OR, 0.623; CI, 0.406 – 0.956).

CXCL12, a CXC chemokine, plays an important role in HIV, because its receptor (CXCR4) is also the coreceptor used by HIV T-cell (T)-tropic strains. The +801G/A single nucleotide polymorphism has been extensively associated with clinical features of HIV infection, although there are some contradictory reports. Even though it was proposed originally that the -801A allele was associated with higher CXCL12 production, later studies indicated the opposite, and other reports claimed that there were no differences in the CXCL12 production by the A or G alleles (Colobran et al., 2007). None of the few studies of this variant marker of susceptibility to infection have definitively implicated it as a predisposing or protective factor in susceptible individuals (Kaslow et al., 2005).

CXCL12 encodes stromal cell-derived factor-1 (SDF-1), and a study by Tiensiwakul (2004) demonstrated in a population of seronegative high-risk Thais that a polymorphism in SDF-1 (SDF1-3’A) confers resistance to HIV-1 infection. This polymorphism induces an increase of SDF-1 chemokine production, in which it competes with HIV-1 in binding to the CXCR4 receptor, and in turn inhibits HIV-1 infection. It is suggested that this polymorphism may represent the resistant mechanism in the extremely rare CCR5Δ32 mutant of other ethnic groups, such as Africans and Japanese.
In a study among highly exposed uninfected Kenyan sex workers, Ball et al. (2007) concluded that polymorphisms in the viral transcriptional regulator IRF-1 (interferon regulatory factor 1) gene were associated with resistance to HIV-1 infection and a lowered level of IRF-1 protein expression. IRF-1 is a transcription factor that regulates the expression of a number of genes whose products play crucial roles in innate as well as adaptive immunity. The expression of IRF-1 is induced by IFN-γ and TNF-α and antagonized by IL-4. IRF-1 also triggers IL-2p40 expression and represses IL-4 transcription, and is therefore central in modulating the balance between Th1- and Th2-type T-cell responses. Three polymorphisms in IRF-1, located at 619, the microsatellite region and 6516 of the gene, showed associations with resistance to HIV-1 infection. The 619A, 179 at IRF-1 microsatellite and 6516G alleles were associated with the HIV-1 resistant phenotype and a reduced likelihood of seroconversion. Peripheral blood mononuclear cells from patients with protective IRF-1 genotypes exhibited significantly lower basal IRF-1 expression and reduced responsiveness to exogenous IFN-gamma stimulation.

As most of the reported genetic polymorphisms were only quite recently discovered, it is not surprising that not much information is available on HIV-1 transmission probabilities associated with these polymorphisms. It is not ruled out that future research will contribute to the identification of more polymorphisms and a better understanding of their role in influencing susceptibility to HIV-1 infection.

3.9 Physical and chemical barrier methods

Physical barrier methods, such as the male and female condom, are widely considered to be the most cost-effective interventions to prevent pregnancy and infection with HIV and other sexually transmitted diseases (STDs).

A review of studies of the male condom by Weller and Davis (2002) determined that, when used consistently, the male condom would result in an 80 percent reduction in HIV incidence. A protective effect of male condom use was confirmed by several other studies. Gregson et al. (2006), for example, found that for men, consistent condom use in casual partnerships reduced the risk of HIV infection (adjusted hazard ratio, 0.38; 95% CI, 0.15 – 0.99). According to a household survey among young people in South Africa, inconsistent condom use was significantly associated with HIV infection (adjusted OR, 1.41; 95% CI, 1.04 – 1.90) (Pettifor et al., 2005). In a population study in Rakai, Uganda, consistent condom use was found to be significantly associated with a reduction in HIV incidence (rate ratio, 0.37; 95% CI, 0.15 – 0.88), syphilis (OR, 0.71; 95% CI, 0.53 – 0.94) and gonorrhoea/chlamydia (OR, 0.50; 95% CI, 0.25 – 0.97) after adjustment for socio-demographic and behavioural characteristics (Ahmed et al., 2001). In the same study, irregular condom use was not protective against HIV (rate ratio, 0.96; 95%
Cl, 0.53 – 1.74), and was even associated with a significantly increased risk of contracting gonorrhoea/chlamydia (OR, 1.44; 95% CI, 1.06 – 1.99).

But despite its protective effect, the proportion of male condom-users in sub-Saharan Africa is extremely low. This was shown by data from surveys conducted in Burkina Faso, Ghana, Malawi and Uganda, where 38, 47, 20 and 36 percent of male adolescents reported consistent condom use in the 3 months preceding the survey, respectively (Bankole et al., 2007).

As a result of gender norms in many African societies, women are often not empowered enough to demand safe sexual practices from their partners. In this context of limited decision-making power, microbicides – vaginally or rectally applied substances aimed at reducing sexual transmission of STDs – could offer these women the possibility to take control of their own protection against HIV infection during sexual intercourse. Space precludes a complete description of all types of microbicidal agents that have been or are currently under evaluation. Therefore, this section is merely intended to provide the reader with a brief general picture of microbicides.

Topical microbicides can be classified into different groups of agents, including surfactants or membrane disruptors, vaginal milieu protectors, viral entry inhibitors and reverse transcriptase inhibitors (Cutler and Justman, 2008). It is already obvious from the word itself that membrane disruptors cause disruption of the viral membrane, thereby inactivating pathogens and preventing them from infecting susceptible target cells in the genital tract. Vaginal milieu protectors, on the other hand, act by maintaining the acidic vaginal pH, and thus, by enhancing the intrinsic vaginal defence mechanisms (Dhawan and Mayer, 2006). Finally, viral entry inhibitors and reverse transcriptase inhibitors provide protection against infection with genital pathogens by binding to the viral envelope to block receptor binding (Dhawan and Mayer, 2006) and by hampering replication of the virus after it has entered the cell, respectively.

But although the development of an effective microbicide has been the subject of intensive research internationally, testing of several experimental microbicides in earlier years yielded disappointing results. However, results from a recent clinical trial involving more than 3,000 women in southern Africa and the United States were encouraging, as one of the candidate microbicides (PRO 2000 gel) was found to have a 30 percent level of effectiveness in preventing male-to-female sexual transmission of HIV (Microbicide Trials Network, 2009). Although this finding was not statistically significant, it certainly points towards a step into the right direction. Several other candidate microbicides are currently being studied in clinical trials, and the results of these trials should be watched very carefully, as microbicides can provide a potential glimmer of hope in additional prevention strategies in the battle against HIV/AIDS.
Because of its higher expression of CD4 cells and CCR5 chemokine receptors and its thinner lining of epithelial cells, the cervix could be more vulnerable to HIV and other STDs than other areas of the female reproductive tract (Matthews and Harrison, 2006). Therefore, cervical barriers, such as the diaphragm, may also provide protection against HIV and other STDs, although this is not yet proven. Observational studies indeed indicate that the diaphragm may protect against the acquisition of HIV and other STDs (Matthews and Harrison, 2006), but a randomised controlled trial by Padian et al. (2007) showed poor efficacy of the diaphragm in preventing HIV infection.

In the meantime, the female condom is the only safe and effective woman-controlled HIV prevention option available. However, it is not frequently used due to issues of availability, secrecy, product costs, discomfort during sexual intercourse, difficulties in use and sensitivity to polyurethane (UNFPA, 2006). Although little research has been devoted to evaluating the specific HIV prevention effectiveness of the female condom, it is likely that it provides at least the same level of protection as the male condom (UNAIDS, 1999). In a report by the United Nations Population Fund (2006), it was stated that perfect use of the female condom by women having sexual intercourse twice a week with an HIV infected partner could reduce the annual risk of acquiring HIV by more than 90 percent.

Although research into the development of topical microbicides has recently generated encouraging results, it will still take some time before these products will be available for widespread use, and the effectiveness of these first agents will definitely not yet approach that of male and female condoms. Therefore, promotion of consistent and correct use of physical barrier methods must be continued and integrated into all HIV prevention services.

3.10 Demographic, socio-cultural and behavioural variables

One of the most puzzling features of the HIV epidemic in sub-Saharan Africa is the large variation in its size among different countries. According to a report by UNAIDS in 2008, the proportion of infected adults ranges from 24 percent in Botswana to less than one percent in Gambia, Somalia, Mauritania and Madagascar (UNAIDS, 2008). Several factors are believed to be conducive to large epidemics, of which demographic, socio-cultural and behavioural characteristics seem to be as equally important as the aforementioned medical variables. Given space limitations, it is not possible to give a detailed overview of all of the potential variables involved. Therefore, the focus will be on age, level of education, wealth status and marriage as demographic factors, on gender inequality, vaginal practices and male circumcision as socio-cultural factors, and on the key determinants of sexual risk behaviour.
3.10.1 Age

In 2008, young people between 15 and 24 years old accounted for an estimated 45 percent of new HIV infections worldwide (UNAIDS, 2008). As the vast majority of people in sub-Saharan Africa – just like elsewhere in the world – become sexually active during adolescence, it is not surprising that a large part of infections occur during adolescence and early adulthood. This hypothesis was confirmed by a study in Tanzania, where HIV acquisition was found to be independently associated with younger age at enrolment (Watson-Jones et al., 2009). Women in the 16 to 19 age group had four times as much risk of acquiring HIV as women in the 30 to 35 age group (hazard ratio, 4.02; 95% CI, 1.67 – 9.68).

Gray and co-workers (2001a) reported that the probability of transmission per coital act was highest for younger individuals aged 15 – 24 years (0.0013) and 25 – 29 years (0.0017), and decreased at older ages (0.0006 and 0.0009 at age categories 30 – 34 years and 35 – 59 years, respectively). Especially women in the 20 to 24 age groups seem to be most susceptible to HIV infection, as an adjusted odds ratio of 4.16 (95% CI, 1.52 – 11.41) was calculated in women in this age group compared with those in the 15 to 19 age groups (Pettifor et al., 2008). Similar findings were found in a Zambian study, where the bulk of the infected group consisted of those aged 20 to 24 years (Michelo et al., 2006). Men in this age group (OR, 1.75; 95% CI, 1.20 – 2.54) as well as women (OR, 3.24; 95% CI, 2.63 – 4.0) had a significantly higher odds of infection when compared to 15- to 19-year-olds, indicating that especially adults in the younger age groups – the active and reproductive population – are vulnerable to contracting HIV, which has important socio-economic implications for infected individuals and society as a whole.

3.10.2 Marriage

Throughout the developing world, marriage is the central social institution that regulates and sanctions sexual behaviour. However, remarkably little research has been devoted to disentangle the precise role of marriage in the spread of the HIV epidemic in sub-Saharan Africa.

In one of the identified studies, there was a significantly higher risk of infection in men (OR, 6.51, 95% CI, 1.06 – 39.84) and women (OR, 4.75; 95% CI, 1.26 – 17.9) who were unmarried and in a steady relationship, and in men who were divorced, separated or widowed (OR, 4.33; 95% CI, 1.32 – 14.25) compared with those who were married (Quigley et al., 2000). Similar findings were reported by Johnson and Way (2006), who found that, compared with married women, widowed women (OR, 10.9), divorced women (OR, 2.3) and women who were one of three or more wives (OR, 3.4) were all at higher risk for being HIV-positive. These results were also confirmed by another study by Bongaarts (2007). Compared
to a reference group consisting of formally married women, the adjusted odds ratios for cohabitation status were all higher than one, but these effects were only significant for widows (OR, 3.01; 95% CI, 1.20 – 7.56 in Ghana, and OR, 8.14; 95% CI, 4.7 – 14.1 in Kenya) and separated groups (OR, 2.69; 95% CI, 1.29 – 5.63 in Ghana, and OR, 3.17; 95% CI, 1.91 – 5.27 in Kenya).

The annual risk of infection was also significantly higher for exposure before (OR, 1.22; 95% CI, 1.07 – 1.40 in Ghana, and OR, 1.21; 95% CI, 1.12 – 1.31 in Kenya) than after marriage (OR, 1.08; 95% CI, 0.94 – 1.24 in Ghana, and OR, 1.11; 95% CI, 1.02 – 1.21 in Kenya). However, over the life cycle, women spend, on average, more years in marriage than they spend being sexually active before marriage. And although it is lower than before marriage, the annual risk of infection within marriage is still substantial, resulting in the occurrence of more infections within than before marriage (Bongaarts, 2007).

The elevated risk of infection among never-married sexually active women is probably caused by a higher rate of partner change and higher levels of infectivity of partners of never-married than of married women (Bongaarts, 2007). However, according to one study in Malawi, marriage might be associated with behaviour that puts women at increased risk of HIV infection, such as higher numbers of lifetime partners, increased coital frequency and decreased condom use, primarily for the purpose of pregnancy (Clark et al., 2006). The partners of married women also tend to be older, and to have higher HIV prevalence levels. However, it is assumed that they are less infectious as a result of a longer duration since infection (Bongaarts, 2007).

3.10.3 Level of education

In the earlier years of the HIV epidemic in sub-Saharan Africa, the level of education was found to be positively associated with the risk of HIV infection. Previous studies found educated individuals to have a higher risk of HIV-1 infection in Africa. In the study by Mmbaga et al. (2007) with results from 1991, primary (adjusted OR, 2.7; 95% CI, 1.3 – 20.0) and secondary/higher education (adjusted OR, 4.5; 95% CI, 1.4 – 24.9) were associated with an increased risk of HIV-1 infection. Smith et al. (1999) also concluded that higher levels of education were associated with a higher HIV seroprevalence in their cross-sectional analysis of a population-based cohort in Uganda in 1990. After adjustment for socio-demographic and behavioural variables, the adjusted odds ratios of HIV infection were 1.6 (95% CI, 1.2 – 2.1) for primary education, and 1.5 (95% CI, 1.0 – 2.2) for secondary education, relative to no education. The association between education and HIV prevalence was found to be only statistically significant in the rural villages of Uganda.
These findings are somewhat surprising, as schooling is generally considered as a factor increasing access to and understanding of health promotion campaigns. However, higher educational achievement is also associated with higher wealth and increased mobility, and therefore with behaviour that potentially increases exposure to HIV infection (De Walque et al., 2005). Moreover, education in earlier years seldom included HIV prevention or behavioural change programmes, simply because the level of knowledge about the disease and its contributing factors was by far not as comprehensive as it is now.

More recent studies have shown that the association between schooling level and HIV prevalence now is reversed. In 2005, the study by Mmbaga et al. (2007) was repeated and a reversed association was observed, where reduced odds of infection were associated with primary (adjusted OR, 0.5; 95% CI, 0.2 – 0.8) and secondary/higher education (adjusted OR, 0.4; 95% CI, 0.3 – 0.9). This was most pronounced among educated men. A corresponding reduction in risk behaviours was also observed. Condom use was much more frequent (adjusted OR, 2.8; 95% CI, 1.1 – 7.3), and a smaller proportion of both educated men and women reported having had two or more sexual partners in the past year. In an analysis that focused on young South African women reporting one lifetime sexual partner, not having completed high school also translated into an increased odds of HIV infection compared with women who had completed high school (adjusted OR, 3.75; 95% CI, 1.34 – 10.46) (Pettifor et al., 2008).

De Walque et al. (2005) described changes in the association between schooling levels, HIV prevalence and condom use in a rural population-based cohort between 1989/1990 and 1999/2000 in Uganda. In 1989/1990, higher educational attainment was still associated with a higher risk of HIV-1 infection, especially among males, although this association was not significant any more after adjustment for age. In 1999/2000, they found a significant relationship between higher educational attainment and lower HIV prevalence for females aged 18 – 29 years, even after adjustment for age, gender, marital status and wealth. Each additional year of education was found to lower the risk of being HIV positive significantly (adjusted OR, 0.86; 95% CI, 0.77 – 0.96). Moreover, condom use increased during the study period, and this increase was concentrated among more educated individuals.

A similar shift towards reduced risks of HIV infection in groups with higher education was seen in a study from Zambia, in which data were collected through serial population-based surveys conducted in urban and rural communities in 1995, 1999 and 2003 (Michelo et al., 2006). During the study period, prevalence patterns were similar in rural and urban populations, remaining stable in lower educated groups, but declining in higher educated groups. Moreover, the overall pattern of reduced prevalence among groups with higher education was more evident in the age group from 15 to 24 years. In 2003, urban individuals in this age group attaining higher education were less likely to be infected with HIV
than lower educated groups in men (OR, 0.20; 95% CI, 0.05 – 0.73) and women (OR, 0.33; 95% CI, 0.15 – 0.72). The same pattern was observed in rural young men (OR, 0.17; 95% CI, 0.05 – 0.59), but was less prominent and not statistically significant in rural women. In respondents aged 25 to 49 years, higher educated urban men had a reduced risk (OR, 0.43; 95% CI, 0.26 – 0.72), which was less prominent in higher educated women (OR, 0.67; 95% CI, 0.52 – 1.1). However, higher educated groups remained at higher odds of infection than groups with less schooling for both sexes in the rural area.

Fylkesnes et al. (2001) also noted a striking diversity in HIV prevalence by level of education, with a decline in prevalence among people with higher levels of education and stable or rising prevalence rates in less educated groups. Differences were most prominent in urban settings and among younger people.

In 1999, a significant negative association between HIV prevalence and years of schooling was observed in the 15 to 24 years age group for both urban men (adjusted OR, 0.85; 95% CI, 0.74 – 0.98) and women (adjusted OR, 0.93; 95% CI, 0.85 – 0.99), but no difference in the rural sample was seen (adjusted OR, 1.04 for men, and 1.01 for women). In this survey, there was evidence in the urban data of more consistent condom use, decreased sexual activity and number of sexual partners and a significant delay in age at first birth among higher educated individuals.

A cross-sectional study in Botswana and Swaziland found that higher educated women were less likely to report lack of control in sexual relationships (adjusted OR, 0.36; 95% CI, 0.36 – 0.37), as well as inconsistent condom use (adjusted OR, 0.72; 95% CI, 0.57 – 0.91) and intergenerational sex (adjusted OR, 0.68; 95% CI, 0.53 – 0.86) (Weiser et al., 2007). No association between risk behaviours and education among men was observed.

Another study, conducted in a rural cohort in South Africa, found a significantly protective effect of education among women (Hargreaves et al., 2007). Attending secondary school versus no or primary education corresponded to an adjusted odds ratio of 0.49 (95% CI, 0.28 – 0.85), whereas having completed secondary school versus no or primary education corresponded to an adjusted odds ratio of 0.25 (95% CI, 0.12 – 0.53).

De Walque (2004) has postulated several theories in an attempt to explain the observed correlation between education and health outcomes. More educated individuals could be healthier because their investment in the future gives them stronger incentives to protect their health. Another theory emphasizes that education enters as a factor in the health production function by giving better access to health-related information and by helping to process that information in order to establish behavioural changes. More educated individuals indeed showed substantial changes in behaviour and sexual practices, in particular condom use and visits to voluntary counselling and testing centers. They were also more likely to start their sexual life at a later age. Among females, schooling reduced their number
of sexual partners, while more educated men tended to have more sexual partners. The combination of increased condom use and a reduced number of sexual partners might explain why the effect of education in reducing HIV prevalence and incidence is concentrated among females.

The recently noted decline in HIV prevalence among higher educated young people once again emphasizes the importance of education, not only as a means to providing knowledge, conferring skills and consequently, beneficial labor market outcomes, but also as a way of reducing people’s vulnerability to adverse health outcomes by shaping their responsiveness to information (UNAIDS, 2008). The notion that both sexes with higher educational attainment experienced reduced risks of HIV infection, suggests that education has an empowering role in women by increasing their bargaining position. Furthermore, it is important to note that more educated groups may be the first to respond positively to HIV/AIDS information and prevention campaigns by effectively reducing their sexual risk behaviour, and this pattern will hopefully diffuse to lower social groups (Michelo et al., 2006).

3.10.4 Level of income

Poverty and infectious diseases have always been linked, simply because the conditions of poverty are some of the very conditions in which infectious diseases thrive (Dinkelman et al., 2008). It can be assumed that a similar reasoning applies to the HIV epidemic as well.

Poverty may raise the probability of contracting HIV via the economically driven adoption of risky behaviours. Poverty and food insecurity are thought to increase sexual risk taking, particularly among women who may engage in transactional sex to procure food for themselves and their children (Gillespie et al., 2007; Dinkelman et al., 2008), although Booysen and Summerton (2002) found little evidence to assume that poverty is associated with risky sexual behaviour. Poverty and the absence of access to sustainable livelihoods also cause higher degrees of labor migration, which itself contributes to the conditions in which HIV transmission occurs (Cohen, 2001). In addition, poor people in sub-Saharan Africa often experience malnutrition, of which is known that it weakens the immune system, which in turn may lead to increased susceptibility to HIV infection in any unprotected sexual encounter (Cohen, 2001; Gillespie et al., 2007; Dinkelman et al., 2008). Finally, poverty-related lack of education and information may act as a barrier to behaviour change, as poor and less educated individuals are less likely to be informed about HIV/AIDS and to use condoms during sexual intercourse (Booysen and Summerton, 2002; Tladi, 2006; Mishra et al., 2007a; Dinkelman et al., 2008).

But although it is reasonable to expect that poverty increases an individual’s vulnerability to HIV by
influencing a host of mediating variables, only a few studies have found a negative association between wealth status and HIV infection, whereas most have found a positive or no association.

In a study examining the association between household wealth status and HIV serostatus in 8 countries in sub-Saharan Africa from 2003 until 2005, HIV prevalence generally tended to be higher among adults belonging to the wealthiest quintiles than among those belonging to the poorest quintiles (Mishra et al., 2007b). A stronger positive effect of wealth on HIV infection was observed among women, suggesting a disproportionately greater vulnerability of women in the wealthier groups. It must be noted that the observed association between wealth status and HIV infection was diminished considerably after adjusting for underlying factors (education, residence, community wealth, sexual risk taking, condom use and male circumcision), indicating that much of the positive association between wealth and HIV is caused by these mediating factors. However, in most cases, wealthier adults remained at least as likely as poorer individuals to be HIV infected.

Evidence from the 2003 Kenya Demographic and Health Survey also points towards a positive association between level of income and HIV infection, with the effect being stronger for women than for men (Johnson and Way, 2006). The wealthiest women were 2.6 times more likely to be HIV-positive than the poorest women, whereas for men, an odds ratio of 2.0 was found when comparing wealthiest with poorest men. Similar findings were reported in Tanzania and Burkina Faso (Gillespie et al., 2007).

However, a number of prospective studies found no or a negative association between level of income and risk of HIV infection. A significantly lower HIV incidence in the wealthiest tercile (15.4 per 1,000 person years) compared with the lowest tercile (27.4 per 1,000 person years) was observed among men in Manicaland, Zimbabwe, but not among women, between baseline and follow-up (Lopman et al., 2007). HIV prevalence also decreased across all wealth groups during the study period, with the largest decrease in the wealthiest tercile for both men and women. A study by Bärnighausen et al. (2007) in rural KwaZulu Natal found that individuals from households in the middle wealth tercile had a significantly higher hazard of HIV seroconversion, whereas there was no significant difference between the wealthiest and poorest terciles after controlling for confounding variables. Finally, Hargreaves et al. (2007) did not find a significant association between HIV seroconversion and economic status in either men or women.

Wealth is associated with several other underlying factors that may influence the relationship between wealth and HIV status in African settings, such as gender, place of residence, mobility, education and risky sexual behaviour. Many women in sub-Saharan Africa face heavy economic, legal and social disadvantages, including entrenched gender roles, relatively small educational enrolment and lower
wages. Economic dependency on male partners and lack of power in relationships make it difficult for these women to negotiate safe sexual intercourse, and may force them into transactional sex (Mishra et al., 2007a; Gillespie et al., 2007). Furthermore, household wealth seems to be associated with urban residence in sub-Saharan Africa, with wealthier people being more likely to live in urban areas, where HIV prevalence tends to be higher, and with a higher level of mobility, which increases the opportunities for casual sexual contacts and makes individuals more difficult to reach for preventive, care or treatment services (Mishra et al., 2007a; Mishra et al., 2007b; Gillespie et al., 2007). Research has also shown that a higher socio-economic status is associated with an increased probability of sexual risk taking. As a result of their greater personal autonomy and spatial mobility, wealthier individuals, especially men, are more likely to have more lifetime sexual partners, to engage in commercial sex, to have non-regular sexual partners, and are less likely to be faithful to their marital partners (Gillespie et al., 2007; Mishra et al., 2007a; Mishra et al., 2007b; Dinkelman et al., 2008; Awusabo-Asare et al., 2008).

In a study in Botswana and Swaziland, wealthier men reported having more sex exchange (adjusted OR, 1.94; 95% CI, 1.59 – 2.37), but were also more likely to report condom use (adjusted OR, 0.78; 95% CI, 0.72 – 0.84), which implies that the risk of HIV infection could be partially offset by the observation that condoms are used more consistently among people with a higher level of income (Gillespie et al., 2007). Similar findings were reported in a prospective follow-up study by Lopman et al. (2007), although these relationships became insignificant after controlling for education level, age and residence, suggesting that the effect of wealth is at least partially the result of differences in education across wealth levels. When looking at women, Hargreaves et al. (2007) found women, but not men, from wealthier households reporting higher levels of condom use (adjusted OR, 2.03; 95% CI, 1.29 – 3.20) when compared to women from poorer households, indicating that wealth could have an empowering effect on women. Better-off women also reported fewer partners and were less likely to engage in transactional sex, indicating that transactional sex primarily acts as a means of survival for women (Lopman et al., 2007).

Apart from condom use, higher standards of living are characterized by other factors that may reduce the risk of HIV seroconversion, such as higher education, more knowledge of HIV prevention methods, a higher rate of male circumcision and a lower prevalence of other untreated sexually transmitted infections. Moreover, a better nutritional status and greater access to healthcare and antiretroviral drugs may improve wealthier people’s survival if infected (Mishra et al., 2007a; Mishra et al., 2007b).

Some authors have suggested that the risk of HIV infection would shift from the wealthier to the poorer as the epidemic progresses. The epidemic could have started out among the wealthier people through their higher-risk behaviours. As a result of growing awareness and the adoption of safer sexual practices,
the prevalence may start to decline among the wealthier, eventually shifting the distribution of the epidemic towards the poorer, who are less empowered to change their behaviour because of their lower socio-economic status. If this trend is realized, the HIV epidemic threatens to become an endemic disease of poverty in sub-Saharan Africa (Mishra et al., 2007a; Gillespie et al., 2007).

From the above, it can be concluded that HIV/AIDS cannot accurately be termed a ‘disease of poverty’ in sub-Saharan Africa. HIV infection is not solely confined to the poorest persons, even though the poor account for the largest absolute number of infections in sub-Saharan Africa. As long as it is unclear whether there is a link between the level of income and the risk of HIV infection, it remains of vital importance that prevention programmes remain equally focused on all socio-economic strata. And even if hard evidence would indicate that wealth, and not poverty, is one of the factors driving the HIV epidemic, poverty reduction is an extremely important goal in itself that should not be neglected.

3.10.5 Gender inequality

It is no longer a bolt from the blue that women account for the vast majority of people living with HIV in sub-Saharan Africa, who acquire the virus largely by heterosexual exposure (see appendix 1). Depending on the sub-Saharan country examined, prevalence rates of HIV in young people (15 to 24 years old) in 2007 were generally 2 to 5 times higher in women than in men (UNAIDS, 2006). In a cross-sectional household survey in South Africa, Pettifor et al. (2005) found that young women were 3 times more likely to be infected with HIV in comparison to men of the same age. Mermin et al. (2008) reported an adjusted odds ratio of 2.4 (95% CI, 1.1 – 5.2) for female sex as a risk factor associated with recent HIV infection in a cross-sectional household survey in Uganda.

Among the many factors contributing to the ‘feminization’ of the HIV epidemic, is the gender-based disparity between men and women in many societies in sub-Saharan Africa. These gender inequalities create environments that decrease women’s ability to protect themselves through negotiation of safer sexual behaviours and hence increase their risk within their regular partnerships (Genberg et al., 2008). Cultural or social norms often restrict women’s enrolment in basic education and their access to information about sexual and reproductive health. And even if women would have access to information and commodities, gender norms that prescribe an unequal and more passive role for women in sexual decision-making undermine women’s autonomy, expose many to sexual coercion, and prevent them from insisting on abstinence or condom use by their male partners (UNAIDS, 2006).

Increased HIV risk among partnered women results primarily from inconsistent condom use within
regular partnerships and the behaviours of their regular male partners. Genberg et al. (2008) reported that the mean number of lifetime partners was consistently higher among males than females. Males were also more likely to have concurrent sexual partners, compared with females. Any lifetime HIV testing was more common among females, most likely partially accounted for by routine testing during antenatal counselling.

Food insufficiency has also been identified as an important risk factor for increased HIV acquisition among women, but not among men (Weiser et al., 2007; Rollins, 2007; Leyna et al., 2007). In unadjusted analysis, women with food insufficiency had over twice the odds of testing HIV positive (adjusted OR, 2.12; 95% CI, 0.87 – 5.19), although the association did not reach statistical significance in adjusted analysis (Leyna et al., 2007). A number of studies have shown that women within households in various parts of sub-Saharan Africa may be less food secure than men as a result of unequal household food allocation. Men are often served both higher quantity as well as quality of food. Malnutrition weakens the immune system and can compromise genital mucosal integrity, thereby increasing vulnerability to HIV once exposed. Food insecurity is also hypothesized to increase sexual risk-taking, especially among women living in poverty, as a means to procure food. After controlling for income and education, HIV knowledge and alcohol use, food insufficiency was associated with inconsistent condom use with a non-primary partner (adjusted OR, 1.73; 95% CI, 1.27 – 2.36), sex exchange (adjusted OR, 1.84; 95% CI, 1.74 – 1.93), intergenerational sexual relationships (adjusted OR, 1.46; 95% CI, 1.03 – 2.08), and lack of control in sexual relationships (adjusted OR, 1.68; 95% CI, 1.24 – 2.28) in a study among women in Botswana and Swaziland (Weiser et al., 2007).

### 3.10.6 Vaginal practices

Vaginal practices have been suggested as risk factors that may increase women's vulnerability to HIV (Myer et al., 2005b; McClelland et al., 2006; Martin-Hilber et al., 2007; Chersich and Rees, 2008; Van de Wijgert et al., 2008). Between 30 to 50 percent of women across sub-Saharan Africa use vaginal practices, such as intravaginal cleansing, drying and tightening by means of antiseptic preparations, traditional medicines or the insertion of fingers or cloths into the vagina, primarily to enhance their male partner's sexual pleasure and fidelity and to exercise control in their relationships (Myer et al., 2005b; Van de Wijgert et al., 2008; Scorgie et al., 2009). Other reasons include genital hygiene, prevention of pregnancy and prevention or self-treatment of vaginal infections (Martin-Hilber et al., 2007).

In a 10-year prospective cohort study among Kenyan female sex workers, McClelland et al. (2006) noted an increased risk for acquiring HIV-1 among women who used water (adjusted hazard ratio (HR), 2.64;
95% CI, 1.00 – 6.97) or soap (adjusted HR, 3.84; 95% CI, 1.51 – 9.77) to perform vaginal washing, when compared to women who did not perform vaginal washing at all. Furthermore, women who used soap or other substances were at higher risk for HIV-1 compared with those who used only water (adjusted HR, 1.47; 95% CI, 1.02 – 2.13). Unlike these findings, vaginal practices were not associated with HIV acquisition in a prospective observational cohort study among women in Zimbabwe and Uganda (Van de Wijgert et al., 2008). When exploring the temporal nature of this association in a cohort of South African women, Myer et al. (2006a) found that intravaginal practices were correlated with prevalent HIV infection at enrolment (adjusted OR, 1.50; 95% CI, 1.22-1.85), but no association between intravaginal practices and incident HIV was noticed during follow-up (adjusted OR, 1.04; 95% CI, 0.65-1.68). These findings might indicate reversal of the causal sequence assumed for this association in cross-sectional studies, as HIV infection intravaginal practices may be performed in response to vaginal infections, which occur more frequently in HIV infected women (Myer et al., 2006a).

Anyway, intravaginal practices could contribute to women's susceptibility to HIV infection by undermining innate defences against pathogens, such as loss of lactobacilli and disruption of the vaginal epithelium (Martin-Hilber et al., 2007; Chersich and Rees, 2008). Bacterial vaginosis, characterized by a loss of lactobacilli, may be an important mediator of the association between intravaginal practices and the risk of HIV infection (Myer et al., 2005b; Martin-Hilber et al., 2007; Chersich and Rees, 2008). In a cross-sectional study of HIV-1 seronegative Kenyan female sex workers, increasing frequency of vaginal washing was associated with a higher likelihood of bacterial vaginosis (Hassan et al., 2007).

But despite biologically plausible mechanisms, there is still not enough evidence to conclude that intravaginal practices increase women's susceptibility to HIV infection, and additional research to elucidate this possible relationship is needed. In addition, in the context of the development of potentially effective microbicides, the effects of vaginal practices on the acceptability, efficacy and safety of microbicidal agents should be considered (Martin-Hilber, 2007).

3.10.7 Male circumcision

The spread of HIV-1 has not been uniform across Africa, and although many biological and behavioural factors likely contribute to country-by-country variation, ecological and large-survey studies suggest that one principal explanation may be differences in the frequency of male circumcision (Baeten et al., 2005), which has been a tradition in many parts of Africa for hundreds of years. It was noticed some years ago that those African groups in which circumcision is routinely done on all boys have fewer cases of HIV/AIDS than are found in groups where circumcision is not a tradition. This finding gave rise to the
idea that circumcision might give a degree of protection against HIV (Williams et al., 2006).

A large body of studies up until now have found that being circumcised is associated with a decreased risk of HIV-1 acquisition. This association means little, however, without taking into account other factors associated with HIV risk that are less prevalent among circumcising than non-circumcising populations (Weiss et al., 2000). Therefore, it is important that results are used after adjustment for sexual behavioural practices and other confounding variables.

Baeten et al. (2005) determined female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. They found that the overall probability of HIV-1 acquisition per sex act was 0.0063 (95% CI, 0.0035 - 0.0091) and that female-to-male infectivity was significantly higher for uncircumcised men than for circumcised men (0.0128 versus 0.0051). After accounting for sexual behaviour, they found that uncircumcised men were at a 12-fold increased risk of acquiring HIV-1 per sex act, compared with circumcised men.

A randomised controlled trial by Bailey et al. (2007), in which the relative risk of HIV-1 incidence was determined in Kenyan men randomly assigned to receive circumcision versus those who did not receive such treatment, revealed that the two-year HIV incidence was 2.1 percent (95% CI, 1.2 – 3.0%) in the circumcision group and 4.2 percent (95% CI, 3.0 – 5.4%) in the control group. The relative risk of HIV-1 infection in circumcised men was 0.47 (95% CI, 0.28 – 0.78), corresponding to a reduction in the risk of acquiring HIV of 53 percent (22 to 72 percent). After controlling for non-adherence to treatment, the adjusted protective effect of circumcision was estimated to be 60 percent (32 to 77 percent).

Auvert et al. (2005) also conducted a randomized controlled intervention trial in a general population of South Africa to test the hypothesis that male circumcision may provide protection against HIV-1 infection. After a follow-up period of 21 months there were 20 HIV infections (incidence rate 0.85 per 100 person-years) in the intervention group and 49 (2.1 per 100 person-years) in the control group, corresponding to a relative risk of 0.40 (95% CI, 0.24 – 0.68%; p = 0.001). This relative risk corresponded to a protection of 60 percent as well (95% CI, 32 – 76%). When controlling for behavioural factors, including sexual behaviour, condom use, and health-seeking behaviour, the protective effect slightly increased to 61 percent (95% CI, 34 – 77%).

Both trials by Auvert et al. (2005) and Bailey et al. (2007) were stopped early when interim analyses revealed results that were so compelling that it was deemed unethical to continue withholding circumcision from the control group. Moreover, modelling studies by Williams et al. (2006) projected that
full coverage of male circumcision has the potential to avert about 5.7 million new HIV infections and 3 million deaths over 20 years in sub-Saharan Africa.

According to a two-year follow-up study among Kenyan men, HIV-incidence rates were 0.79 (95% CI, 0.46 – 1.25) for circumcised men and 2.48 (95% CI, 1.33 – 4.21) for uncircumcised men, corresponding to a hazard rate ratio of 0.31 (95% CI, 0.15 – 0.64). Circumcision in this cohort was associated with a higher educational level, fewer marriages, and smaller age differences between spouses, all of which seem to contribute to a protective effect on HIV-1 transmission. In one model controlling for socio-demographic factors, the hazard rate ratio increased to 0.55 (95% CI, 0.20 – 1.49) and became non-significant (Shaffer et al., 2007).

A systematic review and meta-analysis of studies from sub-Saharan Africa in which the risk of HIV-1 acquisition in circumcised men was compared with this risk in uncircumcised men revealed an adjusted rate ratio of 0.29 (95% CI, 0.20 – 0.41) in men with high-risk behaviours, compared with an adjusted rate ratio of 0.56 (95% CI, 0.44 – 0.70) in general male populations (Weiss et al., 2000). In cohort studies in Rakai, Uganda, circumcision was significantly associated with reduced HIV-1 acquisition in the general population (adjusted rate ratio, 0.53; 95% CI, 0.33 – 0.87), but among frequently exposed men in HIV-1 discordant couples, no seroconversions were observed in 50 circumcised men, whereas HIV-1 acquisition was 16.7 per 100 person years in uncircumcised men. These findings suggest that circumcision may be more protective against HIV acquisition among men at high risk of repeated exposure, compared to men with less frequent HIV exposures (Weiss et al., 2000).

Furthermore, it is also important to notice that prepubertal circumcision seems to have a far larger impact on HIV acquisition than postpubertal circumcision. In a study conducted in Rakai, Uganda, prepubertal circumcision was found to reduce HIV-1 acquisition (RR, 0.49; 95% CI, 0.26 – 0.82), whereas postpubertal circumcision did not (Gray et al., 2000).

Male circumcision as a protective factor against HIV transmission is biologically plausible, as the intact highly vascularised foreskin is vulnerable to trauma during sexual intercourse and to ulcerative and inflammatory lesions, which may act as co-factors for HIV acquisition (Wawer et al., 2005b). Moreover, the inner preputial mucosa of the intact foreskin is not keratinized and contains a large number of Langerhans cells, which are considered as primary target cells for HIV. This is particularly important during heterosexual intercourse, as the foreskin is then pulled back down the penile shaft, and the entire inner surface of the foreskin is exposed to vaginal secretions, providing a large area where HIV transmission might take place. In contrast, the penile shaft and outer surface of the foreskin contain
lower numbers of HIV target cells and are covered by keratinized, stratified squamous epithelium, which provides a protective barrier against HIV infection (Szabo and Short, 2000). After circumcision, the only remaining mucosa is the urethral meatus. The anatomical reduction of vulnerable mucosa may thus reduce the risk of HIV and other sexually transmitted diseases (Wawer et al., 2005b).

Although most of the results from existing studies point towards a strong association between male circumcision and prevention of HIV, the positive effect of male circumcision could be offset by a perceived sense of protection against the acquisition of STDs that may potentially translate into unsafe sexual practices. In a cross-sectional study in South Africa, almost 30 percent of the circumcised men and more than 20 percent of the non-circumcised men believed that male circumcision protects against HIV and other STDs and that circumcised men could safely have sexual intercourse with multiple partners (Lagarde et al., 2003). This indicates that it is highly important that prevention workers emphasize that circumcision does not fully protect against HIV acquisition, and that consistent condom use and other prevention strategies are still needed to lower the risk of HIV transmission.

3.10.8 Sexual risk behaviour

Of all the factors possibly being conducive to large HIV epidemics, sexual risk behaviour is probably among the most extensively studied. Contrary to all the aforementioned variables, literature is unanimous in concluding that sexual risk behaviour – a higher number of lifetime sexual partners, concurrent partnerships, inconsistent condom use and alcohol use – poses both men and women at a significantly increased infection risk.

In a case-control study of risk factors for incident HIV infection in Uganda, a significantly higher risk of HIV infection was found in men (OR, 3.78; 95% CI, 1.20 – 11.93) and especially in women (OR, 20.78; 95% CI, 2.94 – 141.2) who reported at least 5 lifetime sexual partners compared with those who reported at most 1 partner (Quigley et al., 2000). For each additional lifetime sexual partner, Pettifor et al. (2005) observed an increase in the odds of HIV infection by 1.03 (95% CI, 1.01 – 1.06) times for men and 1.09 (95% CI, 1.01 – 1.16) times for women. Gregson et al. (2006) examined changes in HIV prevalence and sexual behaviour between baseline in 1998/2000 and follow-up in 2000/2003 in Zimbabwe. In the cohort of the sexually active individuals uninfected at baseline, HIV incidence was higher in those who reported multiple sexual partners during the 3-year intersurvey period than in those who reported a single partner, with the effect being stronger for women (adjusted hazard ratio, 3.35; 95% CI, 2.13 – 5.27) than for men (adjusted hazard ratio, 1.82; 95% CI, 1.17 – 2.85). The risk rose progressively with increasing numbers of sexual partners for women (adjusted hazard ratio, 1.14; 95% CI, 1.07 – 1.21), but not for men.
Similarly, having concurrent or overlapping sexual partnerships is increasingly recognized as an important factor underpinning rapid growth of the HIV epidemic in sub-Saharan Africa. Modeling and empirical evidence suggest that concurrent partnerships can increase the size of an HIV epidemic, the speed at which it infects a population and its persistence within a population (Mah and Halperin, 2008). Indeed, a reduction in concurrent partners was found to be associated with population-level declines in HIV (Chersich and Rees, 2008). In their cohort study, Guwatudde et al. (2009) found that having sex with a partner of whom was known or suspected of having sex with others was strongly associated with HIV-1 incidence. This risk increased with the number of coital acts with this partner in the past six months, attaining statistical significance with an adjusted rate ratio of 6.3 (95% CI, 1.73 – 23.1).

As already mentioned earlier, condoms offer a high degree of protection against both HIV and other sexually transmitted diseases, when used consistently and correctly. But even after many years of widespread promotion, consistent condom use has not reached a sufficiently high level to produce a measurable reduction in HIV incidence in sub-Saharan Africa. Although condom use is generally higher among males and younger, unmarried and better educated individuals, and those reporting multiple sex partners or extramarital relationships (Ahmed et al., 2001), gaps remain, however, in consistent condom use with long-term partners and to a lesser extent with casual partners (Chersich and Rees, 2008). Persistent low acceptability of condoms within cohabiting couples is particularly concerning, as women in such relationships are often at an elevated risk of HIV.

Research has also repeatedly shown that alcohol use is related to sexual risk behaviour and HIV infection in several populations. In a study among women attending an antenatal clinic in Kenya, HIV seroprevalence was significantly associated with reported alcohol consumption (adjusted rate ratio, 1.6; 95% CI, 1.1 – 2.5) (Ayisi et al., 2000). Consuming alcohol more than 2 days per week was also found to be a significant predictor for HIV-1 infection (adjusted OR, 2.56; 95% CI, 1.12 – 5.88) in female bar and hotel workers in northern Tanzania (Kapiga et al., 2002). Having ever drunk alcohol independently predicted HIV seropositivity in a study among sexually active adults in rural Uganda (Mbulaiteye et al., 2000). Individuals who had ever drunk alcohol experienced an HIV prevalence twice that of those who had never drunk (OR, 2.0; 95% CI, 1.5 – 2.8), an association that remained after adjusting for potential confounders, such as living in a Muslim region (OR, 1.8; 95% CI, 1.2 – 2.7). Zuma et al. (2003) also found alcohol use to be significantly and independently associated with HIV infection among women in an urban South African setting. Having at least one and less than one alcoholic drink a day corresponded to adjusted odds ratios of 1.88 (95% CI, 1.07 – 3.33) and 1.58 (95% CI, 1.05 – 2.38), respectively, when compared to having never drunk alcohol during the last 4 weeks.
Through its psychogenic effects on cognitive processes, such as decision making, reasoning skills and sense of responsibility, alcohol influences sexual risk behaviour, which is often associated with a greater number of sexual partners during a defined period as well as higher rates of unprotected intercourse (Kalichman et al., 2007). Moreover, sexual assault is quite prevalent in sub-Saharan Africa, and it is related to alcohol use and HIV transmission risks. Men who have a history of sexual violence are more likely to drink than men who have not been sexually assaultive. Likewise, alcohol use is associated with having been sexually assaulted among women (Kalichman et al., 2007).

The fundamental role of human behaviour in the continued spread of HIV is increasingly clear. Therefore, changing behaviours that enable HIV transmission is the ultimate goal required for HIV prevention. However, sexual behaviour, which remains the primary target of HIV prevention efforts worldwide, is deeply embedded in a complex web of economic, legal, political, cultural and psychosocial processes. This makes HIV prevention a challenging and long-winded task that requires a persistent commitment of all stakeholders involved in order to ensure that prevention efforts will no longer be outstripped by the pace of the HIV epidemic in sub-Saharan Africa.
4 DISCUSSION

4.1 Limitations

Although I have attempted to make this overview as comprehensive as possible, there are many more factors influencing the risk of HIV-1 transmission in addition to the variables included in this review. However, getting all the pieces of the HIV puzzle to fit would probably require years of research and encyclopaedias of knowledge.

Furthermore, the study designs included in this review have several shortcomings as well. Although cross-sectional studies are suitable for descriptive analyses and for generating hypotheses, one of the most important inherent weaknesses of these study designs is that limited causal or temporal inferences can be drawn from the associations described. This pitfall could be reduced by using longitudinal studies, such as cohort studies, which involve repeated observations of the same items over longer periods of time. Randomized controlled trials, characterized by the random allocation of different conditions or interventions to subjects, are considered the ‘golden standard’ of research and the most reliable form of scientific evidence. These trials eliminate spurious causality and bias that may otherwise influence outcome, but they are not always ethically acceptable to determine whether a cause-effect relation exists between a specific variable and the risk of infection with a deadly virus. Finally, meta-analyses are often typified by the shortcoming that they tend to report only on those publications in which a specific desired association is observed, whereas contradictory or absent associations are often left out of consideration.

In determining the association between behavioural variables and HIV-1 susceptibility, researchers regularly utilize interviews and surveys based on self-reported behaviour. These are often influenced by a considerable degree of social desirability bias or the tendency of respondents to reply in a manner that will be viewed favourably by others. This may result in underreporting of risky sexual behaviours and overreporting of ‘good’ behaviours, thereby undermining the validity of some findings. In addition, results could also be skewed by confounding variables, simply because not all distorting factors are known or because they were not always adequately controlled for in the identified studies.

4.2 Considerations

This review has shown that our precise knowledge concerning factors influencing susceptibility to and infectivity of HIV-1 infection is still limited. For the same variable studied, much of the literature showed inconsistent results, ranging from no associations to statistically significant associations. This
inconsistency in results suggests that more research is needed in order to get more consensus and to implement prevention strategies in which most of the contributing variables are included.

Infectivity of HIV-1 was found to be directly determined by plasma viral load and genital shedding, both of which are influenced by antiretroviral therapy and stage of disease. But to date, it is still not clear which stage of HIV-1 infection accounts for the highest numbers of HIV transmission. Because of extremely high viral levels during primary and late-stage infection, individuals in these stages are considered to be more infectious when compared to the asymptomatic stage. But when taking into account the duration of each stage, the period of clinical latency might contribute more to the risk of HIV-1 transmission over the lifetime of an infected individual, simply because of its longer duration.

The introduction of potent ART has led to a revolution in the care of patients with HIV/AIDS in the developed world, and turned this disease from a plague into a manageable chronic illness (WHO, 2003). Although ART is not a definite cure and its implementation presents new challenges with respect to side-effects and the emergence of drug resistant viral strains, it has dramatically reduced rates of mortality and morbidity and it has improved the quality of life of people living with HIV/AIDS. But despite recent cost reductions and increased access, antiretroviral drugs continue to be unavailable for a large part of HIV infected people in the worst affected regions of the developing world. As a result of reduced mortality under ART, the number of individuals in need of ART would increase even more, putting high pressure on sparse health care budgets. Furthermore, the longer survival period associated with ART could even contribute to HIV-1 transmission, as genital shedding of HIV-1 RNA may still occur despite undetectable plasma viral loads. At the same time, concerns have been raised that compensatory increases in sexual risk behaviour could lessen the impact of ART. Although several studies have shown that this is not the case, education on safe sexual behaviour should always be integrated into all HIV prevention strategies.

The presence of concomitant sexually transmitted diseases, hormonal changes during the menstrual cycle and hormonal contraceptive use could influence both infectivity of and susceptibility to HIV-1 by inducing changes in the level of HIV-1 in genital tract secretions and by increasing the risk of epithelial disruption and immune activation of host cells, respectively.

Since it is well known that sub-Saharan Africa has one of the fastest growing populations worldwide, family planning programmes increasingly emphasize the importance of hormonal contraceptive use in order to avoid unwanted pregnancies. Therefore, more evidence is urgently required to clarify whether hormonal contraceptive use alters the risk of HIV-1 acquisition and/or transmission, as this could have major implications for public health.
Some question marks also remain in the observed association between HIV-1 and concomitant sexually transmitted diseases, but it is postulated by several international guidelines that control programmes for other sexually transmitted diseases should be integrated in all HIV prevention measures. Even if later research would show that their contribution to HIV infection is rather limited, concomitant sexually transmitted infections themselves are important diseases which need to be treated, as they have the potential to cause reduced fertility and major morbidity.

Other identified determinants of susceptibility to HIV-1 include genetic polymorphisms, male circumcision, cervical ectopy and vaginal practices. Individuals with certain protective genetic polymorphisms appeared to have a lower risk of contracting HIV-1, whereas cervical ectopy and vaginal practices may be associated with a higher probability of infection with HIV-1.

Several randomized controlled trials have proved the benefit of male circumcision as a protective factor in controlling the spread of HIV. The World Health Organization (2007) even stated that ‘male circumcision is the most compelling evidence-based prevention strategy to emerge since the finding that antiretroviral medication can reduce mother-to-child transmission of HIV’. But at the same time, individuals must be made aware of the fact that circumcision does not constitute a safeguard for engaging in sexual risk behaviour. Therefore, continued education regarding safe sex messages for circumcised men remains equally essential. Furthermore, it is highly important that this procedure is performed in clinical settings by certified health professionals or by educated traditional practitioners to reduce the risk of adverse medical outcomes, mainly haemorrhage, sepsis and HIV infection.

Evidence also points towards significant associations between specific demographic, socio-cultural and behavioural variables and vulnerability to HIV-1 infection. As younger adults are disproportionately vulnerable to contracting HIV, intervention strategies should focus intensively on these age groups. Marriage, on the other hand, was found to have a protective effect on the acquisition of HIV infection, although this finding must be interpreted with caution, as the number of studies investigating the association between marriage and HIV is too small up to date.

Most HIV prevention interventions to date have focused on changing people’s knowledge, attitudes, and behaviours, but few interventions actually target the underlying circumstances that may foster these behaviours, such as gender inequality, poverty and lack of education. Although a higher level of education in earlier years was associated with a higher risk of HIV infection, the relationship between schooling level and HIV prevalence now appears to be reversed. This finding once again stresses the importance of education, especially among women, in whom education has been proven to have an
empowering role. The ‘ABC’ of HIV prevention – Abstain, Be faithful, use Condoms – indeed fails millions of women who lack the social and economic power to negotiate when and how sexual intercourse occurs and whether protection is used. Efforts to enhance women’s legal and social rights may play an important role in decreasing the spread of HIV among women, although this might require tremendous structural and cultural changes at many levels in society. Foremost, economic and educational interventions should be implemented to help improve women’s bargaining power and decrease their dependence on male partners, which in turn can provide them with a basis upon which to demand safer sexual practices.

Unlike gender inequality and level of education, evidence on poverty as a major driver of the HIV epidemic is rather mixed. This discrepancy could be partially explained by a lack of standardized definitions of poverty. It was surprising to note that none of the studies handled the internationally adopted poverty measures of living of less than one US dollar per day in defining poverty. Instead, most studies focused on relative poverty in the context of generalized poverty, which makes it rather difficult to compare results from different studies. Whether there is an association between poverty and HIV or not, remains an unanswered question for the time being. But what is clear, is that ill health directly reinforces aspects of poverty by undermining labour capabilities and depleting people’s resources due to medical costs.

It has become obvious that none of the preventive approaches implemented up until now have sufficiently worked to call a halt to the spreading of HIV around the globe. As a result, death toll and incidence figures of HIV remain unacceptably high and all parties concerned have set their hopes on the arrival of an HIV vaccine. However, the complex viral pathogenesis in addition to a striking genetic diversity have turned the design of a safe and effective vaccine into an enormous scientific obstacle that has not been overcome so far, despite tremendous progress in HIV research in recent years. However, these unrewarded efforts may not endanger the will to tackle one of the biggest challenges in medical history. As new insights and perspectives beyond the scope of classic vaccinology are urgently needed, even more research efforts should be directed towards the quest for HIV vaccination options.

More efforts should also be made to protect human rights, as the spread of HIV is disproportionately high among those groups suffering from a lack of human rights protection and discrimination. Moreover, interventions should be focused on removing the stigma associated with being HIV-positive, since prejudices and stigmatization are widely considered as partly fuelling the epidemic. Because HIV and AIDS are viewed in many communities as the outcome of reprehensible behaviour, infected individuals are often reluctant regarding HIV testing and treatment to avoid rejection from family and friends.
In the meantime, HIV/AIDS is eroding decades of development gains, increasing poverty and undermining the foundations of society in the worst affected countries (UNAIDS, 2008). It has become a global tragedy consisting of more than thirty million stories that are more about justice than merely about health issues. However, the real tragedy lies in the reluctant response of national governments and policy makers to the epidemic. Although international organizations and charity bodies have donated heavily in the past few years to halt and reverse the spread of the HIV epidemic, national governments – frequently characterized by high levels of corruption – often show less commitment to achieve this goal and to increase the well-being of its people. And even if political commitment may be evident in public statements and policy documents, engagement to ensuring effective allocation of financial resources and implementation of policy programmes is often lacking. But HIV is not merely a story of tragedies. It is also a story of hope, courage and inspiration. It is a story of people giving the disease names and faces. And most of all, it is a story of ordinary people standing up for their rights to life, dignity and equality. Or like Nelson Mandela stated it: ‘AIDS is no longer a disease, it is a human rights issue’.


DHAWAN D., MAYER K.H.: Microbicides to prevent HIV transmission: overcoming obstacles to chemical barrier protection. Journal of Infectious Diseases, 2006, 193, 36-44.


Heterogeneity in susceptibility to and infectivity of HIV


MYER L., WRIGHT T.C., Jr., DENNY L., KUHN L.: Nested case-control study of cervical mucosal lesions, ectopy, and incident HIV infection among women in Cape Town, South Africa. Sexually Transmitted Diseases, 2006b, 33, 683-687.


Heterogeneity in susceptibility to and infectivity of HIV


ROLLINS N.: Food insecurity – a risk factor for HIV infection. Public Library of Science Medicine, 2007, 4, 301.


TIENSIWAKUL P.: Stromal cell-derived factor (SDF) 1-3'A polymorphism may play a role in resistance to HIV-1 infection in seronegative high-risk thais. Intervirology, 2004, 47, 87-92.

Heterogeneity in susceptibility to and infectivity of HIV 55


WILLIAMSON C., LOUBSER S.A., BRICE B., JOUBERT G., SMIT T., THOMAS R., VISAGIE M., COOPER M., VAN DER
RYST E.: Allelic frequencies of host genetic variants influencing susceptibility to HIV-1 infection and disease in South African

WILSON D.P., LAW M.G., GRULICH A.E., COOPER D.A., KALDOR J.M.: Relation between HIV viral load and

WOLDAY D., GEBREMARIAM Z., MOHAMMED Z., DORIGO-ZETSMA W., MELES H., MESSELE T., GEYID A., SANDERS
E., MAAYAN S.: The impact of syndromic treatment of sexually transmitted diseases on genital shedding of HIV-1. Official

WORLD HEALTH ORGANIZATION (WHO): Scaling up antiretroviral therapy in resource limited settings: treatment guidelines


ZUMA K., GOUWS E., WILLIAMS B., LURIE M.: Risk factors for HIV infection among women in Carletonville, South Africa:

APPENDICES

APPENDIX 1: Epidemiology of the HIV epidemic in numbers and figures
APPENDIX 2: WHO staging system for HIV infection and disease in adults and adolescents
APPENDIX 3: WHO and USDHHS guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents
APPENDIX 4: Conceptual framework on heterogeneity in susceptibility to and infectivity of HIV-1
APPENDIX 5: Selection of testimonies from HIV positive people in Nigeria
APPENDIX 1: Epidemiology of the HIV epidemic in numbers and figures

A global view of HIV prevalence among adults, 2007

Percentage of people living with HIV of the total global number of people living with HIV by geographical region, 2007
<table>
<thead>
<tr>
<th>Region</th>
<th>Adults and children living with HIV</th>
<th>Adults and children newly infected with HIV</th>
<th>Adult prevalence (15-49 years) (%)</th>
<th>Adult and child deaths due to AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>22 million [20.5 – 23.6 million]</td>
<td>1.9 million [1.6 – 2.1 million]</td>
<td>5.0 [4.6 – 5.4]</td>
<td>1.5 million [1.3 – 1.7 million]</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>380,000 [280,000 – 510,000]</td>
<td>40,000 [20,000 – 66,000]</td>
<td>0.3 [0.2 – 0.4]</td>
<td>27,000 [20,000 – 35,000]</td>
</tr>
<tr>
<td>South and South-East Asia</td>
<td>4.2 million [3.5 – 5.3 million]</td>
<td>330,000 [150,000 – 590,000]</td>
<td>0.3 [0.2 – 0.4]</td>
<td>340,000 [230,000 – 450,000]</td>
</tr>
<tr>
<td>East Asia</td>
<td>740,000 [480,000 – 1.1 million]</td>
<td>52,000 [29,000 – 84,000]</td>
<td>0.1 [&lt;0.1 – 0.2]</td>
<td>40,000 [24,000 – 63,000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.7 million [1.5 – 2.1 million]</td>
<td>140,000 [88,000 – 190,000]</td>
<td>0.5 [0.4 – 0.6]</td>
<td>63,000 [49,000 – 98,000]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>230,000 [210,000 – 270,000]</td>
<td>20,000 [16,000 – 25,000]</td>
<td>1.1 [1.0 – 1.2]</td>
<td>14,000 [11,000 – 16,000]</td>
</tr>
<tr>
<td>Eastern Europe and Central Asia</td>
<td>1.5 million [1.1 – 1.9 million]</td>
<td>110,000 [67,000 – 180,000]</td>
<td>0.8 [0.6 – 1.1]</td>
<td>58,000 [41,000 – 88,000]</td>
</tr>
<tr>
<td>Western and Central Europe</td>
<td>730,000 [580,000 – 1.0 million]</td>
<td>27,000 [14,000 – 49,000]</td>
<td>0.3 [0.2 – 0.4]</td>
<td>8,000 [4,800 – 17,000]</td>
</tr>
<tr>
<td>North America</td>
<td>1.2 million [760,000 – 2.0 million]</td>
<td>54,000 [9,600 – 130,000]</td>
<td>0.6 [0.4 – 1.0]</td>
<td>23,000 [9,100 – 55,000]</td>
</tr>
<tr>
<td>Oceania</td>
<td>74,000 [66,000 – 93,000]</td>
<td>13,000 [12,000 – 15,000]</td>
<td>0.4 [0.3 – 0.5]</td>
<td>1,000 [&lt;1,000 – 1,400]</td>
</tr>
<tr>
<td>TOTAL</td>
<td>33 million [30 – 36 million]</td>
<td>2.7 million [2.2 – 3.2 million]</td>
<td>0.8 [0.7 – 0.9]</td>
<td>2 million [1.8 – 2.3 million]</td>
</tr>
</tbody>
</table>

Regional HIV and AIDS statistics and features, 2007

Percent of adults older than 15 living with HIV who are female, 1990 – 2007
APPENDIX 2: WHO staging system for HIV infection and disease in adults and adolescents

Clinical stage I
- Asymptomatic
- Persistent generalized lymphadenopathy
  Performance scale 1: asymptomatic, normal activity

Clinical stage II
- Weight loss, < 10 % of body weight
- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
- Herpes zoster within the last five years
- Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)
  And/or performance scale 2: symptomatic, normal activity

Clinical stage III
- Weight loss, > 10 % of body weight
- Unexplained chronic diarrhoea, > 1 month
- Unexplained prolonged fever (intermittent or constant), > 1 month
- Oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis within the past year
- Severe bacterial infections (i.e. pneumonia, pyomyositis)
  And/or performance scale 3: bedridden < 50 % of the day during the last month

Clinical stage IV
- HIV wasting syndrome, as defined by the Center for Disease Control and Prevention
- Pneumocystis carinii pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes
- Herpes simplex virus infection, mucocutaneous > 1 month, or visceral any duration
- Progressive multifocal leukoencephalopathy
- Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
- Candidiasis of the oesophagus, trachea, bronchi or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoid Salmonella septicaemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi’s sarcoma
- HIV encephalopathy, as defined by the Center for Disease Control and Prevention
  And/or performance scale 4: bedridden > 50 % of the day during the last month
APPENDIX 3: WHO and USDHHS guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents

WHO recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection:

If CD4 testing available, it is recommended to document baseline CD4 counts and to offer ART to patients with:

- WHO Stage IV disease, irrespective of CD4 cell count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), with consideration of using CD4 cell counts < 350/mm³ to assist decision-making
- WHO Stage I or II disease with CD4 cell counts ≤ 200/mm³

If CD4 testing unavailable, it is recommended to offer ART to patients with:

- WHO Stage IV disease, irrespective of total lymphocyte count
- WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), irrespective of the total lymphocyte count
- WHO Stage II disease with a total lymphocyte count ≤ 1200/mm³

USDHHS indications for initiation of antiretroviral therapy:

- Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 T-cell count < 350 cells/mm³
- Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count:
  - Pregnant women,
  - Patients with HIV-associated nephropathy, and
  - Patients coinfected with HBV when treatment is indicated
- Antiretroviral therapy may be considered in some patients with CD4 T-cell counts > 350 cells/mm³
- The necessity for patient adherence to a long-term drug regimen should be discussed in depth between the patient and clinician; potential barriers to adherence should be identified and addressed before therapy is initiated


APPENDIX 4: Conceptual framework explaining heterogeneity in susceptibility to and infectivity of HIV-1

**SUSCEPTIBILITY**

- DEMOGRAPHIC VARIABLES
  - Age
  - Marriage
  - Level of income
  - Level of education
  - Urban/rural residence

- SOCIO-CULTURAL VARIABLES
  - Gender inequality
  - Male circumcision
  - Vaginal practices

- BEHAVIOURAL VARIABLES
  - Condom use
  - Alcohol use
  - Age at first sex
  - Concurrent partnerships
  - Number of lifetime sexual partners

**MENSTRUAL CYCLE**
- HORMONAL CONTRACEPTIVE USE
- SEXUALLY TRANSMITTED DISEASES

**INFECTION**

- VIRAL LOAD AND GENITAL SHEDDING
- ANTIRETROVIRAL THERAPY
- STAGE OF DISEASE

**National and international policy**

**HIV counselling and testing**
When I was told about my HIV status, it felt as if world suddenly collapsed. What would become of my children? How could I ever live with the stigma of being HIV positive? It was indeed a death sentence. My husband refused to be tested, and accused me of being unfaithful. I cried a lot with no one to comfort me. However, I got help from a group of people who supported me. I was able to accept what life had to offer me. I really felt relieved when I met other people living with the virus. I regularly went to the hospital, drugs were no problem. My husband got tested later on and he was found to be HIV positive. The truth is that I have been faithful, but who would listen to me, and what use is it anyway? It has been three years now since I heard my diagnosis, and I am better prepared to deal with the future with the knowledge I have and my experiences so far.

OMOWUMI

I was told I was HIV positive when I went for a medical test demanded by my employer. When I heard my diagnosis, I really felt desperate. Apart from the fact that the job was already lost, I was about to get married. How could I tell this bad news to my fiancée? And how could I possibly fit into my family and group of friends? How would they perceive me? This flood of thoughts ran through my brain at rocket speed. I was only 28 years old at the time of my diagnosis, and I was still looking forward to all the wonderful things life could have had in mind for me. All of my dreams and aspirations in life suddenly faded away, and were replaced by feelings of emptiness and depression. I could not even eat or drink any more. Moreover, my fiancée got tested as well, and as she was negative, she left me. The support and assistance from some friends and a non-governmental organization finally enabled me to overcome my initial pessimistic thoughts and to find a better way of accepting and dealing with my HIV status. I will marry soon to a HIV positive patient, just like me.

ANONYMOUS

I was diagnosed with HIV during an ‘HIV Enlightenment Campaign’. I just felt like doing the test after all the information we received throughout the campaign. Initially, I felt really bad, but with the help from my caring family and friends, I was able to cope with my diagnosis little by little. But still, I do realize that my life will never be again like it was before. I sometimes wonder how I got the virus and whom I got it from, but I quickly become aware of the fact that there is actually no point in keep asking myself these questions. I’d rather focus on making the best out of the little time I have left.

JAMES