1. Introduction

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) have been the greatest biomedical challenge in this century and despite of progresses in the understanding of the virus, development of medical agents and diagnostic capabilities, HIV continues to be a major public health problem, also in western Europe (Graham, 1996; Hamers & Downs, 2004; Mindel & Tenant-Flowers, 2001).

The introduction of highly active antiretroviral therapy (HAART) in 1996/1997 has changed the course of HIV so that it can now be assigned as a chronic disease. For medical treatment success, a sufficient and maintaining adherence to drug therapy is a precedent condition, and insufficient adherence can hamper future treatment options (Little et al., 2002; Paterson et al., 2000; Yerly et al., 2001).

The clinical course is difficult to predict and HIV infected individuals have to cope with complex and multiple psychological demands. So it is not surprising that psychiatric disorders, depressive symptoms and emotional distress are highly prevalent in this patient group (Bing et al., 2001; Cohen et al., 2002; Lyketsos, Hutton, Fishman, Schwartz, & Treisman, 1996c; Morrison et al., 2002).

Despite advances in medical treatment of HIV, there remains a great variability in the course of this disease (Leserman, 2003a), which might be explained, at least in part, by the impact of psychosocial variables on disease course. Studies examining the impact of psychosocial variables on morbidity, mortality and immunological parameters in HIV showed a large body of evidence of such an association (Ickovics et al., 2001; Leserman, 2003a; Leserman et al., 2002). So researchers, examining underlying direct (e.g. cortisol, autonomic nervous system activity) and indirect pathways (e.g. adherence, sleep) through which psychosocial variables may influence the disease progression are very important for a biopsychosocial understanding of the illness.

Psychological interventions, such as cognitive behavioural stress management (CBSM) trainings have been shown to have a positive impact on different aspects of psychological well-being as well as on physiological and immunological

parameters (Antoni et al., 1991; Antoni et al., 2000a; Antoni et al., 2002; Cruess et al., 1999; Cruess et al., 2000a).

Based on the aforementioned research findings, we wanted to focus the question whether reported effects hold true in the area of HAART in our study. Additionally, only a few studies ascertained the impact of a CBSM on clinically relevant immunological parameters of HIV disease progression. In addition, many studies examining the effect of CBSM on psychological and emotional well being are limited by not controlling rigorously for HAART or not been performed on HIV patient under HAART.
To answer these questions, we generated and evaluated a CBSM training in HIV infected woman and men under HAART, using a randomized controlled one-year prospective study design.

2. Theoretical Background

In this chapter, basic constructs of the present work are introduced. They can be divided into the specification of HIV and AIDS, the impacts of psychological variables on disease progression and psychobiological pathways between stress and disease progression. Furthermore, the impact of cognitive behavioural stress management trainings on psychobiological well-being in people living with HIV/AIDS is described.

2.1 HIV and AIDS

Infection with HIV leading to AIDS has been the greatest biomedical challenge of this century (Graham, 1998) and the infection with HIV causes a spectrum of clinical problems beginning at the time of seroconversion (primary HIV) and terminating with AIDS and death (Mindel & Tenant-Flowers, 2001). Since the identification of HIV-1, scientific efforts have resulted in a deep understanding of the virus and the molecular interactions with the host cell. Moreover, numerous of antiretroviral therapeutic agents and diagnostic procedures have been developed (Emini & Koff, 2004).

Some of the most important definitions and aspects of the complex broad concepts of HIV disease course and classification as well as medical treatment are described in this chapter. In addition, some epidemiological aspects will be presented.

2.1.1 Definition and Clinical Presentation of HIV/AIDS

There is a persuasive evidence that HIV came to humans from chimpanzee and monkey from central and west Africa (Gao et al., 1999; Hahn, Shaw, De Cock, & Sharp, 2000). HIV type 1 and HIV type 2 (HIV-1, HIV-2) are two distinct viruses. HIV-1 is responsible for the great majority of infections globally, whereas HIV-2 is very rare outside of West Africa (Grant & De Cock, 2001).

Emini and Koff (2004, p. 1913) state: *The "typical immune response against a viral infection involves an effective interaction of both the humoral and cellular arms of the immune system. The humoral arm produces virus-neutralizing anti-*

bodies that, when fully effective, completely prevent virions form infecting new host cells. The cellular arm mobilizes specific CD8+ cytotoxic T lymphocytes (CTLs) that target and kill cells expressing viral antigens. This double assault on a viral infection is uniquely capable of stopping an infection and results in "cure" of the host. But HIV-1 has developed a number of mechanisms to thwart the full effectiveness of the antiviral immune response while tolerating a degree of longer term immunological control. Accordingly, the virus escapes the fate of elimination from the host and persist long-term."

The HI-virus belongs to the group of retroviruses and its genetic information is located on the RNA. Typical target cells of HI-virus are the CD4 cells, which is a receptor with high affinity for gp120 (proteins on the HI-virus which are exposed to antibodies). This glycoprotein is a crucial factor in the ability of HIV-1 to infect new host cells. Through this pathway, the virus wanders into the CD4+ cell where the viral genetic information is rewritten into the DNA by certain intermediate steps (among others by reverse transcription) and is integrated in the genome of the cell. Afterwards the host cell produces viral elements, builds them together (protease) and these new HI-viruses leave the host cell passing the cell membrane (HIV-Arbeitskreis Südwest, 2003).

Between 30-60% of people infected with HIV experience an *acute retroviral (or seroconversion) syndrome* or *acute HIV infection* (see figure 1), which occurs at the time of initial infection (at a time period of weeks after acquisition of the virus). This acute infection includes fever, myalgia, a maculopapular, oral ulcers, neurolocial manifestations and an acute reduction in CD4 lymphocytes (Tindall & Cooper, 1991). The symptoms associated with this syndrome are non-specific and the varying severity of the clinical syndrome may explain why most HIV-infected persons generally do not report the symptoms of primary HIV infection (Fauci, Pantaleo, Stanley, & Weissman, 1996). At this time, tests for HIV antibody in the blood are negative or indeterminate and without treatment the clinical illness subsides, CD4 cells count rebounds (but not back to level before HIV infection) and values for virus decrease to a plateau (Cohn, 1997). Fauci and colleagues state that it is likely that both cell-mediated and humoral immune responses are important in this initial down regulation of HIV replication (Fauci et al., 1996).

So, during the next illness period called *clinical latency*, CD4 cell counts are within normal limits or generally above 350 x 10^6 cells/l and HIV antibodies continue to be detectable in the blood. HIV replication is slow and the amount of virus in blood and lymphoid tissues falls to very low levels (Mindel & Tenant-Flowers, 2001). The duration of clinical latency varies. Progression to the acquired immunodeficiency syndrome (AIDS) typically occurs after a mean of approximately 10 years. So, HIV can persist for 10 or more years in an asymptomatic phase before manifestation of clinical symptoms occurs (Fauci, Schnittman, Poli, Koenig, & Pantaleo, 1991; Mindel & Tenant-Flowers, 2001; Pantaleo, Graziosi, & Fauci, 1993a). Thus, some individuals are asymptomatic for a long time, respond well to medications and undergo few infection-related complications until the disease progresses to AIDS. Other infected patients undergo a rapidly progressing illness with medical complications and opportunistic infections. This course of disease comes along with an impaired quality of life (Kopnisky, Stoff, & Rausch, 2004). Long-term nonprogressors are a subset of persons infected with HIV. Despite their HIV-infection, they have delayed progression and stable CD4 cell count (Rappaport et al., 1997).

A typical feature of HIV-infection is a profound loss of CD4+ T cells throughout the course of HIV disease as well as an increasing viremia (Fauci, 1993; Stebbing, Gazzard, & Douek, 2004; Vergis & Mellors, 2000). During the course of persistent infection, cellular response appears to lose its effectiveness, eventually resulting in loss of virus replication control. This is likely due to the loss of CD4+ cells, as a result of direct virus infection of this cell population (Emini & Koff, 2004). So, a result of a decline in immune competence, which occurs due to increased replication of HIV from sites where it has been latent (triggers for this reactivation are poorly understood), is the progression of HIV infection. Due to this progression, somatic condition decreases and individuals may suffer from constitutional symptoms, skin and mouth problems and haematological disorders (Mindel & Tenant-Flowers, 2001). The Center of Disease Control (CDC) developed the most common used classification for HIV disease. In the revised version from 1993, which will be described in detail below, CDC defins possible symptomatic conditions in category B and AIDS defining conditions in category C. So *acquired immunodeficiency syndrome (AIDS)* is defined due to the presence of one of 25 AIDS-defining conditions, which included Kaposi's sarcoma,

pneumocystis carinii pneumonia, progressive multifocal lukoencephalopahty etc. (CDC, 1992).

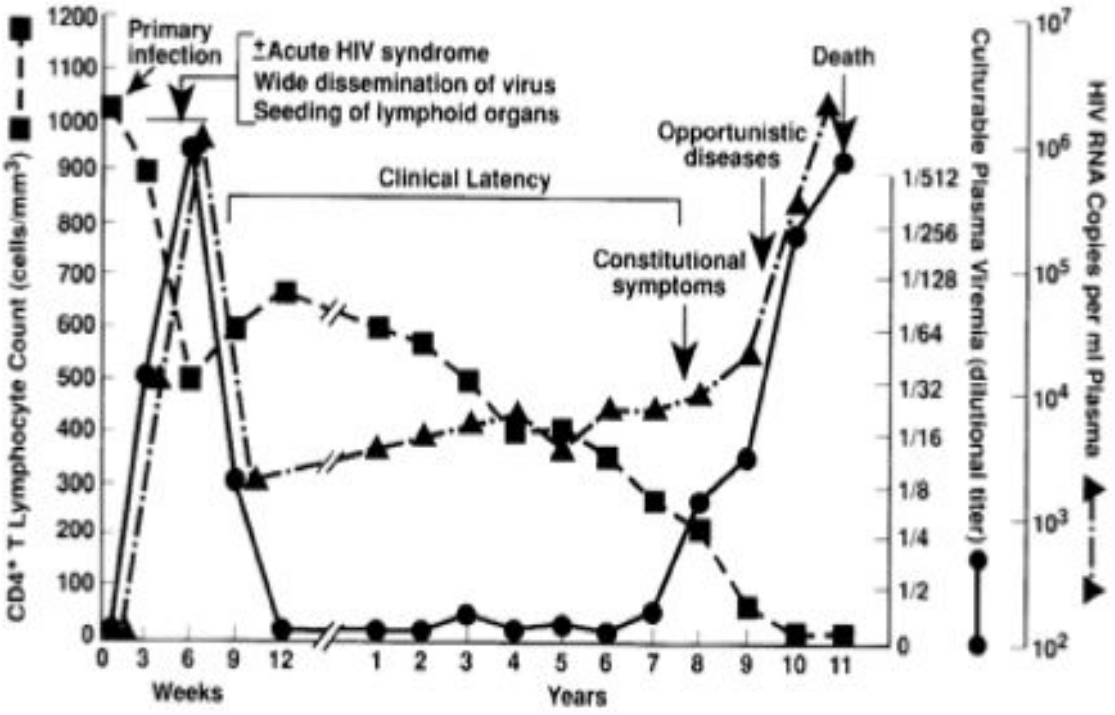

Figure 1: Typical course of human immunodeficiency virus (HIV) infection (Fauci et al., 1996, adapted from Pantaleo et al. 1993. p. 327-35)

Notes: The complex, multifactorial, multiphasic, and overlapping factors of the immunopathogenic mechanisms of HIV disease are shown. Throughout the course of HIV infection, virus replicates and immunodeficiency progresses steadily, despite the absence of observable disease symptoms during the so-called clinical latency period. Immune activation and cytokine secretion vary among HIV-infected persons, sometimes increasing dramatically as disease progresses. Immune activation and cytokine secretion play a major role in pathogenesis.

Historically the stages of HIV disease are categorized as: early ($CD4^+$, > 500 cells/ηL), mid-stage ($CD4^+$, 200-500 cells/ηL), advanced ($CD4^+$, 50 cells/ηL) and end-stage disease ($CD4^+$, 50 cells/ηL) (Vergis & Mellors, 2000). As described above, the currently used classification system for HIV infection derived from the Centers of Disease Control and Prevention (CDC). In 1993, CDC revised the

classification system for HIV infection to emphasize the clinical importance of the CD4+ T lymphocyte count in the categorization of HIV–related clinical conditions. This classification system replaces the system published by CDC in 1986 and is primarily intended for use in public health practice. The revised CDC classification system for adults categorizes persons on the basis of clinical conditions associated with HIV infection (clinical categories A to C) and CD4 + T-lymphocyte counts. So the system is based on three ranges of CD4+ lymphocyte counts and three clinical categories (see table 1). *Clinical category A* consists of at least one the following conditions: asymptomatic HIV infection, persistent generalized lymphadenopathy, acute (primary) HIV infection with accompanying illness or history of acute HIV infection. Classified in *clinical category B* are HIV infected individuals with symptomatic conditions, that are not included among conditions listed in clinical category C and meet al least on of the following criteria: the conditions are attributed to HIV infection or indicative of a defect in cell-mediated immunity. Examples of clinical conditions are candidiasis, herpes zoster, listeriosis and so on. Persons will remain in *category C* (AIDS defining conditions) if at least once a category C condition occurred like Karposi's sarcoma, encephalopathy, wasting syndrome due to HIV etc. (CDC, 1992).

Table 1: CDC classicication 1993 (Mindel & Tenant-Flowers, 2001)

Summary of CDC 1993 classification system for HIV disease			
	CD4 lymphocyte count x106/l		
	≥500	**200-499**	**>200**
(A) Asymptomatic including Groups I, II and III	A1	A2	A3
(B) Symptomatic not A or C	B1	B2	B3
(C) AIDS defining conditions	C1	C2	C3

Concerning the risk of progression and the value of surrogate markers, Mindel and Tenant-Flowers (2001, p.1293) reported: *"Variables associated with rapid disease progression include a symptomatic primary HIV infection, older age at diagnosis and receiving a large inoculum of virus, for example via a contaminated transfusion from a donor with a high viral load. The effect of prophylaxis against opportunistic infections (eg, cotrimoxazole for pneumocystis and*

toxoplasmosis) has been to delay the onset of AIDS and to change the pattern of disease represented by the first AIDS defining illness. Antiretroviral treatment has independently been shown to increase survival before and after AIDS." Plasma viral load and CD4+ lymphocytes count are the most powerful surrogate markers of HIV disease (progression or death) and clinical benefit from antiretroviral therapy, so they provide important prognostic information (Mellors et al., 1996). Valuable information from these two parameters are for example the risk of opportunistic infections (Lane et al., 1994; Phair et al., 1990), as well as information about patients response to antiretroviral therapy and therapeutic failure (O'Brien, Hartigan, Daar, Simberkoff, & Hamilton, 1997).

2.1.2 Epidemiology

Despite the reduction of HIV-related mortality since the introduction of HAART, HIV continues to be a major public health problem, also in Western Europe (Hamers & Downs, 2004). Estimations reason that 520'00 – 610'000 people have an infection that remains incurable and needs costly treatment (Miners et al., 2001; Yazdanpanah et al., 2002). UNAIDS estimates that more than 40 million people worldwide are persistently infected with HIV-1, with the highest prevalence in sub-Saharan Africa. Worldwide, the number of new infections are 14'000 daily, with more than 95% occurring in the developing world (UNAIDS, 2002).

Recent epidemic trends of newly diagnosed HIV infections are available for 12 of 18 countries of Western Europe, which account for 51% (198 million) of the total population. The number of reported new diagnoses in this 12 countries increased by 46% between 1997 (770 cases) and 2002 (11 337 cases). In the same time period, HIV diagnosis decreased gradually among injecting drug users (16%, from 623 to 52) but increased in people infected through heterosexual contact (122%, from 2490 to 5526) because of an increase in the number of cases diagnosed in people originating from countries with generalised HIV epidemics (179%, from 1382 to 3861) (Hamers & Downs, 2004). Concerning the number of people living with HIV/AIDS in Western Europe by the end of 2003, UNAIDS and WHO estimated that 520'000-680'00 people were living with HIV