PSYCHO-IMMUNOLOGY AND HIV INFECTION. BIOPSYCHOSOCIAL DETERMINANTS OF DISTRESS, IMMUNOLOGICAL PARAMETERS, AND DISEASE PROGRESSION IN HOMOSEXUAL MEN INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-1.

PSYCHO-IMMUNOLOGIE EN HIV-INFECTIE. BIOPSYCHOSOCIALE DETERMINANTEN VOOR PSYCHISCHE KLACHTEN, IMMUNOLOGISCHE PARAMETERS EN ZIEKTE-PROGRESSIE BIJ HIV-GEINFECTEERDE HOMOSEXUELE MANNEN.

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Part II

Chapter 1

General Introduction and Scope of the Thesis

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Subjects who have tested positive for the presence of antibodies against Human Immunodeficiency Virus Type I (further abbreviated as HIV), have to live with a life-threatening infection. At present, no definite medical cure is available that prevents progression of HIV infection. Therefore, knowledge of being infected with this virus puts a heavy burden on one's coping capabilities. Although some subjects find a way to live with their HIV infection, others have great difficulties in adjusting to it and may suffer from psychological distress. Whether or not HIV-infected subjects develop psychological distress is determined by several factors. These include for instance the experience of other stressful life events, the type of coping style that is used, and the quality of the social network. However, little is known about the relative importance of each of these variables and the way they interact in predicting distress levels.

HIV-infected individuals may benefit from psychosocial interventions that aim at increasing social support and improving coping strategies. Although several types of psychosocial intervention may be effective, the relative effectiveness of different psychotherapeutic intervention strategies is unknown.

We investigated factors that determine the level of distress and the effectiveness of two different psychosocial interventions in decreasing distress levels in asymptomatic and early symptomatic HIV-infected homosexual men. These studies are described in Part I.

In Part II studies pertaining to the associations between psychosocial factors and progression of HIV infection are described. The length of the period until the development of Acquired Immunodeficiency Syndrome (AIDS) varies considerably among individuals and it is hypothesized that some of the variation is due to psychosocial factors. These factors may include stressful life events, psychological distress, coping styles and social support. In the event that psychosocial factors have an influence, psychosocial interventions may slow down the rate of progression, and enhance the effectiveness of medical treatments. Studying the effect of psychosocial factors on disease progression is therefore of clinical relevance. It is of theoretical relevance because insights are gained into psychoneuroimmunological relationships in a virologically and immunologically mediated disease.

The following research questions were addressed in HIV-infected homosexual men in early stages of infection:

Part I. Determinants of psychological distress:

1. What is the level of psychiatric symptoms and what are the associations between stressful life events, coping, and social support and psychiatric symptoms (chapter 3 and 4)?

2. What are the effects of cognitive-behavioral vs. experiential group psychotherapy on the level of psychological distress, coping styles, social support, and emotional expression (chapter 4)?

Part II. Determinants of immunological parameters and HIV-disease progression:

3. What are the associations between psychosocial factors including psychiatric symptoms, life events, coping, and social support and progression of HIV infection (chapter 5, 6 and 7)?

4. What are the effects of cognitive-behavioral and experiential group psychotherapy on immunological parameters (chapter 8)?

Part I starts with a review of the literature concerning psychosocial problems of HIV-infected men, and implications for psychotherapy (chapter 2). In chapter three a study of determinants of psychiatric symptoms is described. In this study the associations between stressful life events, coping styles and social support on the one hand and the level of psychiatric symptoms on the other hand have been investigated. Part I is completed by an intervention study comparing the effects of cognitive-behavioral and experiential group psychotherapy on psychosocial parameters (chapter 4).

Part II also begins with a review of relevant studies (chapter 5), followed by two studies in which the associations between psychosocial variables, immunological parameters and disease progression have been investigated (chapter 6 and 7). We investigated the associations between coping styles and disease progression in HIV-infected men over a 7-year period (chapter 6). Another study investigated the associations between the experience of stressful life events, psychiatric symptoms, coping styles, and social support and disease progression during one year in asymptomatic and early symptomatic HIV-infected gay men (chapter 7). Lastly, we studied the immunological effects of psychotherapeutic interventions (chapter 8).

The findings presented in part I and II will be discussed in chapter nine.

Three different samples of HIV-infected homosexual men were studied. Two of the samples consisted of men participating in a cohort study for the natural history of HIV infection conducted at the Amsterdam Municipal Health Center (chapters 4, 6 and 8). The third group was recruited among men visiting out-patient clinics in Amsterdam, The Hague and Rotterdam (chapters 3 and 7).

The studies presented here focus on HIV-infected homosexual men, as in the western world the majority of HIV-infected individuals are homo- or bisexual men. Although many issues can be generalized to other populations at risk, such as hemophiliacs, and women, every group has its specific characteristics. For reasons of research methodology, i.e., having a homogeneous group of subjects, we chose to focus upon homosexual men only.

Part I

Biopsychosocial Determinants of Distress in HIV-Infected Homosexual Men

Chapter 2

Acquired Immunodeficiency Syndrome (AIDS) in Homosexual Men: Psychological Distress and Psychotherapy

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Abstract

Infection with HIV causes a decline in immunological functioning with time. This may lead to the occurrence of HIV-related symptoms or AIDS, which is likely to be a terminal condition. The knowledge of having a positive HIV antibody test, therefore, brings about a psychosocial crisis in many individuals. This chapter discusses the type of problems that HIV-infected homosexual men are confronted with during the various stages of the disease, and the characteristics of persons who are particularly vulnerable to developing these problems. Finally, strategies for psychosocial intervention, and recommendations for psychotherapists will be presented.

Introduction

Studies of the natural history of infection with HIV have documented a wide spectrum of disease manifestations. After an asymptomatic period of variable duration, life-threatening conditions referred to as AIDS may develop. AIDS is characterized by severe immunodeficiency, serious opportunistic infections, and cancers (CDC, 1993). Therefore, not surprisingly, knowledge of being infected with this virus causes high levels of psychological distress in many individuals (Atkinson et al., 1988; Chuang et al., 1989). In many western countries, HIV appeared first among - and still disproportionately affects - gay men and injection drug users, although the percentage of HIV-infected heterosexual men and women is rising (Ickovics & Rodin, 1992). At the end of 1991, 60.485 cumulative AIDS cases have been registered in Europe, in a population of 854.655 million people (AIDS Feedback, 1991). The estimated number of HIV-infected individuals in the Netherlands was 7000 at the end of 1988 (Water et al., 1992). In Amsterdam, it is estimated that approximately 17% of the gay- and bisexual are infected with HIV (Veugelers, 1992).

At present, despite massive research, no definite medical cure is available to prevent the destructive effect of the virus on the immune system. To date, 50-75% of HIV-infected homosexual men and patients with hemophilia develop AIDS 8-10 years after infection, and the mean survival time after the onset of AIDS is approximately 1.5-2 years (Peters et al., 1991). The course of HIV infection in intravenous drug users is unknown at present, mostly because these patients frequently die of other causes.

The CD4+ T lymphocyte (further abbreviated as CD4 cell) is the primary target for HIV, and the number of CD4 cells is currently one of the most important immunologic predictors for the course of the infection (Moss & Bacchetti, 1989, Fahey et al., 1990). The course of HIV infection can be divided into several stages, depending on the type of clinical symptoms and the number of CD4 cells observed. A frequently used staging system is the system developed by the Centers for Disease Control (1993). In this system, three clinical stages have been distinguished, each defined by a specific set of symptoms and diseases, ordered according to type, site, severity, and duration of the illnesses (Table 2.1). Every stage can be divided into three substages, depending on the numbers of CD4

cells in the peripheral blood. Biomedical and psychological problems vary across the stages of the infection, as every phase has its own characteristics. Therefore, in this review, the type of problems that HIV-infected homosexual men are confronted with, and possibilities for interventions will be discussed according to stage of the disease.

Table 2.1. 1993 Revised CDC classification system for HIV infection

	Clinical Categories		
	(A) Acute HIV, Asymptomatic, PGL*	(B) Symptomatic**	(C) AIDS-Indicator Conditions**
CD4 cells			
(1) > 499/mm^3	A1	B1	C1
(2) 200-499/mm^3	A2	B2	C2
(3) < 200/mm^3	A3	B3	C3

* PGL = Persistent Generalized Lymphadenopathy
** See CDC (1993) for specifications of symptoms and AIDS-indicator conditions

Reactions to HIV Antibody Testing

When individuals are tested for the presence of antibodies to HIV they provide a blood sample, and then return several days later for their test results. Usually, at most testing sites, the test consists of an enzyme-linked immunoassay (ELISA). If this test is positive, it is usually followed by a confirmatory test of antibodies to HIV protein (Western Blot).

As one would expect, testing HIV seropositive is a dramatic event. This event causes a sudden change in life perspective as the person confronts the reality of progressive physical decline, an insidiously increasing probability of suffering from severe illnesses as the years go by, and a seemingly inevitable early death. Therefore, these individuals have many conflicting feelings and thoughts around the period of an HIV+ serostatus notification (Miller, 1988; Perry et al., 1990, 1993; Antoni et al., 1991a,b). These acute psychological phenomena associated with an HIV+ test result are listed in Table 2.2.

Table 2.2. Acute psychological phenomena associated with HIV infection and disease (from Miller et al., 1988)

Shock of diagnosis and possible death over loss of hopes for good news
Fear and anxiety elicited by the prospect of uncertain prognosis and course of illness disfigurement and disability effects of medication and treatment isolation and abandonment and social/sexual rejection infecting others and being infected by them lover's ability to cope and his possible illness loss of cognitive, physical, social and work abilities
Depression caused by 'inevitability' of physical decline absence of a cure the virus controlling future life limits imposed by ill health and possible social, occupational, emotional and sexual rejection self-blame and recrimination for being vulnerable to infection in the first place
Anger and frustration about inevitability of overcoming the virus new and involuntary health/lifestyle restrictions the uncertainty of the future
Guilt about past 'misdemeanors' resulting in illness 'punishment' possibly having spread the virus to others being homosexual or a drug user
Hypochondriasis and obsessive disorders caused by relentless searching for new diagnostic evidence in the body faddism over health and diets preoccupations with death and decline, and avoidance of new infections

It is interesting that studies conducted before 1988 generally report high and pervasive levels of psychological distress following positive HIV serostatus notification, whereas studies conducted since that year generally indicate lower notification-associated distress levels (Kelly et al., 1992) which do not generally persist longer than a month or two (Perry et al., 1993). This shift in reactions seen in research samples may be due to greater understanding of the difference between HIV infection and AIDS and the emergence of early medical interventions that can forestall AIDS development.

It also seems clear that the amount of psychological distress that occurs after an HIV+ diagnosis is influenced by several other psychosocial factors. These include the personality of the infected person; his previous experiences and psychiatric history, coping capabilities, and social network; and whether or not other stressful life events are experienced concurrently. Perry and colleagues (1993), for instance, found that individuals who were the most distressed after testing HIV seropositive were also those who were most distressed before testing. Antoni and colleagues (1991a), examined whether the type of coping strategies that were used by newly diagnosed HIV+ gay men influenced their distress levels. They found that the use of denial as a coping strategy was associated with higher levels of depression three weeks and one year later. In a study of heterosexual married men with hemophilia (Dew et al., 1990), low social support from one's wife, low family support, and low support from friends were associated with higher depression scores on the SCL-90 symptom checklist (Derogatis, 1983). Finally, negative beliefs, attitudes and feelings about being gay (internalized homophobia) are often related to low self esteem and may also influence the reaction to an HIV positive diagnosis (Hart, 1993). In sum, the distress at diagnosis and subsequent adjustment is influenced by a set of psychosocial factors that include prior history, cognitive appraisals of stressors, coping strategies, and social resources.

Apart from the psychological distress caused by the positive antibody test result itself, the news of an HIV+ diagnosis may lead to the renewed expression of traumas associated with previous painful or emotionally scarring life events, such as the family rejection these individuals experienced when they 'came out' as a homosexual, the death of loved ones, and job loss with consequent financial stressors (Wolcott et al., 1985). Moreover, the suddenly shortened life perspective may bring about a need to deal with issues that have been denied as problems for a long period of time, such as a severed relationship with a parent. Many times during psychosocial interventions these issues come up, and then need to be dealt with.

Psychosocial interventions immediately preceding and following serostatus notification. The awareness that significant distress, confusion and misunderstandings may accompany antibody testing has led to the development of a form of psychosocial counseling at most HIV antibody testing sites. In the U.S.A., this counseling is standardized by the Centers for Disease Control, but in most other nations, as for instance in the Netherlands, counseling activities vary across different sites. These counseling efforts are designed to clarify the meaning of HIV test results, and to answer questions that testees might have at this point in time. The effects of such counseling on the distress and depression resulting from learning about one's seropositive status are likely to be small though such counseling may help to identify the most distressed individuals. One question that has been addressed in research studies conducted over the past seven years is: Does short-term psychotherapeutic intervention -- e.g., stress management -- attenuate the initial impact of a seropositive diagnosis? Therefore, in addition to the mandatory pre- and post-test counseling activities, psychosocial intervention programs have been initiated just prior to the time of serostatus notification. These programs have been shown to 'buffer' feelings of

anxiety and depression.

In one study that incorporated intensive pre-test and post-test counseling (Perry et al., 1990), the level of distress in seropositives was not found to increase on notification of an HIV seropositive status and eventually decreased below prenotification levels. These findings were supported by Antoni and colleagues (1991b), who showed that a cognitive-behavioral stress management group program of 10 sessions was effective in reducing the distress associated with receiving an HIV antibody positive test result.

In conclusion, the diagnosis of an HIV+ serostatus is a life-changing event which may lead to increases in psychological distress. Newly diagnosed HIV+ subjects may benefit from psychosocial interventions such as cognitive-behavioral stress management programs in addition to standardized pre- and post-test counseling.

Living With an Asymptomatic HIV Infection

The duration of the asymptomatic period is unpredictable. After receiving an HIV positive test result, a period begins in which infected individuals are free of all but only mild HIV-related symptoms, if any. The length of this period, however, varies considerably among individuals. As stated above, 50-75% develop AIDS 8-10 years after infection (Moss & Bacchetti, 1989), though a number of factors, including pharmacologic intervention, biological characteristics of the virus, host-related factors, and life style factors, may either accelerate or delay its onset. Many feel that pharmacologic intervention initiated early in the disease process may retard progression to frank AIDS. Recent research suggests that the early use of antiretroviral medications, for instance zidovudine (AZT), dideoxyinosine (ddI), or dideoxycytidyne (ddC) (Volberding et al., 1990; Collier et al., 1991; Hamilton et al., 1992), prolongs the asymptomatic period, although once a patient becomes ill, the disease process may be more rapid (Hamilton et al., 1992). Other factors that are considered to influence the duration of the asymptomatic period are the virulence of the HIV-1 variant infecting the person (Miedema et al., 1990), and life style factors such as having unprotected sexual intercourse with a person who has AIDS (Griensven et al., 1990).

Psychosocial problems during the asymptomatic phase. For an HIV-infected individual, the duration of the asymptomatic period, and the moment of developing the first HIV-related symptoms is a matter of uncertainty which may cause anxiety and depression. Unexpectedly, however, two studies in Miami and Amsterdam, respectively, have shown that the levels of psychological distress during the asymptomatic period, at least in gay men, were not as high as one might expect (Blaney et al., 1990; Mulder et al., in press). In both studies, HIV-infected homosexual men were found to have somewhat higher levels of psychological distress as compared to healthy non-HIV-infected norm groups, but on average these distress levels were not in the range of distress levels found in psychiatric patients. These studies suggest that the early asymptomatic stage of the disease -- of recognition of an HIV seropositive status -- may not necessarily be a time of turmoil, and that HIV infection can be effectively managed, at least for a time. In the same vein, high

levels of hope and low levels of current syndromal psychiatric disorder or depressive symptoms were found in a selected group of well-educated HIV-infected homosexual men in New York (Rabkin et al., 1990), suggesting, possibly, that the subjects were able to preserve a sense of faith in their future and conviction that living was still worthwhile.

These results show that asymptomatic HIV-infected individuals may cope well with the threat of AIDS. Indeed, it has been shown in a group of asymptomatic HIV-infected homosexual men that subjects primarily coped with the threat of AIDS by adopting a fighting spirit, reframing stress to maximize personal growth, planning a course of action and seeking social support (Leserman et al., 1992). However, those men who demonstrated dysphoria and poor self esteem used more helpless coping, less fighting spirit coping and had less of a tendency to use the experience as an opportunity for personal growth. Interestingly, using denial of HIV infection as a coping strategy was related to more depression, anger and helpless coping. In this study (Leserman et al., 1992), black subjects were found to use more denial, to be more helpless, and to have less social support as compared to the non-black participants in the study. In agreement with these findings, Australian investigators showed that HIV-infected asymptomatic homosexual men who reported more depression, also reported more helplessness and fatalism (Kelly et al., 1991).

The greater use of denial and helpless coping may affect the relationship between the patient and the medical care provider, and ultimately the patient's compliance with medical treatment. Therefore, psychological intervention may be of value in helping the patient cope with his illness, particularly when the relationship between care provider and patient is compromised. For a discussion of psychosocial interventions for asymptomatic individuals see chapter 4.

Living with a Symptomatic HIV Infection

Dealing with the initial development of symptoms. Once HIV-related symptoms start to develop, the likelihood of developing AIDS increases, which may increase the experience of emotions and intrusive thoughts that have been suppressed during the asymptomatic phase. These include fear of death, of abandonment, and the dread of becoming dependent on healthy persons. The question "Why me?" , followed by rage and the experience of punishment for what is socially condemned as a sinful or evil life, may also arise at this time.

The experience of increasing distress during the symptomatic period was supported in a study which found that a greater number of HIV-related symptoms was associated with greater depression among gay men (Hays et al., 1992). The increase in depression after developing HIV-related symptoms may partly reflect the anticipation of an AIDS diagnosis which may appear more inevitable. In line with these findings a study by Atkinson and colleagues (1988) found lower distress levels in AIDS patients (n=15) as compared to symptomatic patients without AIDS (n=13). Although the number of participants in this study was small, these findings may indicate the experience of 'relief'

of an AIDS diagnosis, that puts an end to a period of uncertainty and anticipatory anxiety. However, in a study in an out-patient clinic in the Netherlands, no differences in psychological distress were found between 56 symptomatic HIV-infected patients and 61 patients with AIDS (Beuzekom et al., 1991). Both groups had higher SCL-90 scores (Derogatis, 1983) than a healthy normative group and cardiac out-patients, but lower than psychiatric out-patients. It was concluded from the Dutch study that more psychosocial help is needed for both groups of these HIV-infected patients.

Receiving an AIDS diagnosis. A diagnosis of AIDS is based on the observation of a variety of different diseases, including certain opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), certain cancers such as Kaposi's sarcoma and neurological disease such AIDS-dementia complex (ADC). Each of these diseases has its own characteristics and can vary significantly in severity. Patients with Kaposi's sarcoma, for instance, have a longer survival time as compared to patients with opportunistic infections (Peters et al, 1991). Survival time after an AIDS diagnosis is, on average, approximately 1.5-2 years (Peters et al., 1991). The length of survival varies considerably among individuals, partly because of the heterogeneity of the AIDS diagnoses and other known and suspected biological "co-factors". However, a substantial proportion of the variance in survival appears to be determined by unknown factors. Differences in disease manifestation may also have psychological ramifications. For instance, patients who have developed very aggressive opportunistic infections may be relatively more at risk for developing psychological problems as compared to patients with relatively less aggressive AIDS-defining conditions such as Kaposi's sarcoma (Fawzy et al., 1989a).

Adjusting to neurocognitive impairments. Neurocognitive impairments frequently occur during HIV infection (Wilkie et al., 1990). These deficits include, for instance, fatigue and impairment in language, memory and integrative abilities. Hence, psychiatric consultation may be initiated at a relatively early stage of disease to assess high risk patients and determine neuropsychiatric deficits and CNS involvement. One of the first HIV-related symptoms that may occur is fatigue. The fatigue can be very serious and incapacitating, thereby interfering with important activities such as employment and driving. In a study of Darko and colleagues (1992), HIV-infected patients were found to be more likely to feel fatigued through more hours of the day, to sleep more, and to nap more, as compared to a non-HIV-infected control group. The fatigue and sleep disturbances may be caused by humoral mediators (e.g., increases in peripheral levels of cytokines such as interleukin-1 and tumor necrosis factor) and suggest the possibility for medical intervention in the future to clinically treat HIV-related fatigue. Until now, however, no specific treatments have been available. Another possible reason for the occurrence of fatigue may be HIV infection of the central nervous system (CNS). In that case fatigue may precede CNS dysfunction, possibly leading to ADC, as is found in 30-40% of AIDS patients (Faulstich, 1987). Other non-specific symptoms such as malaise, social withdrawal, lethargy, and reduced sexual drive may also precede ADC onset, though these may also be secondary to a reactive depressive disorder. Over a period of several weeks or months psychomotor

retardation, incontinence, confusion, and, sometimes, hallucinations may develop.

If an HIV-infected individual develops ADC, caretaking for the patient may be needed, which can place a burden on the partner, friends and relatives. Therefore, patients as well as caretakers may benefit from interventions that provide information about the consequences of ADC as well as an opportunity for asking questions and expressing mutual concerns.

Bereavement. A stressor that is 'unique' to people who are infected by HIV, is the frequent experience of bereavement, because many HIV-infected individuals have one or more friends who have been diagnosed with or who have died from AIDS. In a study of a community sample of 745 gay men in New York City, bereavement was experienced by 27% of the men since the start of the epidemic in 1980 (Martin, 1988). It was found that the number of bereavements experienced was directly related to the level of psychological distress, the amount of recreational drug use, and the use of psychological services to address AIDS concerns. It was concluded that gay men are not adapting psychologically to repeated experiences of AIDS-related bereavement. Therefore, counseling programs that help individuals to work through the grieving process may be necessary for these individuals. Intervention programs that are offered to bereaved individuals in a group format can be helpful in restoring the decreased social support caused by the bereavement (Beckett et al., 1990). However, little research has been done regarding the effects of such interventions. At the present time behavioral scientists at various research institutions in the U.S. are testing the efficacy of different types of psychosocial interventions with this population. These interventions focus upon increasing emotional support, altering cognitive appraisals and facilitating the use of different coping strategies.

Suicide and euthanasia as options for coping with the disease. The rate of suicide among infected individuals reflects the magnitude of psychosocial problems in people with AIDS. In a study in New York City, the risk of suicide in men with AIDS was found to be 36 times that of men of the same age without HIV infection (Marzuk et al., 1988). No differences were found in suicidal ideation rate across the various stages of HIV infection, demonstrating that the symptomatic phase of the infection is not necessarily leading to more suicide attempts (O'Dowd et al., 1993; Wöller et al., 1993). Several characteristics have been found that could predict suicidality among HIV-infected men. These include the lack of appreciation by key persons (Wöller et al., 1993), having an Axis I (DSM-III-R) disorder and being of a younger age (Hutelmeyer et al., 1993).

As a way of dealing with problems occurring during the terminal phase of the disease, at least in Amsterdam, euthanasia is chosen by a substantial number of people with AIDS. In Amsterdam, the incidence of euthanasia is approximately 35% among people with AIDS, and the majority of them have signed a euthanasia document (Laane, 1993). Under the Dutch law the doctor will not be prosecuted after assisting in the euthanasia, when he/she can demonstrate to have acted carefully (Pijnenborg et al., 1993). The decision to conduct euthanasia is a delicate matter, which has to be made after consultation of all persons involved, including friends, family, and professionals who take

part in the treatment and care for the patient. The AIDS patient himself needs to make the final decision, although this is not always possible in ADC cases or if the patient is unconscious. It is important that psychosocial interventions provided for HIV-infected individuals address the issue of euthanasia in early stages of the infection, thereby helping the subjects in their decision-making.

Psychosocial interventions for symptomatic patients. One of the few psychosocial interventions for homosexual men who have HIV-related symptoms and/or AIDS that has been described was developed by Fawzy and his colleagues (1989b). In this 10-week structured group intervention program patients were taught stress management techniques, relaxation training, problem solving skills and effective coping styles, and received and gave emotional support. Although the results of this study have to be interpreted cautiously because of the absence of a control group and the absence of information on the statistical significance of intervention-related changes, the levels of anxiety and depression appeared to decrease after group intervention, suggesting the positive effect of the intervention.

In AIDS psychotherapy groups, often members die because of AIDS, and grieving the loss of a member becomes an important issue. Such an event exacerbates member's fears about whether they will die soon too. Fear of death is a dominant affect that pervades these groups. Its particular contours are highly individual; religious or spiritual beliefs about life after death may determine whether patients see death as final or transitional. For some the prospect of dying is itself preoccupying, while others seem to concern themselves more with the circumstances accompanying the death. They may fear neurologic deficits, pain, shortness of breath, unwanted medical interventions or dying alone. It is therefore crucial that death and its implications be openly acknowledged and discussed at the time of losses of group members (Beckett & Rutan, 1990; Tunnell, 1991).

What remains to be elucidated is which types of psychosocial interventions are most effective with individuals at different stages of the HIV spectrum disease. Testing the relative effectiveness of different intervention strategies will provide important information for health care providers to choose which types of interventions should be offered to the patients.

Therapist qualifications. Counseling HIV-infected homosexual men and patients with AIDS requires knowledge about gay lifestyles, and about the course of HIV infection and its consequences. Such information allows therapists to be able to better understand their client and to provide information when needed. In the counseling process the therapist may come across unresolved issues in him- or herself such as specific morals about sexual behavior or fears about sickness and dying. Therapists may need to examine their own beliefs about sexuality, God, death and the afterlife because these beliefs may have a powerful effect on the course of counseling (Hoffman, 1991). Therapists may need to be prepared to work with their HIV-infected clients until the client's death. If the client is hospitalized, counseling sessions might be conducted in the hospital or at the client's home as he recuperates.

There may be no other counseling issues that require so much from therapists in so many ways as do those surrounding this disease. Enormous demands are placed on one's energies, professional skills, and resources; burdens which are not without consequences. This is illustrated by a recent study that demonstrated that 25% of the 170 health workers working in AIDS units in 14 large public hospitals in Italy had pathological levels of anxiety and depression (Bellani et al., 1993). Therefore, prevention of occupational burnout, and feelings of depression and helplessness become important issues for the health care personnel working with this group of patients. This may be achieved by being involved in some type of support group in which the experiences with HIV-infected clients can be discussed together with other health care workers (Nichols, 1986).

Conclusion

Homosexual men who have to adjust to the mental and physical consequences of being HIV-infected frequently seek psychological help. In providing these services, therapists need to take into account the subject's stage of infection, social circumstances, personality characteristics, and cognitive functioning. Providing individual or group support and education can help in reducing distress and increasing social support, as was shown in several intervention studies using different types of short-term group interventions. However, more research is needed to test the relative effectiveness of these interventions with individuals in different stages of this disease.

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Chapter 3

Stressful Events and Coping Resources as Determinants of Psychiatric Symptoms during One Year in HIV-Infected Homosexual Men

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Abstract

The occurrence of psychiatric illness during one year as measured by the Present State Examination (PSE) at baseline and the General Health Questionnaire (GHQ) during follow-up was studied in 57 HIV-infected asymptomatic and early symptomatic homosexual men. At baseline, 14 subjects (26%) were defined as having a psychiatric diagnosis according to the PSE. We found that the most significant predictor for psychiatric symptoms scores during follow-up was the GHQ score at baseline. While adjusting for GHQ scores and the presence of HIV-related symptoms at baseline, stressful life events that were not related to the somatic course of the disease, and social support showed significant associations with GHQ scores during follow-up. Subjects who used active confrontational coping as a way to cope with HIV infection showed higher GHQ levels in relation to the experience of stressful life events, whereas having an optimistic attitude was associated with lower levels, though these moderator effects were only evident for the mean GHQ scores during one year for active confrontational coping and 3-month follow-up for optimism. Psychosocial interventions may be effective in reducing psychiatric illness and consequently distress levels by aiming at improving the social network, and teaching individuals how to deal with stressors that are not necessarily related to their disease.

Introduction

Infection with HIV is a life-threatening condition. Despite the extension of the period between initial infection and the onset of AIDS due to recent treatment advances, persons with HIV infection still face the prospect of chronic, debilitating illness and early death. In western countries, the AIDS epidemic has exerted a profound psychological toll on gay men, and this group has been shown to be at risk for developing psychiatric problems (Chuang et al., 1989; Brown et al., 1992). However, studies surveying the severity of emotional distress in HIV-infected gay men have been contradictory. Some studies detected elevated levels of depressed mood and anxiety in asymptomatic HIV-infected men (Brown et al., 1992) and in men in mixed stages of infection (Chuang et al., 1989). Other studies detected only transient elevated levels of depressed mood and anxiety ten weeks after HIV-positive serostatus notification (Perry et al., 1990a), or relatively low levels during asymptomatic stages (Blaney et al., 1990; Mulder et al., in press). These discrepant findings may be due to individual differences, time of measurement and different research instruments. Several studies showed that depressed mood and anxiety levels may depend on the person's actual health status, optimism or fatalism concerning health outlook, adequacy of social support, presence of other life stressors, and general coping style (Antoni et al., 1991a; Leserman et al., 1992; Hays et al., 1992; Kelly et al., 1993a).

In a cross-sectional study, Leserman and colleagues (1992) examined the associations between coping styles and depressive symptoms. In this study, men who

coped with the threat of AIDS primarily by reframing stress to maximize personal growth, planning a course of action and seeking social support, reported a lower number of depressive symptoms and mood disturbances. On the other hand, high levels of mood disturbances were found in men who demonstrated more helpless coping behavior, and less personal growth as coping strategies. Antoni and colleagues (1991a) found that using denial as a coping strategy was associated with higher levels of depressed mood three weeks and one year after notification of an HIV positive serostatus. Another study demonstrated a relationship between symptoms of depression and occurrence of HIV-related somatic symptoms in gay men (Hays et al., 1992). In this study, social support levels at study entry appeared to buffer feelings of depression associated with experiencing HIV-related symptoms one year later. These results were confirmed by Kelly and colleagues (1993a) who showed an association between lower perceived social support, a greater number of HIV-illness symptoms and higher levels of depressed mood in a group of predominantly gay men. Finally, Blaney and colleagues (submitted) found that social support and active coping (a combination of problem focused coping and emotion focused coping) also appeared to reduce the impact of stressful life events on the level of mood disturbances in asymptomatic HIV seropositive gay men.

Although the above mentioned studies suggest that levels of mood disturbances may be influenced by a combination of individual differences in a variety of psychosocial factors such as social support, coping style and health status, little is known about the relative importance of each of these variables and the way they interact in predicting mood disturbances. Moreover, a theoretical model combining the various determinants is still lacking. Blaney and colleagues (1991) propose a 'stress-moderator' model in HIV infection, in which the effects of stressful life events on the level of experienced distress is moderated by the type of coping styles employed and the adequacy of the social network.

In the present study we investigated whether the components of this model (stressful life events, coping, social support, and physical health) were related to the presence and occurrence of psychiatric symptoms during one year, in a group of asymptomatic and early symptomatic HIV-infected homosexual men. One important goal of this work is to identify the features of persons who are at increased vulnerability for developing psychiatric symptoms, and to help therapists and clinical researchers in designing mental health programs that will be effective for HIV-infected gay men.

Subjects and Methods

Subjects. This study took place from July 1991 through December 1993. During this period 57 HIV-infected homosexual men were recruited from two university hospitals, and four smaller hospitals in the Netherlands. Subjects were included in the present study if they fulfilled the following criteria: (1) being homosexual; (2) age 18-65 years; (3) no IV drug use; (4) no antiretroviral medication other than zidovudine (AZT); (5) no AIDS-defining symptoms or diagnoses (CDC, 1987); and (6) ability to read and understand the psychological self-report questionnaires.

After providing informed consent, data were collected on age, known duration of seropositive status, education, employment, having a partner, and previous psychiatric history.

Psychosocial Assessments.

Psychiatric symptoms were assessed with the *Present State Examination* (PSE) (Wing et al., 1974). The PSE is a structured psychiatric interview, and is accepted as a standard for diagnosis in psychiatric research (Wing et al., 1974). The PSE has been translated into Dutch and validated in a Dutch psychiatric population (Sloof et al., 1983). For the present study, the PSE was tailored for this specific population (Hemert et al., 1993). Accordingly, the items relating to psychosomatic symptoms were replaced by specific questions to enable diagnosis of somatization disorder according to DSM-III-R criteria (APA, 1987; Hemert et al., 1993). The MALT was used to assess alcohol abuse. The MALT is a self rating instrument and was especially designed for screening of alcohol abuse in medical populations (Feuerlein et al., 1979; Walburg & Van Limbeek, 1987). The PSE and MALT were obtained only at baseline.

At baseline, and during follow-up, the presence of non-psychotic psychiatric symptoms were detected with a Dutch translation of the 30-item *General Health Questionnaire*, a self-report screening instrument (GHQ-30) (Goldberg, 1972, 1978). The GHQ-30 does not include somatic symptoms, which supports the selection of this scale for the detection of psychiatric symptoms in patients with a somatic illness such as HIV infection (Huppert et al., 1989). The GHQ has been translated into Dutch by Koeter & Ormel (1991), and has been validated as a case finding instrument in patients of a Dutch general medical out-patient clinic by Hemert et al. (in press). Subjects endorsed the occurrence of a particular symptom during the last four weeks on a 4-point scale. As recommended by Goldberg (1972; 1978), answers were dichotomized into 'usual and less than usual', and 'more or much more than usual' (Cronbach's alpha=0.93). Validity of the GHQ-30 has been established by Tarnapolsky and colleagues (1978).

Stressful life events were measured with the 'HIV Life Events List', a Dutch translated adaptation of the Life Experiences Survey (Sarason et al., 1978). This instrument (49 items, NcGv, 1991) assesses life stressors with respect to 4 areas: (1) work (e.g., involuntary unemployment; (2) family and friends (e.g., illnesses or death of partner/friends; (3) personal circumstances (e.g., housing), and (4) financial issues. Subjects rated the experienced events on a 7-point Likert-type scale ranging from -3 (very negative) to +3 (very positive). A total score was calculated by adding the individual item-scores. At baseline, stressors that occurred during the prior year were rated, whereas 6-month periods were used at the follow-up measurements. Stressors related to somatic symptoms were not included in the analyses, to prevent overlap with the presence of clinical symptoms, one of the other predictors.

Coping styles were assessed with the HIV Coping List (HCL, 34 items) (Kroon et al., 1992; Gremmen et al., in preparation). The HCL measures HIV specific coping and was adapted from a Dutch translation of the COPE, originally developed by Carver et al. (1989). The HCL comprises the following subscales: seeking social support (7 items),

depressive reaction pattern (7 items), positive reinterpretation (7 items), active problem solving (8 items), and denial (5 items). Subjects rated every item on a 4-point Likert-type scale ranging form never to always. In order to reduce redundancy among the predictor variables, a second order factor analyses was carried out on these scales. Using varimax rotation, two factors were generated accounting for 70% of the variance in the scales. On factor 1 the positive reinterpretation scale loaded positively and the depression reaction pattern scale loaded negatively. This factor was called optimistic attitude (eigenvalue 2.0; 40% of variance explained). Factor 2 consisted of the scales seeking social support, active problem solving, and the inverse of the denial scale. This factor was called active confrontation (eigenvalue 1.5; 30% of variance explained).

Social support. Social support was assessed with a Dutch self-report questionnaire measuring the respondent's satisfaction with their social network (Sonderen, 1991), including satisfaction with everyday emotional support, emotional support in problematic situations, appreciation, instrumental support, and informational support (42 items, alpha = 0.96). The total score reflects the subject's satisfaction with his social network. The construct validity of this questionnaire has been established previously (Sonderen, 1991).

Procedures. Patients were invited for the study by their physicians. After obtaining informed consent, the psychiatric interview was conducted (C.L.M.), and the psychological questionnaires were completed by the subjects at either the out-patient clinic setting or, if a subject wanted this, at his home.

Assessment schedule. The GHQ was administered at baseline, and at 3-month intervals over a period of one year (5 times in total). Life events, coping styles and social support were rated three times, six months apart. At 6- and 12-month follow-up subjects were asked about life events that were experienced during the previous six months. Subjects were seen by their physician every six months for medical follow-up.

Design, data analyses and statistics. The design of the study was a prospective longitudinal study over a one-year period. The symptoms of the PSE were rated with the computer program CATEGO (Wing, 1974). The program generates an Index of Definition and a classification of psychiatric disorders according to ICD-9 (WHO, 1978). Psychiatric cases were defined as having an Index of Definition of 5 or more (PSE-ID5+; Wing, 1974). Patients with a score of 6 or more on the MALT (Walburg & Van Limbeek, 1987) were also defined as cases (alcohol abuses).

Bivariate Pearson correlations between the predictor variables and GHQ scores were calculated, followed by partial correlations controlling for GHQ scores, and the presence of HIV-related symptoms, both at baseline (symptoms were coded 0 if absent or lymphadenopathy only, or 1 in case of symptoms according to CDC-IVA, CDC-IVC2 or CDC-IVB (peripheral neuropathy); CDC, 1986). We decided to control for the presence of HIV-related symptoms at baseline, as HIV-related symptoms were shown previously to be an important predictor of distress (Hays et al., 1992; Kelly et al., 1993a). Finally, multivariate regression analyses with and without interaction terms were conducted to assess the unique part of the variance accounted for by each of the predictor variables.

Baseline GHQ scores and the presence of HIV-related symptoms at baseline were taken into account, by forcing these into the equation, followed by backwards stepwise regression for the other predictor variables.

Determinants of psychiatric distress, taking into account changes over time in the predictor variables. We calculated bivariate Pearson correlations between changes in the predictor variables and in the GHQ scores from baseline to 6-month and 12-month follow-up, respectively, followed by multiple regression analyses, taking into account baseline GHQ levels. Clinical progression was defined as progressing from an asymptomatic stage to a symptomatic stage (CDC, 1986) or AIDS (CDC, 1987) or from a symptomatic stage to AIDS. The α-value was set 0.05 (two-tailed). Alpha was set at 0.10 (two-tailed) when reporting trends.

Results

Demographic and biomedical characteristics. Mean age of the subjects was 38.2 (range 21-55) years. Mean time since diagnosis of HIV infection was 32 months (range 1-122 months). Thirty-one men (54%) were in an asymptomatic stage of infection (CDC, 1986). Thirty-three (58%) of the men were employed, and 22 (39%) were college educated. Thirty-one subjects (54%) had a regular sexual partner. Thirty-four men (60%) received professional psychological or psychiatric help during their lifetime. Four (7%) of these men had been admitted to a psychiatric hospital.

Drop-outs. Seven subjects dropped out from the study during the follow-up period: due to death (n=2) and having emotional difficulties with filling in the questionnaires (n=5). Because of vacations of the participants or illnesses of longer duration, a few measurements were not obtained during the follow-up period (see degrees of freedom in the tables).

Psychiatric diagnoses. Fifteen patients (26%) were defined as cases according to the PSE or the MALT. The ICD diagnoses are listed in Table 3.1. The most frequent diagnosis was depressive neurosis. Only one person was defined as a case according to the MALT, and this man did not have a PSE diagnosis. There were no patients with psychotic features, or somatization disorders.

Table 3.1. Frequencies of psychiatric diagnosis for PSE disorders and alcohol abuses in 57 HIV-infected homosexual men

ICD-diagnosis according to the PSE	
Depressive Neurosis	10 (18%)
Anxiety Neurosis	2 (4%)
Phobic Neurosis	2 (4%)
All PSE disorders	14 (26%)
Alcohol abuse according to the MALT	1 (2%)

At baseline, there were no differences between the groups with and without a psychiatric diagnosis with respect to age, known duration of HIV seropositive status, having a partner, previous psychiatric history, life events, coping, social support, and the presence of HIV-related symptoms (all p's>0.10). However, psychiatric cases were less well educated, were less employed (Chi-square, p's<0.02), had lower scores on the optimistic attitude factor (t-test, p<0.003), and higher GHQ scores as compared to non-cases. The mean GHQ scores were 15.4 (SD: 6.6) and 3.8 (SD: 4.4) for cases and non-cases, respectively (p<0.001). Table 3.2 presents the means and standard deviations of GHQ scores, and scores of negative life events, coping and social support. There were only minor changes in the means of these variables over time. As expected, stressful life events scores were lower during follow-up as compared to baseline due to the shorter period for which the occurrence of stressful life events was rated.

Table 3.2. Means and standard deviations (SD) of General Health Questionnaire (GHQ), life events, coping and social support

	Baseline	3 months	6 months	9 months	12 months
General Health Quest.	6.8 (7.2)	7.5 (7.5)	8.1 (8.8)	6.8 (6.9)	5.9 (7.0)
Life events	7.2 (12.0)		5.1 (13.1)		2.4 (9.0)
Active Confrontation	27.5 (7.8)		26.9 (7.6)		26.9 (6.0)
Optimistic Attitude	6.6 (6.6)		5.9 (7.4)		6.8 (6.1)
Social Support	107 (17)		106 (22)		111 (18)

Psychosocial Determinants of Psychiatric Symptoms as Measured by the GHQ

Relationships between GHQ scores and other variables. GHQ scores were significantly associated with more live events and having less optimistic attitude across all measurements (Table 3.3). Experiencing more life events was also associated with being less satisfied with the social network and having lower optimism. Within scales correlations across the three measurements were all significant (results not shown).

Table 3.3. Cross-sectional Pearson correlation coefficients between GHQ scores, stressful life events scores, coping scores and social support scores measured at baseline, 6-month and 12-month follow-up (mean scores)

	Life Events	Social Support	Active Confrontation	Optimistic Attitude
		Baseline		
General Health Quest.	0.31*	-0.22	0.10	-0.51**
Life Events		-0.36*	0.11	-0.35*
Social Support			0.05	0.15
Active Confrontation				0.00
		6-month	follow-up	
General Health Quest.	0.51**	-0.47**	-0.05	-0.63**
Life Events		-0.31*	-0.12	-0.48**
Social Support			0.10	0.32*
Active Confrontation				0.34*
		12-month	follow-up	
General Health Quest.	0.42**	-0.59**	0.11	-0.48**
Life Events		-0.44**	0.00	-0.27*f*
Social Support			-0.07	0.26*f*
Active Confrontation				-0.01

f:p<0.10 *:p<0.05 **:p<0.005

Longitudinal associations with GHQ scores. Partial correlations, controlling for baseline GHQ scores and the presence of HIV-related symptoms, showed that stressful life events were associated with 3- and 6-month follow-up GHQ scores. Optimistic attitude was no longer related to GHQ scores, in contrast to the zero-order correlations mentioned above. Social support was associated with 12-month follow-up GHQ scores only (Table 3.4).

Table 3.4. Partial correlations# between stressful life events, coping, and social support, measured at baseline, and GHQ scores at 3-, 6-, 9-, and 12-month follow-up, and the mean GHQ scores during one year.

	Partial correlations with GHQ scores at follow-up				
	3 months	6 months	9 months	12 months	mean GHQ
Life Events	0.38**	0.45**	0.24*f*	0.28*f*	0.41**
Optimistic Attitude	0.01	-0.08	-0.16	-0.26*f*	-0.16
Active Confrontation	0.02	-0.05	-0.03	0.13	0.02
Social Support	-0.21*f*	-0.15	-0.15	-0.40**	-0.21*f*

f:p<0.10 *:p<0.05 **:p<0.005

Adjusting for GHQ scores and the presence of HIV-related symptoms at baseline.

The relative importance of the predictor variables was determined using multiple regression. We found that baseline GHQ score was a significant predictor for GHQ scores at all follow-up time points. The presence of HIV-related symptoms at baseline was only associated with 3-months follow-up GHQ scores. Above and beyond baseline GHQ scores, life event scores predicted GHQ scores significantly at 3- and 6-months follow-up, as well as the overall means of the GHQ scores of each individual during one year. Social support was associated with GHQ scores only at 12-month follow-up (Table 3.5).

Table 3.5. Beta's[1] of multiple regression analyses for predicting GHQ scores during follow-up, adjusting for baseline GHQ scores and the presence of HIV-related symptoms at baseline.

GHQ scores at:	3 months	6 months	9 months	12 months	Mean GHQ&
Predictor variables assessed at baseline:					
GHQ	0.28*	0.41**	0.49**	0.37*	0.36**
HIV-Related Symptoms	0.27*	-0.19	-0.07	-0.11	-0.04
Life Events	0.39**	0.50**	0.27*f*	0.18	0.42**
Optimistic Attitude	-0.03	-0.11	-0.19	-0.25	-0.12
Active Confrontation	0.0	0.01	0.02	0.16	0.07
Social Support	-0.20*f*	0.02	-0.19	-0.44**	-0.12
Opt * Events[2]	-0.23*	-0.21*f*	-0.17	-0.02	-0.20*f*
Act * Events	0.19*f*	0.15	0.16	0.13	0.24*
SS * Events	-0.03	-0.08	-0.03	-0.04	-0.12
Adjusted R^2	0.48**	0.46**	0.19**	0.24**	0.25**
F Value	F(4,37)= 10.6**	F(3,36)= 12.0**	F(2,35)= 5.3**	F(3,36)= 5.1**	F(4,40)= 10.0**

f:p<0.10 *:p<0.05 **:p<0.005 &:Mean GHQ scores during one year for each individual

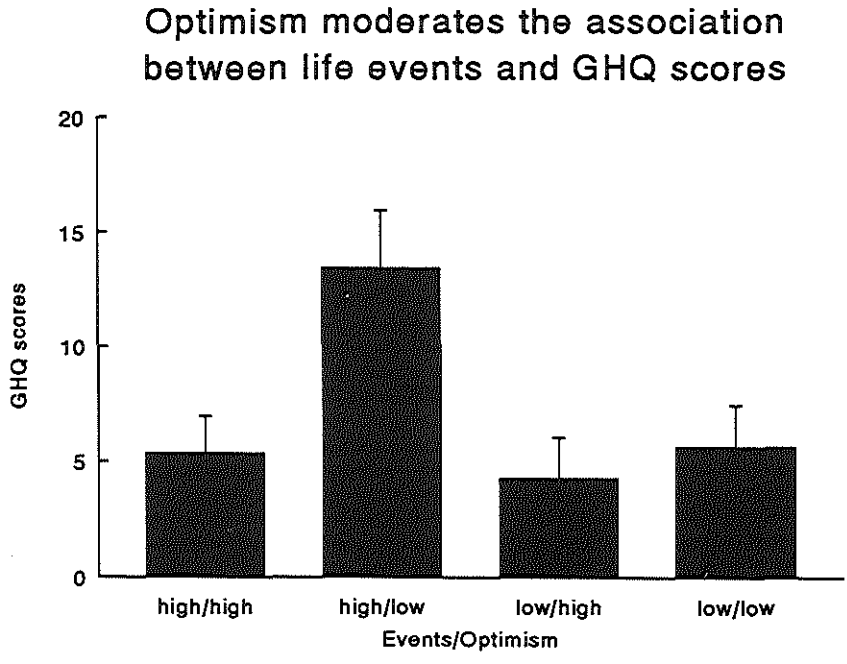
Testing of the interaction terms showed that the effect of life events on mean GHQ scores during follow-up was moderated by the coping styles active confrontation and optimistic

[1]Beta's: standardized regression coefficients

[2]Testing for interaction between variables

attitude for the mean GHQ score and the 3-month follow-up, respectively. Subjects reporting a more active confrontational coping style and less optimistic attitude showed higher GHQ levels in relation to the experience of stressful life events. The moderating effect of optimistic attitude on the association between GHQ scores and life events is illustrated in Figure 3.1. Social support satisfaction did not moderate the effect of stressful life events on the GHQ score.

Figure 3.1. The moderating effect of optimistic attitude on the association between GHQ scores and life events. The four groups are created on the basis of having a high or low stressful life event score in combination with a high or low level of optimism, respectively. 'High' or 'low' was defined by a median-split. Optimism and life events were assessed at baseline and GHQ scores at 3-month follow-up.



Determinants of Psychiatric Distress, Taking into Account Changes over Time in the Predictor Variables

During the 12-month follow-up, 13 subjects showed disease progression. Because there

were no differences in GHQ score changes between subjects who progressed from an asymptomatic stage to a symptomatic stage or AIDS (n=8) and subjects who progressed from a symptomatic stage to AIDS (n=5; $p<0.3$), we combined the subjects that showed clinical progression. Significant correlations were found between changes in GHQ scores and changes in optimistic attitude and social support over the first 6 months and changes in social support over the 12-month period, respectively (Table 3.6).

Table 3.6. Pearson correlation coefficients between changes in GHQ scores and changes in life events, active confrontation, optimistic attitude and social support over 6 and 12 months, respectively.

	Changes in GHQ scores	
Changes in:	0-6 months	0-12 months
Life Events[3]	-0.03	0.21
Optimistic Attitude	-0.55**	-0.26*f*
Active Confrontation	0.02	0.01
Social Support	-0.57**	-0.35*

f :$p<0.10$ *:$p<0.05$ **:$p<0.005$

Using multivariate analyses, while controlling for GHQ scores, and the presence of HIV-related symptoms at baseline, downward changes in social support and optimistic attitude were found to be related to increases in GHQ scores over the 6-month period, whereas changes in life events and social support were related to 0-12 month GHQ score changes (Table 3.7).

[3]When calculating the associations between changes in life events and in GHQ scores from baseline to 12-month follow-up, the 6-month and 12-month life events scores were added.

Table 3.7. Beta's of multiple regression analyses for predicting GHQ scores changes during 0-6 months and 0-12 months, respectively, using clinical progression, changes in stressful life events, coping, and social support over the concurrent time period as predictors, and controlling for baseline GHQ scores and the presence of HIV-related symptoms.

	Changes in GHQ scores	
	0-6 months	0-12 months
Baseline GHQ	-0.24*f*	-0.60**
HIV-Related Symptoms	-0.09	-0.01
Changes in:		
CDC Stage	-0.18	-0.23*f*
Life Events	0.10	0.35**
Optimistic Attitude	-0.39*	-0.18
Active Confrontation	0.13	-0.18
Social Support	-0.34*	-0.32*
Adjusted R^2	0.38**	0.48**
	F(4,36)=7.1**	F(4,36)=10.4**

f :p<0.10 *:p<0.05 **: p<0.005

Discussion

Psychiatric disorders. About a quarter of the subjects had a psychiatric diagnosis. The percentage of cases found in our study was higher than in another group of 91 medically ill patients (Chi-square, p<0.10). This comparison group consisted of patients with a variety of medical diagnoses (predominantly patients with infectious diseases, peptic disorders and hypertension), who also visited internal medicine out-patient clinics in the Netherlands. These patients were screened for psychiatric disorders also using the PSE and the MALT. In this group, 14 patients (15%) were defined as psychiatric cases (Hemert et al., 1993). However, it remains unclear whether this difference in prevalence of psychiatric

disorders is due to HIV-related stressors such as the prospect of a debilitating illness and early death, or to the kind of population studied.

We found that psychiatric cases were less employed and had lower levels of education. This was also found in a study with men with hemophilia, investigating psychosocial factors associated with increased vulnerability to psychiatric distress (Dew et al., 1990). The direction of causality of these associations, however, remains to be determined. It may be that HIV-infected subjects with lower levels of education are less likely to find employment, leading to higher distress levels. Future studies need to investigate these associations further, as it may have implications for social services offered to these people.

In line with another study of HIV-infected individuals with 77% (46/60) gay men (Seth et al., 1991), depressive illness was the most frequently encountered problem in our sample. In some patients, depression may be due to CNS pathology, which has consequences for the type of therapy offered (Perry, 1990b). For patients without overt signs of CNS pathology, depressive symptoms have been shown to be effectively treated by several interventions, including psychotherapy (Antoni et al., 1991b; Kelly et al., 1993b, Mulder et al., in press) and/or antidepressants (Rabkin et al., 1990). For patients with signs of CNS involvement AZT treatment (with antidepressants) may be indicated (Portegies et al., 1989).

Determinants of psychiatric symptoms as measured with the GHQ.

Life events experienced in the year prior to baseline were associated with GHQ scores during follow-up. However, the diminishing association over time may reflect an gradual extinction of the effect of prior stressful life events. In agreement with the findings obtained by Blaney and colleagues (submitted), changes in life events scores over a one-year period were related to changes in GHQ scores. This confirms the importance of looking at non-HIV-disease related stressors when investigating distress levels in HIV-infected individuals. Interestingly, clinical progression per se was not related to increases in GHQ scores. The distinction in asymptomatic, symptomatic and AIDS, however, may have been too general to detect a relationship with distress. The number of HIV-related physical symptoms is perhaps a more sensitive predictor of distress, as was shown in the studies of Hays and colleagues (1992) and Kelly and colleagues (1993a).

Coping. Having a less optimistic attitude was associated with higher GHQ scores during follow-up. However, when baseline GHQ scores and the presence of HIV-related symptoms were taken into account using partial correlations, optimistic attitude was no longer a significant predictor of GHQ scores. However, during follow-up, a trend towards an association became apparent, indicating that those subjects who showed an optimistic attitude may have less distress in the long run. This was in line with the finding that changes in optimistic attitude were associated with changes in GHQ scores. Taylor and her colleagues (1992) found that unrealistic optimistic beliefs about the likely future consequences of HIV were associated with better psychological adjustment and with more active coping, without compromising health behaviors or risk-related sexual behavior in gay men. Similar findings have been obtained in early stage breast cancer patients (Carver

et al., 1993). It was found that breast cancer patients who reported an overall optimism about life at the time of diagnosis showed less distress levels during a one year follow-up period. These results show that optimism may be an important determinant of distress levels in people who are confronted with a life-threatening disease.

Active confrontational coping, however, was not directly related to the GHQ scores. Interestingly, subjects reporting a more active confrontational coping style, and less optimistic attitude showed higher GHQ levels in relation to the experience of stressful life events. This result is in contrast with the results of Blaney and colleagues (submitted), who reported an attenuating effect of active coping on the effects of negative live events. However, their factor 'active coping' consisted of scales measuring a combination of problem focused coping (active coping, planning, suppression of competing activities, restraint coping and seeking instrumental support), and emotion focused coping (positive reinterpretation, seeking emotional social support, and acceptance). The active confrontational coping factor used in the present study, however, consisted of scales measuring active problem solving, seeking social support and the inverse of the denial scale. Thus, it may be that stressful life events are acknowledged more by subjects using an active confrontational coping style, resulting in higher distress levels. A longer follow-up is needed to determine whether or not these subjects benefit in the end from this coping strategy. On the other hand, subjects who have an optimistic attitude, seem to deal with stressful events in a less problematic way and report less psychiatric symptoms.

Social support. The association between social support measured at baseline and GHQ scores was significant for the 12-month follow-up only, possibly showing a long-term beneficial effect. Looking at change scores, we found that decreases in social support were significantly related to increases in GHQ scores. These findings confirm earlier findings of others who showed the importance of social support for the level of distress in HIV-infected individuals (Blaney et al., 1991; Hays et al., 1992; Kelly et al., 1993a). HIV-infected men frequently experience loss of lovers and friends due to AIDS-related deaths (Martin, 1988). Moreover, HIV-infected men often experience social isolation due to unsupportive family members and important others. Providing adequate support for HIV-infected individuals, for instance through group support programs, may therefore be effective in managing distress, as shown by several studies (Antoni et al., 1991b, Mulder et al., in press, Kelly et al., 1993b).

Unexpectedly, we found an association between social support and life events. It may be that there is a third factor involved that explains this association. This factor could be, for instance, the personality of the subject. In a recent study it was found that HIV positive individuals with a personality disorder suffered significantly more emotional distress, as well as social conflict with others than those without personality disorder. However, the occurrence of stressful life events was not reported in that study (Perkins et al., 1993).

Conclusion

In line with the 'stress-moderator' model as proposed by Blaney et al. the various components were significantly associated with the presence of psychiatric symptoms as measured by the GHQ. Our findings confirm the usefulness of the proposed model, in that the level of psychiatric symptoms in HIV-infected homosexual men is determined by the experience of environmental stressors, their coping styles and the support of the social network. Psychosocial interventions, focussed on improving the quality of a supportive social network and on developing adequate coping strategies may be effective in reducing the level of psychiatric symptoms and experienced distress.

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Chapter 4

Cognitive-Behavioral and Experiential Group Psychotherapy for Asymptomatic HIV-Infected Homosexual Men: a Comparative Study

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Abstract

The knowledge of being infected with the HIV brings about psychological distress and social problems including anxiety, depression and social isolation. Participating in psychosocial intervention programs can help to reduce these problems. To date, however, very little is known about the efficacy of different intervention strategies. We implemented a study with a randomized experimental design to investigate the effectiveness of a cognitive-behavioral group psychotherapy (CBT) and an experiential group psychotherapy (ET) program for 39 asymptomatic HIV-infected homosexual men. Both therapies consisted of 17 sessions over a 15-week period. The major finding of this study was that psychosocial intervention, independent of the therapeutic orientation, decreased distress significantly, as compared to a waiting-list control group (WCG). There were no significant changes in the intervention groups as compared to the WCG in coping styles, social support, and emotional expression. Finally, CBT and ET did not differ in their effects on psychological distress or on the other psychosocial variables measured in this study.

Introduction

Those living with HIV infection may suffer from the 'Sword of Damocles' syndrome, a phenomenology very commonly reported by infected individuals who have not (yet) developed overt signs of the infection. Not surprisingly, these people are known to experience sustained levels of psychological distress and are at increased risk for receiving a DSM-III-R Axis I diagnosis (Atkinson et al., 1988; Chuang et al., 1989). HIV-infected persons are also faced with chronic, uncontrollable and unpredictable stressors (e.g., disease occurrence, stigmatizing behaviors) (Redfield & Burke, 1988), and loss of social support due to, for instance, the death of friends who have developed AIDS (Martin, 1988; Fawzy et al., 1989).

Psychosocial interventions may offer help in managing the distress related to this life-threatening infection, as was shown in several studies with HIV-infected people at the early stages of the HIV spectrum (for a review of studies focusing on the entire range of the HIV spectrum, see Mulder & Antoni, 1992). Perry and colleagues, for instance, evaluated three types of psychoeducational interventions during the period of HIV antibody testing (Perry et al., 1991). Patients were randomly assigned to either standard pre- and post-test counseling (SC), a combination of SC and stress prevention training (SPT), or a combination of SC and an interactive video program (IAV). The SPT was based on cognitive-behavioral treatment for depression, stress, and anxiety, as originally developed by Beck and colleagues (1979). Finally, the IAV consisted of three weekly, 45-minute sessions also starting one week after notification. The SPT program was found to be more effective in decreasing emotional distress than the other two programs.

In another study, homosexual men who participated in a 10-week cognitive-

behavioral stress management (CBSM) group program showed significantly less psychological distress and social isolation after testing HIV seropositive than did a no-treatment control group (Antoni et al., 1991; Antoni et al., 1992). This CBSM intervention was comparable to some extent to the SPT program used in the study of Perry et al. study (1991) in that it used several techniques developed by Beck and colleagues (1979), but in addition used a group format and a 10-week program.

The above mentioned studies have been done with asymptomatic subjects around the time of serostatus notification. It is important, however, also to evaluate the effects of psychosocial interventions for those who have known their HIV positive serostatus for a substantial period of time. The number of such persons will increase over the next decade, as biomedical advances extend the asymptomatic period. Furthermore, these people may still experience increasing anticipatory anxiety and depression because of their rising risk over time of developing HIV-related symptoms. As has been shown in studies among patients dealing with other chronic medical conditions such as cancer, interventions such as the ones described herein, which seek to build social support, facilitate emotional expression and reinforce positive coping strategies, may optimize adjustment and decrease distress during this stressful period of life (Spiegel et al., 1981; Moorey et al., 1989; Trijsburg et al., 1992; Andersen, 1992).

At present, little is known about the relative efficacy of different psychosocial intervention programs for HIV-infected individuals. Only one study has compared the efficacy of different types of psychosocial intervention strategies within the same group of HIV-infected subjects around the time of serostatus notification (Perry et al., 1991). Insight into the relative effectiveness, and perhaps shared features (e.g., group support) of such interventions, might provide a basis for decision-making regarding the use of a certain intervention strategy. In the present study, we chose to compare cognitive-behavioral therapy (CBT) and experiential-oriented therapy (ET) for their effectiveness in reducing distress among asymptomatic HIV-infected homosexual men. The CBT program was chosen because positive effects of CBT were shown in prior work with HIV-infected individuals (Fawzy et al., 1989; Perry et al., 1991; Antoni et al., 1991). The ET program used in the present study is based on the humanistic and existential theory and therapeutic strategies (Gendlin, 1962; Perls, 1969; Yalom, 1980), and was chosen because the content of this program was thought to fit some of the pressing needs of HIV-infected men. While previous studies demonstrated the efficacy of ET in patients with cancer (Mahrer, 1980), and major depression (Elliot et al., 1990), little is known about the efficacy in HIV-infected individuals. We provided both interventions in a group format to be able to compare the results to some extent to the results of other group intervention studies (e.g., Antoni et al., 1991). Moreover, by conducting each intervention in groups of similar size and duration, we matched treatment conditions on social support availability -- a factor that may be the key component in determining the effectiveness of such interventions (Spiegel et al., 1981; Antoni et al., 1991). In the present study, a hypothesis as to which intervention might be superior was not put forward. There were arguments in favor of beneficial effects of both therapies, depending on the therapeutic school of thought consulted.

A final impetus for this study derived from the fact that despite a growing number of empirical reports concerning the use of similar interventions with U.S. samples of HIV-infected people, little is known about the cross-cultural generalizability of such findings. Our work focuses on a cohort of HIV-infected homosexual men living in the Netherlands. Specifically, we conducted a randomized experimental design to investigate the effectiveness of a cognitive-behavioral group psychotherapy vs. an experiential group psychotherapy program in this population.

Subjects and Methods

Subjects. Thirty-nine subjects were recruited from a group of 188 HIV-seropositive homosexual men (20.7%), who were participating in a longitudinal cohort study at the Municipal Health Service of Amsterdam, the Netherlands (Griensven et al., 1987), and who were eligible for the present study. Eligibility criteria were: (1) being in an asymptomatic stage of infection (CDC-stage II or III; CDC, 1986); (2) no reported use of antiretroviral medication; (3) no psychotherapy for HIV-related problems; (4) age between 18 and 65 years; (5) physically and mentally able to participate in a group intervention program, and to complete the psychosocial assessments; and (6) no history of diagnosed alcohol or drug dependency.

Subjects were informed about the intervention study by their study physicians. If an individual was willing to participate, the procedures were explained to him in detail by the first author (C.L.M.). Subjects were told that we were interested in how they were coping with their HIV seropositive status and whether they might benefit from psychosocial intervention. After providing informed consent, they were randomly assigned to one of the following conditions: (a) cognitive-behavioral group therapy (CBT), (b) experiential group therapy (ET), or (c) a waiting-list control group (WCG). After a waiting period of four months subjects in the WCG were also randomly assigned to either CBT (WCG-CBT) or ET (WCG-ET). In total, two CBT groups and two ET groups were conducted. Before the start of the intervention, one man dropped out of the study for practical reasons and no psychosocial data were obtained. Three men in the WCG dropped out before starting therapy. During therapy, three men dropped out from the CBT groups and five men from the ET groups. The data of these drop-outs were not included in the present analyses; although the deletion of drop-outs theoretically may bias the data, the results presented here do not change when drop-outs are included. Thus, the sample sizes of the four groups that were analyzed were: CBT (n=8), ET (n=7), WCG-CBT (n=6), and WCG-ET (n=6).

A screening battery including one item each on depression, anxiety and fear of getting AIDS was administered to the 188 men who were initially invited to participate in the study to allow us to characterize differences in participants vs. non-participants. Each item in this battery was keyed on a 9-point scale. The sum-score of these three items was used as an abbreviated screening measure of psychological distress (alpha = 0.81). In addition, coping behavior was assessed by 10 items selected from the HIV-related coping instrument that was administered *in toto* to subjects who ultimately consented to join the

study. These 10 items were selected from two scales, measuring active coping and seeking social support. There were no statistically significant (t-tests) differences in psychological distress, active coping, seeking social support scores, age and known duration of seropositive status between participants and non-participants (all p's>0.10). Thus, the reason for refusal to participate in the study could not be attributed to differences in the parameters measured.

Psychosocial interventions. The aims of both therapy programs were to reduce psychological distress, to improve coping with HIV infection, to increase social support, and to increase the expression of emotions. Both therapy conditions consisted of 15 sessions of 2.5 hours duration and an 8-hour day in the middle of the program. Before entering the study, it was explained to the participants that CBT is a structured form of therapy in which an HIV-related topic is introduced in each session, followed by exercises and group discussions. The ET was explained as being less structured with the main part of the sessions consisting of group discussions facilitated by the group leaders. Groups consisted of six to nine men and were led by two therapists. The therapists were selected on the basis of their qualifications and experience in the specific type of therapy, as well as in working with groups of HIV-infected homosexual men. All therapists were gay men. CBT and ET were administered according to treatment manuals developed before the commencement of the study (Stein et al., 1991; Siemens et al., 1991). These treatment manuals are available upon request. Three months after the completion of therapy, there was a single follow-up session. All therapy sessions were audiotaped in order to assess therapists' adherence to the manual guidelines. Patients in both conditions completed the same schedule of assessments.

Cognitive-behavioral therapy. For the CBT condition, subjects received training in cognitive restructuring (Beck et al., 1979), behavior change strategies, and assertiveness skills (Lange et al., 1976), and were provided with information on the psychological, social and physiological aspects of stress responses. The importance of the context for using various stress management techniques was explicated by teaching the differences between problem-focused active coping strategies used with controllable stressors (e.g., controlling excessive work load) vs. the preferential use of emotion-focused coping (e.g., ventilation) for uncontrollable stressors (e.g., being HIV-infected or experiencing bereavement) (Folkman et al., 1991).

In the beginning of the program, an individually-tailored behavioral action plan was developed together with each group member. Elements of a behavioral action plan included increasing physical exercise, or practising relaxation exercises on a daily basis. Throughout the program, the progression of these plans was discussed regularly. Each week, group members received homework related to the topics at hand. Topics included the importance of a healthy lifestyle, relaxation, enhancing of self esteem, expression of intense emotions, sexual relationships, the importance of a social network, and communication skills. Every session was structured in such a way that the homework was reviewed, then the topic of the week was introduced by one of the group leaders followed by group discussions and therapeutic interventions. Each session ended with a relaxation

exercise consisting of progressive muscle relaxation exercises according to the method of Bernstein and Borkovec (1973). Subjects were encouraged to practice these relaxation exercises at home on a daily basis.

Experiential therapy. This program was based on the principles of the humanistic-existential therapy tradition (Gendlin, 1962; Perls, 1969; Yalom, 1980). The aims of the program were to enhance the individual's ability to act and speak from a personal awareness of their inner experiential process, and to develop an authentic experience of their life situation, including both what is happening in the present, and how they chose to live their life in the future. The main function of the therapists was to help the men to become aware of incongruences between emotional, cognitive and behavioral schemata and to restore congruence. The therapists refrained from giving advice or making interpretations, and worked actively with the clients to help them develop insights and solutions to problems. Self-disclosure, sharing mutual fears and concerns, and addressing feelings about a shortened life perspective, illness and death were facilitated by the group leaders.

Members were invited to introduce which issues they wanted to address in detail during the intervention. We observed that "becoming more emotionally expressive" and "developing a new life perspective" were chosen by many of the men. Developing a greater awareness in the here and now and an enhanced understanding of the concept of contact and contact boundaries were central process issues in the program (Perls, 1969). Content themes discussed included mastering of crises by learning from previous experiences, the importance of a social network, sexuality, dealing with bereavement, dealing with a shortened life perspective, anxiety about future illness and death, and finding a purpose in life. In collaboration with each subject, specific tasks ('homework') were developed aimed at providing the men with means to practice what they learned during the therapy program concerning their responses and adaptation to HIV infection.

Waiting-list control group. Subjects in the waiting-list control group received either CBT or ET after a waiting period of four months. During this waiting period they did not receive any additional psychosocial or psychiatric treatment from sources outside the context of this study. This was assessed by a self-report questionnaire administered to the subjects of the WCG at the completion of the waiting period.

Assessment

Demographic characteristics. At the start of the study we obtained information on each subject's age, mean known duration of HIV seropositive status, education level, relationship status, and employment.

Psychosocial Assessment. The psychosocial measurements used to assess intervention effects were chosen to address the goals of the interventions and included measures of affective state, psychiatric symptoms, coping behavior, social support, and emotional expression.

Affective state. Affective state measures included a Dutch adaptation of the *Profile of Mood States* (POMS) (McNair et al., 1971; Wald & Mellenbergh, 1990), and the 21-item *Beck Depression Inventory* (BDI) (Beck et al., 1961; Bouman et al., 1985). The Dutch POMS is a shortened version of the original 65-item POMS and consists of 32 items. The Dutch POMS has five subscales (it does not include the confusion/bewilderment subscale of the original POMS; McNair et al., 1971): depression, anger, fatigue, vigor, and tension. The total mood disturbance (TMD) score can be computed by adding the negative scales and subtracting 'vigor' (alpha of 32-item POMS=.89). High POMS scores indicate high levels of mood disturbance for the seven days preceding assessment. The English version of the POMS (McNair et al., 1971) was demonstrated to be sensitive to change in psychosocial group intervention studies with cancer patients (Spiegel et al., 1981; Fawzy et al., 1990) and HIV-infected men (Fawzy et al., 1989; Antoni et al., 1991).

Psychiatric symptoms were screened with a Dutch version (Koeter & Ormel, 1991) of the 30-item *General Health Questionnaire* (GHQ), a widely used and well validated instrument (Goldberg, 1972; Goldberg & Miller, 1978). For each item, subjects rate the occurrence of a particular symptom during the last four weeks on a 4-point scale of 'less than usual', 'no more than usual', 'more than usual', and 'much more than usual' (alpha=.94). The GHQ score used in this study, as recommended by Goldberg and Miller (1978), treats only the last two response categories as indicating pathological deviation from the usual pattern.

Coping strategies. HIV-related coping responses were measured by a Dutch adaptation of part of the situational version of the COPE, originally developed by Carver and colleagues (1989). Eight of the 13 original COPE subscales were translated into Dutch and administered in a separate study to 117 HIV-infected men. Factor analyses revealed that there were three subscales (21 items total): seeking social support (7 items, alpha=.79); depressive reaction pattern (7 items, alpha=.80); and positive interpretation (7 items, alpha=.79) (Kroon et al., 1992). In another study, two extra subscales were added, measuring problem-focused behavior (8 items, alpha=.64) and denial (5 items, alpha=.72) (Gremmen et al., in preparation).

Social support. Social support was measured by a 49-item *Social Support Questionnaire* measuring both the availability of and satisfaction with the social network (Sonderen, 1991). The questionnaire has five subscales: everyday emotional support, emotional support in problem situations, appreciation, instrumental support, informational support. Two total scores can be computed yielding a total availability score (alpha=.94) and a total satisfaction score (alpha=.97). The construct validity of this questionnaire has been established previously (Sonderen, 1991).

Emotional expression. Emotional Expression was measured with a Dutch adaptation (Ploeg, submitted) of the *Emotional Expression Scale* of Watson & Greer (1983). The tendency for a patient to control (verbally or physically, 6 items, alpha=.86), to suppress (6 items, alpha=.79) or express (6 items, alpha=.86) anger, anxiety, and depression are measured on a 4-point Likert-type scale in each of the 18 items comprising this measure.

Subjective evaluation of therapy benefits. Participants were asked at the end of the

groups and at the 6-month follow-up: "To what degree did you benefit from the program". This question was answered on a 5-point scale ranging from 'not at all' to 'very much'.

Procedures. Psychological data were collected before the intervention (baseline), immediately after the intervention, three months after the intervention (for the POMS only), and six months after the intervention. The patients in the WCG filled out an extra battery of tests at the end of the waiting period. This measurement also functioned as a baseline measurement for the their subsequent intervention experiences.

Statistical analyses. Study data were analyzed using two distinct experimental designs. Firstly, we tested whether there were differences between the two intervention groups of the first wave combined (n=15: CBT (n=8) + ET (n=7)) vs. the WCG (n=18), to analyze intervention effects without differentiating for the type of therapy. To do this, an analysis of covariance (ANCOVA) model was used to test intervention effects on the POMS-TMD, GHQ, and BDI scores as our primary post-treatment outcome variables with baseline POMS-TMD, BDI and GHQ scores as covariates.

Exploratory analyses evaluated post-intervention differences in coping, social support and emotional expression scores as these are variables that have been proposed as important in the process of adjustment to HIV infection, and formed the theoretical model that guided the development of the interventions used for this study. We chose to combine the first two therapy groups, and not to analyze these groups individually, because the number of subjects would have been too small to draw meaningful conclusions.

In the second design, we investigated whether there were differences between the effects of the CBT condition (n=14), and the ET condition (n=13), after both WCG cohorts had completed their intervention arms and had been combined with their respective non-WCG counterparts. This was done by using a 2 (CBT + WCG-CBT vs. ET + WCG-ET) x 3 (time: pre, post and follow-up) design. Data were analyzed using repeated measures analysis of variance (RM-ANOVA), with POMS-TMD, GHQ and BDI scores as primary outcome variables. Exploratory analyses were carried out to analyze differences in the effects of each intervention on coping, social support and emotional expression, also using RM-ANOVA.

Results

Demographic characteristics. There were no differences on the demographic variables assessed between the intervention and waiting-list control groups, nor were there differences between the two specific therapy conditions (t-tests, Chi-Square tests, $p>.10$). The mean age of the entire sample was 40.4 (range 26-60) years, and mean time since diagnosis of HIV infection was 60 months (range 12-84 months). Twenty-seven subjects (69%) had a regular sexual partner of which 16 (60%) were HIV seropositive, five (19%) were seronegative, and six (22%) were of unknown serostatus. Thirty-three (83%) men were employed, and 22 (58%) were college educated.

Psychosocial measurements: baseline levels. The scores on the Beck Depression Inventory and the General Health Questionnaire were within symptomatic ranges of depression (≥16) or psychiatric symptoms (≥6) for 12% and 46% of our sample, respectively (Beck, 1979; Bouman et al., 1985; Goldberg, 1972; Goldberg & Miller, 1978)[4]. There were no significant differences between the first two intervention groups combined vs. the WCG, nor between the CBT and ET groups on any of the distress measurements or the other measurements used (p>.10).

Intervention effects on affective states (Figure 4.1). Post-intervention results were analyzed with ANCOVA's (results refer to main effects of group assignment), using the pre-intervention score as a covariate. The POMS-TMD, BDI and GHQ scores in the CBT and ET group of the first wave combined (n=15) decreased significantly as compared to the WCG (n=18, Figure 4.1.). Specifically, the intervention groups in the first wave showed lower POMS-TMD ($F(1,30)=4.9$, $p<0.04$), lower BDI scores ($F(1,30)=7.2$, $p<0.01$), and lower GHQ scores ($F(1,30)=5.7$, $p< 0.02$) as compared to the WCG group after the intervention and waiting-list period, respectively[5].

The within groups changes in POMS-TMD, BDI, and GHQ scores were analyzed using paired t-tests. After applying a Bonferroni correction factor and adjusting alpha to $p=0.005$, the ET and CBT group of the first wave combined showed a significant decrease in BDI scores, $t(14)=3.74$, $p<0.002$. However, there were no significant within group distress changes for the other measures (POMS-TMD and GHQ, all p's>0.10).

For analyses of the differences between the CBT and ET conditions, we combined the two CBT groups and the two ET groups from the two waves of this study. This was justified because the baseline levels of emotional distress (POMS-TMD, BDI, and GHQ) were the same for the subjects in the therapy groups of the first wave and the subjects in the second wave (t-tests, all p's > 0.25). Moreover, there were no wave x therapy condition interaction effects for the POMS-TMD-change scores, the BDI-change score, or the GHQ-change score as analyzed with ANOVA's (all p's > 0.5).

There were no statistically significant differences in affective state changes (POMS-TMD, BDI, GHQ) between the CBT and the ET conditions over the intervention period, nor across the 6-month follow-up (RM-ANOVA, all p values >0.3). Finally, there were no significant within-group distress changes in the two CBT groups or the two ET

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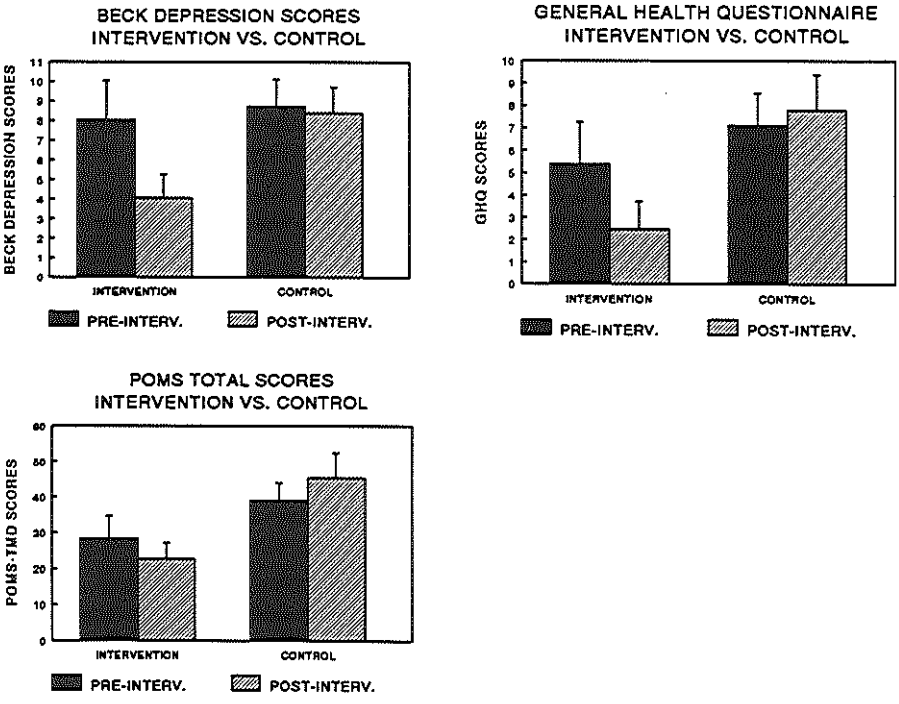
[4]GHQ scores, POMS-TMD scores, as well as BDI scores will be referred to through this report as psychological distress scores. Because of the high percentage (88%) of the present sample scoring in the low to mild range of the BDI at baseline, syndromal depression will not be distinguished separately.

[5]The pre-post intervention distress scores (POMS-TMD, BDI, GHQ) were also analyzed with a Repeated Measures (RM)-ANOVA. The RM-ANOVA's showed a trend for significant group by time interactions for the POMS-TMD and the BDI scores ($p<0.10$). In case of the GHQ the group by time interaction was not significant ($p< 0.16$). Although we do not know the precise reason for the disparities between the results obtained with ANCOVA and RM-ANOVA, it should be noted that the downward changes in the experimental group may have been suppressed by a floor effect in that their post-treatment values were approaching zero. In fact, of the fifteen subjects in this condition, nine subjects produced post-treatment values of 0 on the GHQ, whereas this was the case for two out of nineteen subjects in the control condition. Moreover, the control group showed no change in mean GHQ scores.

groups of the two waves combined using paired t-tests (all p's>0.10).

Figure 4.1. Effects of intervention vs. waiting-list control on psychological distress. The POMS-TMD, BDI and GHQ scores in the first CBT and ET groups combined (n=15) decreased significantly as compared to the WCG (n=19).



Intervention effects on coping, social support, and emotional expression. There were no significant differences between the combined CBT and ET group of the first wave and the WCG after the intervention and waiting-list period respectively on coping, social support and emotional expression (as analyzed with ANCOVA, main effects of group assignment).

Results for the coping analyses were as follows: seeking social support: $F(1,30)=2.4$, $p=0.13$; depressive reaction pattern: $F(1,30)=3.7$, $p<0.07$; positive interpretation: $F(1,30)=1.4$, $p<0.29$; problem focused coping: $F(1,30)=0.09$, $p<0.77$; and denial: $F(1,30)=0$, $p<0.99$. For social support, results showed no differences in availability of support: $F(1,30)=0.55$, $p<0.47$, or satisfaction with support: $F(1,30)=0.2$, $p<0.66$. Regarding emotional expression there were no significant differences in suppression of emotions, $F(1,30)=3.2$, $p<0.09$, expression of emotions, $F(1,30)=2.7$, $p<0.1$, or emotional control, $F(1,30)=0.02$, $p<0.9$.

There were also no significant group x time interaction effects between the CBT and ET therapy conditions over the intervention period nor over the 6-month follow-up, all p's > 0.2.

Evaluation of subjective therapy benefits by the participants. Participants evaluated the ET program as more beneficial shortly after the program as compared to the CBT (Mann-Whitney U - Wilcoxon Rank Sum W Test; $U=46.5$, $W=226$, $p<0.02$). However, at 6-month follow-up, there were no statistically significant differences in perceived benefits between groups.

Discussion

Treatment effects. We found that asymptomatic HIV-infected gay men randomized to either a CBT or an ET program showed significant post-intervention reductions in psychological distress when compared to a group of HIV-infected gay men awaiting assignment to one of these treatment conditions. No evidence was found that the magnitude of distress reduction varied as a function of the type of therapy used. These findings parallel the findings of Perry et al. (1991) and Antoni et al. (1991), who also found a significant beneficial effect of psychosocial intervention on psychological distress as compared to a control group. In the Perry et al. study, Beck Depression Inventory (BDI) scores decreased significantly more after a Stress Prevention Training (SPT) program (BDI-change $M=-5.3$, $SD=8.2$) than after a Standard Counseling (SC) program (BDI-change $M=-1.1$, $SD=7.8$) that was used as a control group. The BDI-change scores in this SPT program were comparable to the change scores obtained in the intervention conditions of the first wave in the present study ($M=-4.0$, $SD=4.1$), whereas the changes in the WCG condition ($M=-0.78$, $SD=6$) were comparable to the those in Perry et al.'s SC condition.

The intervention effects on distress scores were analyzed using ANCOVA. When a repeated measures ANOVA was used, only a trend for significance was found for changes in the BDI and POMS-TMD scores. One reason for these discrepancies may be the low power of the study. Another reason may be that the intervention had a modest impact on participant's distress. This may be partly due to the relatively low distress scores at baseline, causing a floor effect, as was described earlier for the GHQ.

Despite showing significant reductions in distress scores, the intervention groups

did not show significantly greater changes in coping, social support or emotional expression than the WCG condition. This may have been caused by the use of a limited cross-over design, causing a beneficial anticipation effect on some of these intermediary variables for the men in the WCG condition. Moreover, it may be that the coping questionnaire, and the social support questionnaire used in the present study -- in the absence of major systematic environmental stressors -- measure dispositional factors more than they do situational factors. This may have prevented us from detecting situational changes regarding these outcome measures. Previous studies with HIV-infected men were conducted in the context of the men's anticipation, immediate reaction, and adjustment to learning their HIV antibody status (e.g., Perry et al., 1991; Antoni et al., 1991; Antoni et al., 1992). In such a context, coping and social support measures may indeed reflect shifts in situational strategies and available resources.

Fawzy and colleagues (1990), using a 6-week group intervention in malignant melanoma patients, and Spiegel and colleagues (1981) using a one-year supportive group therapy program in metastatic breast cancer patients, found less maladaptive coping (e.g., excessive alcohol consumption) and lower mood disturbance scores in the intervention groups as compared to the no-treatment control groups. Although there is limited generalizability between studies using HIV-infected homosexual men and studies using cancer patients, some of the differences in effects between these studies and the present study may be attributable to variations in the contents and duration of the intervention programs used. It may be that in newly diagnosed patients, as in the studies of Antoni et al. (1991), Perry et al. (1991), and Fawzy et al. (1990), short-term interventions are more effective in reducing distress, and altering maladaptive situational coping strategies, whereas long-term interventions, such as Spiegel's (1981) are needed to change already established coping styles in patients who have lived with their diagnosis over a longer period of time. The latter may have been the case for the subjects in the present study.

One question concerns the generalizability of the findings in the present study to other HIV-infected populations, including HIV-infected homosexual men in more advanced stages of HIV infection, those who contracted HIV through injecting drugs, and HIV-infected women. It is plausible that these interventions can be of benefit to these other populations, although of course some topics in the intervention program need to be altered (e.g., discussion of topics related to sexual relationships). It is also possible that subjects in more advanced stages of the HIV infection benefit more from a therapy program in which the emphasis has shifted somewhat from issues surrounding coping skills and stress management strategies towards existential issues including dealing with illness, death and dying. In addition, other people dealing with the burden of chronic life-threatening illnesses such as cancer might also benefit from the use of these programs (for review, see Trijsburg et al., 1992; Andersen, 1992).

Changing high risk sexual behavior was not a primary aim of the intervention program used in the present study. The majority of the homosexual men in the natural history study from which the study participants were recruited had shown an increase in safe sex practices during the prior period from 1984-1988 (Coutinho et al., 1989). However, after the intervention programs were finished, a trend towards an increase in

unsafe sex practices in the participants of the cohort study was noticed (Wit et al., 1992). Therefore, although the 39 men in this study may not resemble the total cohort, in future psychosocial intervention programs it may be an important additional goal to discuss and evaluate strategies for modifying sexual behavior to facilitate primary and secondary prevention of HIV infection (Coates, 1990).

Comparisons of CBT and ET. There were no differences in distress reduction effects between the CBT and ET conditions used in this study. The lack of difference between both therapies may have been caused by similarities in non-specific group and therapist qualities (Stiles et al., 1986). Both therapy conditions shared common elements: group support, therapist support, opportunity for emotional expression, and homework. Another possible reason for the lack of differences between the treatment conditions may have been the fact that pre-intervention distress levels were fairly low, thus leaving little room for improvement (i.e., floor effect). Before entertaining these alternative hypotheses, it is important to consider the fact that the number of participants may have been too small to detect possible differences in any two therapy conditions in any context. However, even when we analyzed the data with the p-level set at 0.30, no differences between the two conditions emerged.

We did find a difference between the ET and CBT in subjects' perceived benefit after the intervention in favor of the ET condition. One of the explanations for this observed difference may be that the men in the ET condition had more opportunity for group interaction than the men in the CBT groups. As stated by the men in the ET groups, these moments of group interaction were considered to be very important. In contrast, the members of the CBT reported that there had been too few opportunities for group interaction, due to the highly structured character of the program. Another possible explanation is that the difference in perceived benefit is attributable to the differential drop-out rate between CBT (n=3) and ET (n=5) groups.

There were no significant decreases in psychological distress scores within either of the ET and CBT cohorts. This is an apparent inconsistency with the finding that the psychological distress scores decreased significantly in the ET and CBT group of the first wave combined, when compared to the waiting-list control group. However, it is difficult to interpret these within group distress changes in the absence of a control group for these analyses. It may be that the intervention 'buffered' an increase in distress that would have occurred in a control group. This possible distress buffering effect was also found in a previously mentioned study using a cognitive-behavioral stress management program in homosexual men at time of HIV serostatus notification (Antoni et al., 1991).

Treatment implications. There were no differences between CBT and ET in the present study. Future studies may show whether there are individual characteristics that can predict which persons benefit more from CBT vs. ET, including variables such as baseline levels of psychological distress, coping patterns and certain personality types. For instance, subjects with high baseline levels of psychological distress might benefit more from cognitive-behavioral intervention, because this type of intervention places more attention on stress management activities. On the other hand, patients who tend to be more

introspective, and who want to explore their feelings concerning their illness, could benefit more from experiential therapy.

In evaluating the effects of different intervention strategies it will be important to use measurement strategies that are in line with the type and goals of a specific intervention. For example, when measuring the effect of an experiential therapy program, an observer scale such as the Experiencing Scale (Klein et al., 1969) may be a more sensitive measure to detect intervention-related changes in subtle cognitive and emotional processes, as compared to self-report questionnaires tapping outward distress levels.

Finally, there are many other psychosocial intervention strategies than the ones evaluated in this study, including, for instance, coping effectiveness training (Folkman et al., 1991), spiritual counseling (Nelson et al., 1987) and individual counseling (Hoffman, 1991). However, no reports have been published, in which the efficacy of these strategies in HIV-infected individuals is evaluated.

Conclusion

We observed that psychosocial group intervention decreased psychological distress in a group of HIV-infected homosexual men who were asymptomatic. These findings may have consequences for psychosocial services offered to HIV-infected homosexual men, and possibly also for other HIV-infected individuals. Because no differences between CBT and ET were found in the present study, it may be worthwhile for clinicians to provide their patients with the opportunity to choose between both types of therapy.

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Part II

Biopsychosocial Determinants of Immunological Parameters and Disease Progression in HIV-Infected Homosexual Men

Chapter 5

Psychosocial Correlates of Immune Status and Disease Progression in HIV-Infected Homosexual Men

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Abstract

The course of HIV infection varies widely, and is determined by virological, and host-related factors. Above and beyond biomedical factors, psychosocial factors may have an effect on the course of infection. These effects can be mediated by the immune system of the host, which, based on psychoneuroimmunological findings, can be affected by psychosocial factors. We present a short review of putative psychoneuroimmunologic pathways and their possible implications for HIV-infected individuals. We next summarize the findings of psychoneuroimmunological work with HIV seropositives and discuss the methodological problems in studying the psychoneuroimmunologic aspects of HIV infection. Psychoneuroimmunologic research in HIV seropositives is a rapidly developing field, yielding contradictory findings so far, but which in the long run could provide important knowledge for psychosocial interventions targeted at optimizing psychosocial functioning, as well as preserving immune status and retarding disease progression.

Introduction

The course of HIV infection varies widely. Some patients deteriorate rapidly while others live for years, even after an AIDS-defining illness. It is hypothesized that one's adaptive coping or fighting spirit - i.e., a highly optimistic attitude accompanied by a search for greater information about HIV - might slow down progression of the disease, and conversely, that distress and despair might measurably accelerate progression (Antoni et al., 1990).

The aim of this chapter is to review recent findings regarding psychosocial correlates of immune status and disease progression in HIV seropositive homosexual men. Two types of research in this field may be distinguished: (1) correlational studies on the associations between psychosocial factors and immunological parameters, onset of AIDS-related symptoms or survival time, and (2) experimental studies about the immunological and clinical effects of behavioral interventions.

Firstly, current concepts of the pathogenesis of HIV infection will be discussed briefly, as this is important as an introduction for discussing psychoneuroimmunological (PNI) relationships in HIV infection. To provide a rationale for studying PNI relationships in HIV infection, a short overview is presented of results of PNI studies in non-HIV-infected individuals, followed by a discussion of possible biological mechanisms involved. Further we discuss psychosocial correlates of immune status and disease progression in HIV-infected homosexual men, results of behavioral intervention studies, and the methodological problems encountered in studying PNI aspects of HIV infection.

Pathogenesis of HIV Infection

Fifty (50%) to 75% of homosexual men develop AIDS 8-10 years after infection with

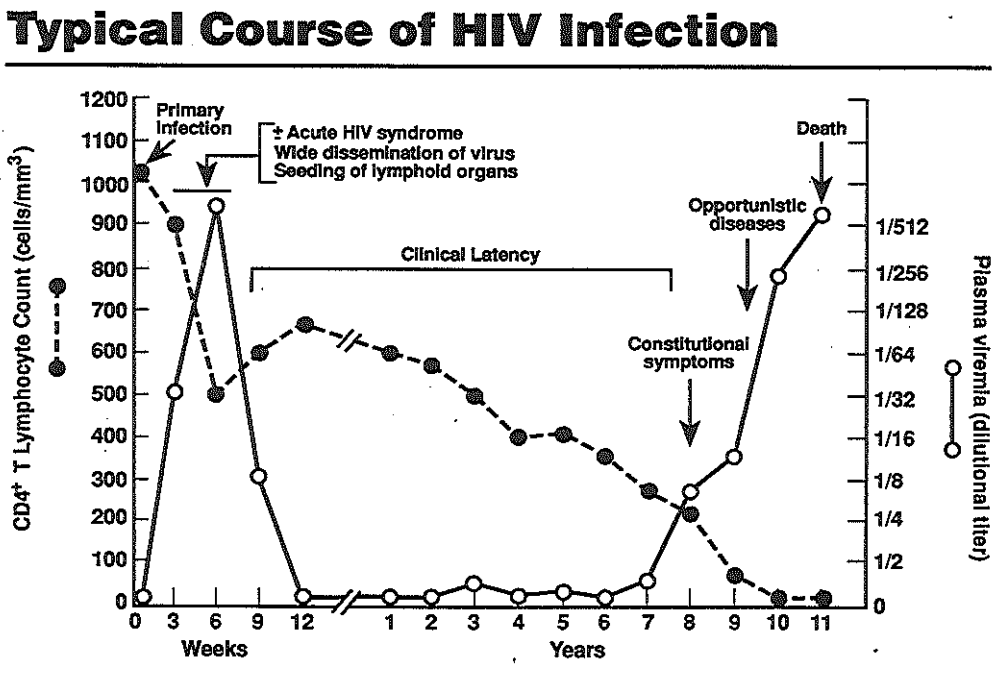
HIV. To date, mean survival time of patients with AIDS is approximately 1-2 years (Rothenberg et al., 1987; Moss & Bacchetti, 1989; Lemp et al., 1990; Peters et al., 1991). Five year survival rate was 3.4% and 15% in two samples of AIDS patients studied by Lemp et al. (1990) and Rothenberg et al. (1987), respectively.

Laboratory markers that have become most noticeably established as predictors of progression from asymptomatic HIV infection to AIDS are (1) declining numbers and percentages of peripheral T-helper (CD4) cells (Philips, 1992; Easterbrook et al., 1993; Keet et al., 1993); (2) appearance of persistent serum levels of HIV p24 core protein (Keet et al., 1993); (3) the appearance of syncytium-inducing fast replicating HIV variants (Koot et al., 1993), (4) decreasing T cell responses to anti-CD3 monoclonal antibody (mAb) (Schellekens et al., 1990), and (5) elevated serum beta$_2$-microglobulin concentrations, and to a somewhat lesser extent, elevated serum and urine neopterin concentrations (Lange et al., 1989; Fahey et al., 1990, Lifson et al., 1992), (6) cytotoxic T cell responses (Klein et al., 1993) and finally (7) the genetic makeup of the host (Kaslow et al., 1990). Although the course of infection is different among individuals, essentially no true cofactors for progression of HIV infection have been firmly established, including age, and other infectious diseases (Moss & Bacchetti, 1989).

The pathogenesis of HIV infection has been reviewed by Miedema et al. (1990), and Pantaleo et al. (1993). Briefly, the HIV virus infects cells that express the CD4 antigen on their membranes. These include immune cells such as CD4 cells and monocytes, and cells of the central nervous system such as dendritic cells, astrocytes and microglial cells. The CD4 cell plays a central role in the immune system by inducing the effector functions of many other cells such as cytotoxic T cells, macrophages and B cells (B cells produce antibodies). After HIV enters the CD4 cell, viral RNA becomes transcribed into proviral DNA by the enzyme reverse transcriptase. Once subsequent CD4 cell activation occurs, proviral DNA transcribes viral genomic RNA and messenger RNA. Active viral replication takes place and the CD4 cell is usually killed. In contrast to CD4 cells, monocytes are infected by the virus but not necessarily killed by it and serve as a reservoir for the virus (Gartner et al., 1986). Decreased CD4 cell numbers and functional defects of T cells are observed in asymptomatic seropositive individuals (Schellekens et al., 1990). Such changes characterize and explain the depression of cellular as well as humoral immune function that is evident at the earliest stages of the infection. Cellular and humoral deficits occur in many different immune functions such as T cell cytotoxicity, mitogen responsivity, NK cell activity, monocyte function and B cell functioning (Baron et al., 1985; Fauci, 1988). At the point of profound immunosuppression, opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP) infections, toxoplasmosis-related phenomena including meningoencephalitis, or candida esophagitis, and neoplasms such as Kaposi's sarcoma may be more likely to develop (Moss & Bacchetti, 1989). Miedema and colleagues (1990) proposed a dynamic model of AIDS pathogenesis in which (1) the immune system can initially suppress virulent HIV variants, maintaining an asymptomatic state; (2) persistent low grade HIV infection induces an increased CD4 cell turnover, resulting in a selective depletion of memory T cells in asymptomatic individuals; and (3) a critical loss of immune reactivity is eventually reached, at which point the emergence and

overt replication of highly virulent HIV variants induces progressive depletion of CD4 cells and development of disease. However, the immunopathogenic mechanisms of HIV infection are still a matter of debate. One other recently developed theory proposes that resistance to HIV infection and/or progression to AIDS is dependent on an imbalance between T-helper cells type-1 (Th-1) clones and T-helper cells type-2 (Th-2) clones. This theory is based on the findings that (1) progression to AIDS is characterized by loss of Interleukin-2 (IL-2) and gamma-interferon production by Th-1 clones concomitant with increases in IL-4 and IL-10 production by Th-2 clones; and (2) many seronegative, HIV-exposed individuals generate strong Th-1-type responses to HIV antigens (Clerici & Shearer, 1993). However, several additional mechanisms have been proposed including autoimmune mechanisms, the superantigen stimulation theory, and activation-induced cell death (Pantaleo et al., 1993). For a description of the typical course of HIV infection, see Figure 5.1.

Figure 5.1. Typical course of HIV infection (Pantaleo et al., 1993; Reprinted with permission of dr. A.S. Fauci)



Psychoneuroimmunologic Relationships in Non-HIV-Infected Individuals and their Implications for HIV Infection

During the last decade, the effects of many psychosocial factors on the immune system have been studied (Ader, 1991), including specific stressors such as bereavement (Irwin et al., 1987; Schleifer et al., 1983), the quality of social relationships (Kiecolt-Glaser et al., 1993), coping with stressors (Locke et al., 1984; Labaaij et al., 1993), and depression (Stein et al., 1991).

The relationships found, appear to generalize across a wide range of populations and may have implications for HIV-infected individuals. For instance, conjugal bereavement due to the loss of a spouse, has been found to be associated with a decrease in T cell proliferative responses and an impairment of NK cell activity (Bartrop et al., 1977; Schleifer et al., 1983; Irwin et al., 1987). For many HIV seropositive individuals and people with AIDS, bereavement is a frequent experience in their lives (Martin, 1988), and due to the fact that most of their losses involve AIDS-related deaths (their own likely demise), the bereavement process is likely to be qualitatively different than for those populations previously studied, e.g. husbands of breast cancer patients (Schleiffer et al., 1983). As shown by Goodkin and colleagues (1991), bereavement may affect immunological parameters in HIV-infected men. Specifically, they found negative associations between bereavement and T cell proliferative responses to PHA. However, the impact of bereavement on the clinical course of HIV infection remains as yet unstudied.

Symptoms of depression have been related to immunological alterations, especially with decreases in NK Cell Cytotoxicity (NKCC), in a number of studies (Stein et al., 1991). In one study, a decrease in the absolute number of T and B cells was found in peripheral blood in depressed psychiatric patients, as compared to non-depressed controls (Schleifer et al., 1984). As shown by Burack and colleagues (1993), depression was also associated with a steeper decline in CD4 cells in HIV-infected individuals over a 6-year period.

In PNI studies, psychosocial factors have not only been related to immunological cell counts or function, but also to cytokines, which is a group of substances regulating the function of immune cells. Cytokines are secreted by a variety of cells including lymphocytes (e.g. gamma-interferon, interleukin-2 [IL-2]) and monocytes (interleukin-1, [IL-1] (Balkwill & Burke, 1989). The production of gamma-interferon by concanavalin-A stimulated lymphocytes has been shown to be depressed under stressful situations (Glaser et al., 1987). It is of interest that gamma-interferon is one of the cytokines that stimulates the function of NK cells. NK cell function is important for viral surveillance in non HIV-infected individuals (Herberman & Ortaldo, 1981), and known to be depressed during the course of HIV infection (Hahn et al., 1989). However, the importance of NK cell function in controlling HIV infection is unknown at present. Given that CD4 cells and their related functional markers (e.g., lymphocyte proliferative responses to anti-CD3 mAb's; Schellekens et al., 1990) are known to be significantly impaired in early HIV infection, it is arguable that NK cells may help to compensate for this loss in Major Histocompatibility Complex restricted cell-mediated immunity. It is intriguing that NKCC decrements have

been associated with the bereavement process (Stein et al., 1991). This suggests that a highly prevalent stressor among HIV-infected men is associated with an immunologic function that may contribute to their continued ability to resist viral pathogens. Conversely, this would provide an impetus to study bereavement-associated coping as it relates to NKCC, cytokines related to this immune function, and subsequent disease progression in HIV-infected individuals.

Immunologic status is affected by other humoral substances in addition to cytokines. Those most commonly studied in the role of mediators of psychoimmunological correlations include stressor-associated neuroendocrines and neuropeptides.

Immunomodulating effects of hormones and neuropeptides. The immunomodulating effects of hormones and neuropeptides could be one of the possible mechanisms responsible for the association between psychosocial factors and immune function (Ader, 1991). The distribution and the function of T cell subclasses in the peripheral blood, for instance, is known to be influenced by various substances including cortisol (Parillo & Fauci, 1979), epinephrine (Crary et al., 1983) and opioids (Morley et al., 1989). Psychosocial stressors can result in elevated serum levels of these hormones and neuropeptides (Chodzko-Zajko & O'Connor, 1986), which in turn can alter the distribution and function of lymphocyte subsets in the peripheral blood (Khansari et al., 1990). Furthermore, psychosocial states such as depression are known to be associated with elevated serum levels of corticosteroids such as cortisol (Kronfol et al., 1986; Chodzko-Zajko & O'Connor, 1986). However, significant correlations of cortisol levels and immune functions are not always observed (Stein et al., 1991). HIV replication has been reported to be enhanced (in vitro) by the administration of hydrocortisone (Markham et al., 1986). Whether or not elevated serum levels of cortisol actually influence HIV replication (in vivo) remains to be determined. Beyond the potential for modulating viral replication, stress-associated hormones such as cortisol could transiently impair cell-mediated immune functioning and might thereby contribute to the clinical course of the HIV infection (Daruna and Morgan, 1990). Gorman et al. (1991) investigated the associations between glucocorticoid level and neuropsychiatric symptoms and numbers of CD4 and CD8 cells in 113 HIV seropositive homosexual men who did not meet CDC criteria for AIDS (CDC, 1987). They found small but significant positive correlations between 24-hour urinary free cortisol and medical status, level of depression, and level of anxiety. However, there were no correlations between cortisol level and the number of CD4 or CD8 cell counts or the CD4/CD8 ratio.

It may be extraordinarily difficult to isolate the contribution of changes in stressor-associated neuroendocrines to concurrent or subsequent immunologic changes. HIV infection itself is associated with adrenal dysfunction, though these findings have been restricted in large part to studies of persons with AIDS, for whom modulation in endocrine function may be secondary to opportunistic viral infections (e.g., cytomegalovirus) and neoplasias (e.g., Kaposi's sarcoma), and the treatments used to combat these problems (Aron, 1989).

It is plausible that asymptomatic HIV seropositive individuals may differ from the uninfected samples in the magnitude and temporality of their neuroendocrine responses to acute and chronic stressors (Antoni et al., 1991a).

Taken together, the neuroendocrine/neuropeptide studies provide important information on the biological mediators of psychoimmunological correlations. There is a need for more in-depth studies of how these possible mediators relate to both psychosocial stressors and immunologic measures in HIV-infected individuals before generalizations are made from earlier PNI studies.

Reactivation of latent viruses. Some investigators have demonstrated that psychosocial stressors are associated with reactivation of latent viruses including cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes simplex virus (HSV) I and II (Katcher et al., 1973; Glaser et al., 1985; Silver et al., 1985; Glaser et al., 1987; Kemeny, 1987; Kiecolt-Glaser et al., 1987a; Kiecolt-Glaser et al., 1987b; Kiecolt-Glaser et al., 1988a; Esterling et al., 1990; and Robertson et al., 1990). As these viruses are ubiquitous in the environment, they are also harbored by many HIV-seropositive people (Rahman et al., 1989). An elevation of antibody titers (reflecting poorer immunologic control) against the mentioned viruses in HIV seronegatives was demonstrated in relation to medical school exams (Glaser et al., 1987), the stress of taking care of patients with Alzheimer's disease (Kiecolt-Glaser et al., 1987a), marital separation (Kiecolt-Glaser et al., 1987b, 1988), loneliness (Glaser et al., 1985), and a downward change in antibody titers to EBV was observed after writing an essay about a previously undisclosed stressful event (Esterling et al., 1990). Also, depression and unhappy mood were associated with HSV-I reactivation (Katcher et al., 1973; Kemeny, 1987). In HIV seropositive men, Robertson et al. (1990) reported significant positive correlations between psychological distress and higher HSV-1 antibody titers, but not with antibody titers to CMV or EBV. Silver et al. (1985) showed the importance of coping strategies with respect to the recurrence rate of genital herpes infections in men and women. They found that the recurrence rate was higher in persons with a lower internal locus of control and in those who showed a tendency to use more emotion-focused wishful thinking. Although some investigators argue that reactivation of one or more of these ubiquitous viruses may result in HIV replication by activating HIV-infected CD4 cells directly, or by inducing the production of cytokines which cause HIV expression, this is an area of much controversy (Fauci, 1988).

In conclusion, there appears to be some convincing evidence for the effects of psychosocial factors on the activation of latent virus infections in non-HIV-infected samples. However, this is largely unknown in HIV-infected individuals, as are the possible consequences for the course of HIV infection.

Psychosocial Correlates of Immune Status and Disease Progression in HIV-Infected Homosexual Men

Description of studies. As shown above, psychosocial factors may have an impact on the

immune system. Because HIV-infected individuals are confronted with many psychosocial problems (chapter 2), it is plausible that some of the functions of the immune system are compromised because of the negative effect of these problems, above and beyond the deteriorating effect of HIV. Until now, several groups of investigators examined the relationships between one or more psychosocial variables (e.g., stressful life events, coping, and psychological distress), and immunological or clinical parameters in HIV-infected individuals. We chose to focus predominantly on CD4 counts as an immunologic marker in this summary, because they are currently one of the most important immunologic predictors of the course of HIV infection (Philips, 1992). It is arguable that it might also be important to review findings concerning T cell function and NK cell counts and function. However, given that very few studies related psychosocial variables to these immunological parameters in HIV-infected individuals, we chose to refer to these in the text. We selected studies that were published, or will be published in peer-reviewed journals, and not abstracts from conferences etc., as these abstracts provided little information on methods and statistics. Moreover, all of these studies took relevant biomedical markers for progression into account when analyzing the associations between psychosocial factors and progression of HIV infection. The findings presented here are summarized in Table 5.1.

Table 5.1. Associations between psychosocial parameters, CD4 cell counts, HIV-related symptoms, progression to AIDS and survival (see text).

Psychosocial Predictors		Dependent Variables: CD4	Symptoms	AIDS	Survival	Months of Follow-Up	N	Authors
1. Life events		0	0	nm	nm	36	1011	Kessler et al., '91
		0	0	nm	nm	6	124	Rabkin et al., '91
		nm	+	nm	nm	6	90	Goodkin et al., submitted
2. Coping	active	nm	-	nm	nm			
	fight*	0	-	nm	nm	12	100	Solano et al., '93
	denial	0	+	nm	nm			
		0	nm	+	nm	12	23	Ironson et al., '94
	realistic acceptance	nm	nm	nm	-	24	74	Reed et al., in press
	various	0	nm	nm	nm	48	286	Griensven et al., '90
3. Distress		0	0	nm	nm	6	124	Rabkin et al., '91
		0	0	nm	nm	12	221	Perry et al., '92
4. Depression		-	nm	0	0	66	277	Burack et al., '93
		0	nm	0	0	96	1809	Lyketsos et al., '93

+ = positive association; - = negative association; 0 = no association; nm = not mentioned; * = fighting spirit

Stressful life events. Goodkin et al. (submitted) found that the number of negatively rated events predicted the number of physical symptoms, including HIV-related symptoms, six months later, after controlling for baseline number of symptoms, and CD4 cell count. However, Kessler et al. (1991) did not find an association between stressful life events and progression of HIV infection in a 3-year prospective study. They found no associations between stressful life events (assessed as the numbers of lovers, friends, and acquaintances who were diagnosed with AIDS, or had died of AIDS, and by scores on a checklist of 24 more general serious stressor events), and a drop in % CD4 cell counts of at least 25% between pairs of examinations (six months apart) and onset of thrush and/or fever lasting for a minimum of 2 weeks over this period. However, Kessler et al. (1991) do acknowledge that the odds ratio (0.97-2.97, 95% confidence interval) between the stress of AIDS diagnoses and/or deaths in the men's social networks and prospective decrements in their CD4% values was "fairly large". The large odds ratio range obtained in this analysis highlights the need to examine individual differences in the men's *perceptions* of these stressors and in their resources for coping with them. It may be that this cohort represented subgroups of men who were using more or less adaptive vs. maladaptive cognitive, emotional, and behavioral coping strategies for dealing with these critical events. The findings of Kessler et al. were corroborated by Rabkin and colleagues (1991), who also did not find an association over a 6-month period between stressful life events, CD4 cell counts and HIV-related symptoms, respectively.

Coping. Coping characterized by a fighting spirit, and using less denial to cope with HIV infection were found to be associated with less progression from an asymptomatic stage of HIV infection to symptomatic disease (Solano et al., 1993). The use of denial to cope with an HIV+ diagnosis was also found to be predictive of greater immunological impairment at one year follow-up (CD4 counts and PHA responses) and greater likelihood of progression to symptoms and AIDS at two year follow-up in a study by Ironson and colleagues (1994). Goodkin and colleagues (1992) found in a cross-sectional study that active coping was positively associated with NKCC (N=62). This study also showed the importance of including in the analyses variables such as alcohol use, smoking and nutritional status. Only when these variables were included in the regression analysis was the association between active coping and NKCC significant. Goodkin and colleagues (submitted) also showed that active coping prospectively predicted number of physical symptoms over a 6-month period in a sample of 90 homosexual men in early stages of infection. Baseline CD4 cell counts, number of physical symptoms, CDC stage, and nutritional status were taken into account in the analyses.

One other study showed some unexpected results. While theoretical accounts of adaptation in the terminally ill suggest that "realistic acceptance" of one's disease is adaptive, Reed and colleagues (in press) noted that realistic acceptance as a coping strategy predicted *decreased* survival time among 74 gay men with clinical AIDS. This effect held after controlling for numerous confounders including CD4 cell counts, use of AZT, and alcohol and substance abuse. An inspection of the 4-item realistic acceptation factor reveals that the items center around the individual's focus upon accepting, preparing for and ruminating about the future course of their HIV infection. It may be that the

"realistic acceptance" factor partially reflected an attitude of fatalism. Interestingly, having a fatalistic attitude was associated with poorer disease outcome in breast cancer patients (Greer et al., 1979). It is difficult, however, to interpret the association between realistic acceptance and decreased survival, given that higher denial scores were associated with more disease progression as mentioned above (see also chapter 6).

Finally, Griensven et al. (1990) showed in a four year follow-up study with asymptomatic seropositive homosexual men, that several coping styles as measured with the 'Utrecht Coping List' (UCL) (Schreurs et al., 1984), were not associated with the presence of risk factors for progression to AIDS (presence of HIV antigen, absence of antibody to HIV core antigens or less than 500 CD4 cells/mm^3).

Psychological distress and depression. Perry et al. (1992) correlated psychosocial factors (e.g., anxiety, depression, social support, and hardiness) with total CD4 cells in a mixed sample of seropositive men and women from various risk groups. Significant correlations were found at study entry between total CD4 cells and both state anxiety and the experience of the death(s) of a spouse or a close sexual partner during the past two years. However, none of the 22 psychosocial factors measured at entry were predictive of total CD4 cells twelve months later after controlling for the initial immune measures by hierarchical regression. The researchers concluded that psychosocial factors do not directly affect total CD4 cells. Rabkin and colleagues (1991) also did not find significant correlations between a broad range of psychosocial measures (Hamilton Rating Scale for Depression, Hamilton Anxiety Scale, Brief Symptom Inventory, Beck Hopelessness Scale, Demoralization Scale, Social Conflict Scale, and Life Experiences Scale) both cross-sectionally and during a 6-month period, and CD4 and CD8 cell counts or illness stage.

Recently, two groups of investigators reported on the effect of depression on the decline of CD4 cells, onset of AIDS, and survival (Burack et al., 1993; Lyketsos et al, 1993). These two studies are especially interesting because they used very similar methods. Since 1985 both studies enrolled homosexual men with HIV infection but without AIDS, assessed them every 6 months with the same self report measure (the Center for Epidemiological Studies-Depression scale, CES-D), defined "depressed" as a CES-D score of 16 or higher, controlled for similar confounds (initial CD4 counts, and HIV-related physical symptoms), and used hierarchical multiple regression to evaluate the effect of depressed mood. However, both groups did not obtain the same results. Lyketsos and colleagues found no significant difference in the rate of decline between 365 depressed and 1353 nondepressed subjects, whereas Burack and colleagues found that the average rate of decline among 50 depressed subjects was (slightly) greater than the decline among 227 non-depressed subjects. Both studies did not find an association between depressed mood and the onset of AIDS or survival.

There are some explanations for these disparate findings. It could be that the finding of Burack et al. was chance (type I error). Their sample size was one-sixth as large as the sample studied by Lyketsos et al.. The effect reported by Burack et al. might also be due to less reliable measures of CD4 decline; Lyketsos et al. based their rate of decline on 'at least five' assessments, whereas Burack et al. based their rate of decline on 'at least three' assessments. Because of the fluctuations in CD4 cell counts within a given

subject, having more assessment points improves reliability. However, there may have been other reasons for not finding an effect on CD4 decline in the Lyketsos et al. study, and not finding an effect on progression to AIDS and survival in both studies. It could be that some of the subjects under investigation recover from their depressed mood over time, or did receive psychiatric treatment. Additionally, a larger proportion of the Burack et al. sample was asymptomatic at the point of depressed mood testing than was the case for the Lyketsos sample. It may be that as the disease progresses, psychosocial factors are less predictive of clinical changes -- due to increased viral load or simple floor effects -- than they are in the asymptomatic or early symptomatic stages of the infection.

Long-term survivors. To date, there is much interest in this particular group of HIV-infected individuals. Long-term surviving with AIDS (LSWA) was defined by the CDC (Hardy, 1991) as living at least three years after diagnosis of an AIDS defining opportunistic infection. Rabkin and colleagues (1993) described several psychosocial characteristics of 53 of these men living in New York city. These were predominantly well educated white men. Almost all of the men had experienced more than one episode of an HIV-related life-threatening illness, and many had been led to believe that they had only months to live. Nevertheless, low rates of current syndromal disorders were found. It was stated by Rabkin et al. that 'nearly all study participants displayed extraordinary resilience and shared the conviction that good times lay ahead and that life continued to be worthwhile'. The absence of a comparison group of those who did not live three years after diagnosis, however, precluded drawing conclusions of the psychosocial findings with respect to causation of the long-term survivorship.

Interpretation of the Contradictory Findings

In this small number of studies, which represent the very beginning of this research enterprise, a troubling inconsistency is apparent. Several issues may have contributed to this inconsistency:

(1) Most studies used different psychosocial assessments, various lengths of follow-up, included different biomedical markers for progression, and used different outcome measures, thereby making comparisons across studies difficult. However, also some more fundamental problems may have contributed to the contradictory results.

(2) Several studies used a mixed sample with respect to source of infection, disease stage, gender, ethnicity, and drug abuse of subjects at the point of study entry (Perry et al., 1992; Solano et al., 1993). The inclusion of women and IV drug abusers, along with homosexual men, introduces several extraneous factors, some potentially inflating and some masking the actual relationships between study variables. Such factors may influence both psychosocial predictors (e.g., gender-mediated willingness to report affective distress) and immunologic criterion measures (e.g., independent effects of IV drugs and related lifestyle behaviors).

(3) The studies of Rabkin et al. (1991), and Perry et al. (1992) focused more on measures assessing the prevalence of psychopathological behavior than on distress levels

in the normal range, despite the fact that the majority of HIV-infected individuals followed in longitudinal studies do not manifest a current psychiatric disorder (Mulder et al., in press). Measures such as the Profile of Mood States (McNair, 1971) or the General Health Questionnaire (Goldberg, 1972) may be more sensitive and appropriate when studying distress levels in this population.

(4) Most studies did not take into account changes in the psychosocial predictors over time. For instance, when assessing the effect of depression on the decline of CD4 cells it is important to obtain multiple assessments of depression.

(5) The studies listed above did not assess the impact of (risk) behaviors. These include alcohol use, cigarette smoking, sexual activity, physical exercise and sleep deprivation. All of these have been previously described for PNI research (Kiecolt-Glaser et al., 1988b), and shown to be of possible importance for PNI relationships in HIV infection (Goodkin et al., 1992).

(6) Most studies did not use a theoretical rationale interrelating the broad set of psychosocial and psychiatric measures assessed and driving the statistical hypotheses as, for instance, in the studies by Rabkin et al. (1991) and Perry et al. (1992). This prevents assessing, for instance, individual differences in transactional variables such as coping strategies used to deal with specific stressors. In other reports, a theoretically driven psychosocial model interrelating stressful life events, coping and social support has demonstrated associations with immunological parameters and health status in HIV-infected homosexual men (Goodkin et al., 1992; Solano et al., 1993; Ironson et al., 1994). Importantly, studies using coping assessments have yielded significant relationships with progression of HIV infection (Solano et al., 1993; Ironson et al., 1994), whereas studies that measure only stressful life events and/or distress tend to find non-significant relationships (Kessler et al., 1991; Lyketsos et al., 1993).

Goodkin et al. (1994) propose a model for investigating the associations between psychosocial factors and progression of HIV infection: the 'stress-coping-social support' model (see also chapter 9). In this model, direct effects as well as interaction effects of stressful life events, coping styles, and social support on HIV-disease progression are hypothesized. However, until now, the studies that employed this model were comprised of relatively small numbers of participants, and short follow-up periods. Thus, although using this model may be useful, too few data are available to determine the predictive value of this model for the course of HIV infection.

In future studies the above mentioned issues have to be taken into account. Moreover, some important issues have not been studied. These include the temporal courses of psychosocial factors, mediators and disease pathology, and the chronicity of stressors (Cohen et al., 1991). We know little about how long an exposure to stress is required to alter biologic or behavioral pathways. And how long must these pathways be altered before they may have an impact on disease progression? Thus, future studies should try to characterize more carefully stressor chronicity and timing to help clarify conditions under which stressors may influence disease progression.

Psychoimmunologic Interventions

If psychosocial stressors can influence the host's immunologic status, and possibly the course of HIV infection, it is crucial to investigate whether psychosocial interventions can influence immune function and clinical outcome. As demonstrated by Kiecolt-Glaser et al. (1985, 1986) and Fawzy et al. (1990a), psychological interventions may alter immunological parameters in healthy individuals and individuals with cancer, respectively. Kiecolt-Glaser et al. (1986) provided relaxation training to medical students before their examination period, and showed that CD4 cell counts and NKCC could be enhanced by reducing examination related stress through relaxation techniques. In a geriatric population, this same team found a significant decrease in antibody titers to HSV following relaxation training (Kiecolt-Glaser et al., 1985).

Few psychoimmunologic intervention studies have been done with physically ill patients. One very well designed study was done by Fawzy and colleagues (1990a, b). They reported on the efficacy of a 6-week psychiatric intervention program in patients with curatively treated malignant melanoma. Following the intervention, subjects reported a reduction in psychological distress and improvement in active coping strategies (Fawzy et al., 1990b), and also displayed a significant increase in percentages of large granular lymphocytes and NK cells. Moreover, after six years of follow-up, patients from the control group showed a significantly greater rate of death, and a trend for more recurrence of malignant melanoma (Fawzy et al., 1993). This is the first study demonstrating an effect of a behavioral intervention on immunological parameters as well as survival.

To date, three psychosocial intervention studies have been reported in which the immunological effects were investigated in HIV-infected individuals. Antoni et al. (1991b) tested the effects of a 10-week cognitive-behavioral stress management group program for gay men who were first learning about their HIV serostatus. They found that the group participants (n=9) showed significant increases in CD4 cell counts, whereas subjects randomized to a no-treatment control group showed decreases (n=9). Two year follow-up showed, however, that the intervention did not have an effect on disease progression (Ironson et al., 1994). Within the intervention group, better adherence to treatment was found to be predictive of less progression to AIDS (controlling for baseline CD4 counts). Although definitive conclusions can not be drawn from this study due to the very small number of participants, these data show the importance of looking at individual gains of such interventions, above and beyond treatment assignment alone.

Another study investigated the effect of an 8-week intervention consisting of thermal feedback, guided imagery, and hypnosis (Auerbach et al., 1992). The treatment group showed significant decreases in HIV-related physical symptoms (fever, fatigue, headache, nausea, etc.), and significant increases in hardiness (Kobasa et al., 1982) and vigor (McNair, 1971), as compared to a waiting-list control group. No effects on CD4 cell counts were observed. However, these results have to be interpreted cautiously because of the small number of participants (n=18).

Coates et al. (1989) also did not find significant immunological changes after an eight week stress reduction program with 64 seropositive gay men. Importantly, it has to

be noted that in this latter study no significant changes in psychological distress, social support or coping strategies were found either. Changes in distress are one of the central goals of these treatments and may be seen as a key element for establishing their clinical efficacy and possible impact on the immune system (Antoni et al., 1990).

The three intervention studies presented above, however, were of limited duration, used small numbers of participants (Antoni et al., 1991b; Auerbach et al., 1992), and used short follow-up periods. It is likely that interventions with follow-up periods of longer duration may be necessary in to investigate effects on disease progression and survival. In conducting these studies, there is a need to control for possible extraneous effects such as intercurrent pharmacologic regimens (e.g., zidovudine) that are now available for even asymptomatic HIV seropositive individuals, as well as the compliance with these treatments.

The optimal duration of such interventions, and which type of intervention strategy is most effective is unknown. Therefore, studies that compare outcomes of different treatments are needed (see also chapter 2).

These intervention studies should examine the role of individual characteristics (including coping styles, social network, and experience of stressful life events assessed at baseline, and gains from interventions, and adherence to treatment), as they relate to intervention-associated changes in psychological and physical health status.

Conclusion

Results of studies conducted until now do not provide conclusive evidence for the impact of psychosocial parameters on the course of HIV infection. However, there is a need to conduct studies from a more theoretical perspective, assessing individual differences in transactional variables including psychosocial stressors, coping and social support. In these studies biomedical markers for HIV-disease progression, and behavioral factors should be taken into account. When investigating the effects of behavioral intervention programs, individual characteristics should be taken into account as they relate to intervention associated changes. Long follow-up periods are needed to investigate effects on disease progression, using multiple immunological measurements to obtain reliable measures of immunological decline.

Until now, however, the studies show that clinicians should be cautious in suggesting that HIV-infected patients need to avoid stressful situations or reduce their depression because of its direct effects on their disease progression.

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Chapter 6

Distraction as a Predictor of the Biological Course of HIV Infection over a Seven Year Period in Homosexual Men

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Abstract

The associations between coping styles and progression of HIV infection over a seven year period were investigated in 181 homosexual men who were asymptomatic at the beginning of the study. Analyses were done using Cox proportional hazards model and multiple regression, and taking into account a number of biomedical and behavioral factors that have been previously associated with progression of HIV infection. We found that using a coping style characterized by distraction from problems in general was associated with a lower rate of decline in CD4 cells, less progression to immunologically defined AIDS (dropping under 200 CD4 cells/mm^3) and less appearance of syncytium-inducing HIV variants. Distraction coping was not related to the development of AIDS-defining clinical symptoms. Coping characterized by having a 'fighting spirit' was not related to the outcome measures. These results suggest that distraction coping might be associated with less progression of HIV infection. Future studies should aim at replicating these findings and studying the mechanisms underlying these possible associations.

Introduction

The diagnosis of HIV seropositivity is a major stressor. The majority of individuals dealing with this infection in the western world are homosexual men (HIV/AIDS surveillance, May, CDC, 1993). These men need to cope with a life-threatening infection, which puts a heavy burden on their coping capabilities. Some men cope by involving themselves in active confrontation with the situation, and by taking appropriate actions such as seeking out up-to-date medical information and social support. However, coping strategies of other subjects may become overwhelmed, sometimes resulting in the use of maladaptive coping styles. These include palliative behavioral responses such as using alcohol or other substances, or denying and avoiding the problems at hand (Namir et al., 1987; Hays et al., 1992; Leserman et al., 1992).

Coping generally refers to "the cognitive and behavioral efforts to manage specific external and/or internal demands appraised as taxing or exceeding the resources of the individual" (Folkman & Lazarus, 1988). Although it has been assumed that active strategies are more adaptive than passive strategies, only a few studies have delineated the mental and physical health correlates of a variety of coping styles in people with HIV infection (Namir et al., 1987; Griensven et al., 1990; Hays et al., 1992; Leserman et al., 1992, Goodkin et al., 1992; Ironson et al., 1994). Adaptive coping characterized by adopting a fighting spirit -- reframing stress to maximize personal growth, planning a course of action and seeking social support -- has been related to less dysphoria and better self esteem (Leserman et al., 1992). In contrast, having the opposite set of characteristics -- fatalism, denial, helpless coping, and withdrawal from others -- has been related to more depressed mood and distress (Namir et al., 1987; Hays et al., 1992; Leserman et al., 1992), and greater immunologic impairments (Goodkin et al., 1992). Until recently very little was known about the possible influence of these attitudes and coping strategies on the course

of HIV-related disease. In one study, Griensven et al. (1990) found no differences in coping styles, such as active problem solving, seeking social support and avoidance, between subjects (n=128) who remained at low risk for disease progression during a 4-year follow-up period as compared to subjects who developed risk factors for progression (n=158). Risk factors for progression were defined as the presence or absence of HIV antigeneamia, antibody to HIV core antigen, or a number of CD4 cells lower than 500/mm^3. On the other hand, Ironson and colleagues (1994) found that the use of denial to cope with a newly learned HIV seropositive diagnosis, and poorer adherence to behavioral intervention predicted lower CD4 cell counts one year later and a greater likelihood of progression to clinical AIDS two years later among 26 gay men. These findings held after controlling for men's CD4 counts at study entry. Another recently completed study appears at first glance to contradict the findings of Ironson et al.. Reed and colleagues (in press) noted that realistic acceptance as a coping strategy predicted *decreased* survival time among 74 gay men with clinical AIDS. Again, this effect held after controlling for numerous confounders including CD4 cell counts, use of AZT, and alcohol and substance abuse. An inspection of the 4-item realistic acceptation factor reveals that the items center around the individual's focus upon accepting, preparing for and ruminating about the future course of their HIV infection. These qualities appear to characterize a pattern that detracts from an individual's ability to distract himself from his infection. How can one reconcile these apparent disparities in the studies of Ironson et al. and Reed et al.? It is possible that some form of distraction may be the common feature that predicts slower disease progression in *each* of these studies. First, it is important to note that the pattern associated with lower likelihood of clinical progression in the Ironson et al. (1994) study included better adherence to behavior intervention strategies such as progressive muscle relaxation exercises -- a very reasonable strategy for periodically distracting oneself from the demands of daily life in general and this chronic disease in particular. Second, the men in Ironson's cohort who were not using denial as a coping strategy may have developed other less drastic means -- such as distraction by or involvement in other activities -- that may have enhanced their sense of well-being and helped them to remain connected to more meaningful and controllable aspects of their lives. However, because these alternatives were not assessed in that cohort, they must remain mere speculations at this point.

A final concern about these two studies is that they deal with two different ends of the HIV spectrum: Ironson and colleagues followed asymptomatic men who had just learned their serostatus, while Reed and colleagues followed men with AIDS. The individuals in these two cohorts are likely to differ significantly in the HIV-related demands that confront them on a daily basis. One strategy for addressing these disparities and measurement concerns, is to study gay men who are at an intermediate stage of the infection and who have known their serostatus for some time and to more directly assess the influence of distraction on clinical and subclinical laboratory markers of disease progression over an extended period of time.

In the present study we investigated the associations between coping strategies, including distraction strategies, and fighting spirit, and markers of progression of HIV

infection and the development of AIDS over a seven year period, while controlling for baseline immunological and virological parameters, as well as life style factors.

Subjects and Methods

Subjects. The subjects (n=181) were HIV-infected homosexual men who participated in a larger cohort study that started in 1984 at the Municipal Health Service of Amsterdam, the Netherlands (Griensven et al., 1987). Subjects were included in the present study if they were in an asymptomatic stage of infection or had lymphadenopathy only (Centers for Disease Control stage II/III; CDC, 1986), had knowledge of their HIV-positive serostatus for at least 6 months, had >200 CD4 cells/mm^3, and did not use antiretroviral medication or prophylactic treatments for opportunistic infections.

Predictor variables. Coping style was measured by means of a self-report questionnaire on one occasion at baseline (mid 1986) using the Utrecht Coping List (UCL). On five-point Likert scales ranging from "never" to "always" subjects were asked how they coped with problems *in general.* The UCL (47 items) is a well validated and frequently used coping questionnaire in the Netherlands (Schreurs et al., 1984; Sanderman et al., 1992). The UCL comprises 7 subscales: active problem solving, avoidance, depressive reaction pattern, seeking social support, palliative responses, expression of emotions, and comforting cognitions. In order to reduce redundancy among the predictor variables a factor analysis using varimax rotation was performed. Two factors emerged (Table 1) which together explained 27% of the variance (eigenvalue = 6.03 and 5.04, respectively). The first factor was named '*fighting spirit*' (22 items, Cronbach's alpha = 0.84, 15% of the variance explained), consisting of items such as optimism about the future, goal directed approaching the issue in order to solve it, and realizing that after rain comes sunshine. The second factor was called '*distraction*' (19 items, Cronbach's alpha = 0.82, 12% of the variance explained). This factor consisted of items such as trying to avoid difficult situations, focusing on other things to take your mind off things, and trying to withdraw from the situation. For the items comprising the fighting spirit and distraction scales, see Table 6.1. The factor scores of these two factors were used as predictors variables.

Table 6.1. Factor analysis of Utrecht Coping List

Fighting Spirit Factor	Factor Loading
1. Being optimistic about the future	0.64
2. Goal directed approaching the issue in order to solve it	0.59
3. Realizing that after rain comes sunshine	0.59
4. Trying to feel more comfortable in one way or another	0.57
5. Realizing that others will have their problems too	0.53
6. Intervening immediately in case of problems	0.53
7. Going through all points	0.52
8. Looking at the issue from all angles	0.52
9. Putting courage into oneself in times of troubles	0.51
10. Trying to find different solutions to solve a problem	0.50
11. Keeping cool in difficult situations	0.48
12. Appraising problems as a challenge	0.47
13. Feeling unable to do something	- 0.47
14. Looking for the humoristic site of a problem	0.44
15. Trying to relax	0.41
16. Sharing your worries with somebody	0.40
17. Discussing the problems with friends or relatives	0.40
18. Realizing that even worse things can happen	0.39
19. Expressing your emotions	0.34
20. Asking somebody for help	0.32
21. Trying to find comfort and understanding	0.26
22. Telling others that you are worried	0.16

Table 6.1. Factor analysis of Utrecht Coping List (Continued)

Distraction Factor	Factor Loading
1. Giving in order to avoid difficult situations	0.63
2. Focusing on other things to take your mind off things	0.63
3. Trying to withdraw from the situation	0.61
4. Reconciling one self to the facts	0.59
5. Letting things take their course	0.59
6. Trying to avoid difficult situations as much as possible	0.58
7. Turning one's mind to things not having to do with the problem	0.55
8. Escaping in fantasies	0.53
9. Taking a gloomy view of things	0.52
10. Worrying about the past	0.49
11. Dispelling one's worries by getting away from them	0.47
12. Searching for jolly company in case you feel worried or upset	0.45
13. Waiting for better days	0.45
14. Fully isolating yourself from others	0.40
15. Seeking distraction	0.39
16. Becoming completely occupied by the problems	0.39
17. Trying to decrease your distress by smoking, drinking etc.	0.33
18. Passively accepting the problems	0.31
19. Using tranquillizers in case you feel tense or nervous	0.29

Biomedical and behavioral predictor variables. The following variables were collected at baseline: sociodemographics (age, profession, income), known duration of HIV seropositive status, biomedical parameters including the absolute CD4 cell count at baseline (the mean of the three measurements surrounding the time men completed the coping questionnaire), the rate of decline of CD4 cells prior to coping assessment, the presence or absence of p24 antigen, number of physical complaints during the year preceding the coping measurement (mild complaints including night sweats, tiredness etc.) and Quetelet index (a measure of overweight), and behavioral factors including the amount of alcohol use, the number of cigarettes, drug use, having unprotected anal intercourse, and intercourse with a person with AIDS during the previous year. Although the importance of these parameters as markers for progression of HIV infection is not completely elucidated, we selected these parameters since they have been associated with progression of HIV infection in several studies (Fahey et al., 1990; Van Griensven et al., 1990; Philips et al., 1991; Nieman et al., 1993; Haverkos et al., 1985). Subjects were followed-up until September 1993, or until they developed AIDS (CDC, 1987). Excluding development of AIDS, forty subjects (40/100=40%) dropped out from the study during follow-up for various reasons including moving to another area, or no longer willing to

participate in the natural history study. All available data of these subjects were included in the analyses.

Dependent variables. Dependent variables were markers of progression of HIV infection, including the rate of decline of CD4 counts (CD4-slope), and the shift from non-syncytium-inducing (NSI) variants of HIV to syncytium-inducing (SI) variants. CD4-slope has been shown to be an important prognostic marker for the development of AIDS (Schellekens et al., 1992). NSI variants can be detected throughout HIV infection, whereas SI variants generally only develop in the course of HIV infection and tend to precede the development of AIDS in 50-70% of patients (Koot et al., 1993). The development of AIDS was defined as dropping under the level of 200 CD4 cells/mm^3 (immunologically defined AIDS; CDC, 1993), and the onset of AIDS-defining clinical symptoms (CDC, 1987), respectively. The date of a physician's diagnosis was considered the time of clinical AIDS onset.

Laboratory methods used have been described previously (Gruters et al., 1991; Koot et al., 1993). In order to document HIV-related changes over time, subjects were seen every three months for an interview regarding medical status, a physical examination, and the collection of blood samples for immunological and virological testing. Determining of SI variants began in July 1990.

Statistics. For determination of the change in absolute CD4 cell counts, subjects were followed until September 1993. The average rate of change in CD4 cells per year was operationalized by calculating the slopes of the least-squares regression lines fit through each subject's immunological data collected at 3-month intervals. Only subjects who had 3 or more data points available were included in this analysis, as meaningful rates of change can not be calculated in subjects who have only 2 data points.

Time to less than 200 CD4 cells/mm^3 was defined as having less than this number of cells at two subsequent points in time. Developing an SI variant was defined as changing from a NSI variant to an SI variant during the study period. Subjects who had an SI variant at the first assessment (n=4) were not included in the analysis. Thirty-two men were not assessed for the presence of NSI/SI variants until the end of the study (final n=145 for this analysis).

The associations between coping, biomedical and behavioral parameters and CD4-slope were calculated using backward stepwise multiple regression analysis. Cox proportional hazards regression analyses were performed, using the stepwise backward method to analyze the associations between the coping factors, the biomedical and behavioral parameters and the dependent variables[6]. The significance level of a variable to be removed using the maximum partial likelihood ratio test was 10%.

In order to reduce type I error, only those predictor variables that reached statistical significance ($p<0.05$) in predicting at least two of the four dependent variables were

[6]The proportionality assumption of the Cox proportional hazard regression method was found not to be violated for all dependent variables after including a time dependent covariate in the model.

included in this report.

Results

Demographical, biomedical and behavioral characteristics at baseline. The mean age of the subjects was 36.8 at baseline (Table 2), and the men were predominantly well-educated middle class Caucasian men, mainly living in Amsterdam. The mean known duration of seropositivity was 18 months. The men had relatively well preserved numbers of CD4 cells (mean: 630 cells/mm^3). The majority used one or more form of drugs and approximately threequarters reported to have had unprotected anogenital intercourse in the previous year.

Table 6.2. Demographical, medical, and behavioral characteristics at baseline

Age	36.8 (range 23-54, SD=6.4)
Profession	Blue collar 5.8% Employees 47.7% White collar 46.5%
Mean known duration of seropositivity (months)	18 (range 6-26, SD=3.3)
Net monthly income (Dutch guilders (Hfl); Hfl=0.5 US dollar)	< 1100 17.8% 1100 - 2500 57.2% > 2500 25.0%
Mean CD4-slope (cells/mm^3/year) prior to baseline [a]	39 (SD=336) [4.6]
Mean CD4 cells/mm^3 [b]	630 (SD=208)
p24 antigen positive	20.0% (36/180)
Smoking, cigarettes per day	0 36.3% 1-10 19% >10 44.7%
Use of soft drugs [c]	78.2% (140/179)
Use of hard drugs [d]	24.0% (43/179)
Alcohol intake [e]	2.1 (range 0-15, SD=2.1)
Mean number of physical complaints	2.9 (SD=2.1)
Mean Quetelet index (in kg/(10·m^2))	221 (SD=21)
Having had sex with people with clinical AIDS [f]	28.7% (35/122)
Having had unprotected anogenital intercourse [f]	4.3% (133/179)

[a]: Mean number of measurements of CD4 counts ; [b]: Mean CD4 cell counts across three occasions immediately before, at, and after baseline; [c]: % that used marijuana, hashish or poppers in the year preceding baseline; [d]: % that used cocaine, LSD or amphetamines in the year preceding baseline; [e]: Mean number of glasses of alcohol per day in the year preceding baseline; [f]: In the year preceding baseline

Associations among the dependent variables. Subjects who dropped under the level of 200 CD4 cells/mm^3 had a steeper CD4-slope (Mann-Whitney U test, $p<0.001$), more frequently developed an SI variant, and more frequently developed clinical AIDS (Chi-square tests, p's<0.001). A steeper CD4-slope was also found for subjects who developed an SI variant and subjects who developed clinical AIDS (Mann-Whitney U test, $p<0.001$). There was a trend for subjects who developed an SI variant to develop AIDS (Chi-square test, p's<0.054). These results show that some of the outcome parameters are related (as expected), but not identical, thereby justifying separate analyses for the influence of coping on each.

Predicting the course of HIV infection.

CD4-slope. The mean CD4-slope was -103 CD4 cells/mm^3/year (SD=135). This calculation was based on a mean of 21.5 CD4 measurements per individual. A faster rate of decline was associated with less distraction, lower Quetelet index, the presence of p24 antigen, and older age (Table 3).

The development of SI variants. During follow-up NSI variants converted into SI variants in 34% (50/145) of the men. The development of SI variants was associated with less distraction, and there were trends for having a lower Quetelet index and being p24 antigen positive. The association between distraction and the development of SI variants is illustrated in Figure 6.1.

Development of immunologically defined AIDS. Seventy-one men (71/181=39%) dropped under the level of 200 CD4 cells/mm^3 for at least two time points in this study. This event was associated with less distraction, being p24 antigen positive at baseline, and having less CD4 cells at baseline. The association between distraction and CD4-drop below 200 is illustrated in Figure 6.2.

Development of clinically defined AIDS. Eighty-one (81/181=45%) subjects developed AIDS-defining clinical events during the study-period. The majority of the AIDS diagnoses included *Pneumocystis Carinii* Pneumoniae (26%), Kaposi's sarcoma (21%), candidiasis of the oesophagus (14%), and lymphoma (8%). Mean time to development of AIDS was 3.6 years (SD=1.8). The development of AIDS was associated with being p24 antigen positive, and having lower CD4 counts at baseline, being older, and having a lower Quetelet index. Distraction was not associated with progression to AIDS ($p<0.14$).

Fighting spirit was not significantly associated with more than one outcome measure. Thus the results indicate that distraction coping predicts lower rate of CD4 decline, less appearance of SI variants, and less development of immunologically defined AIDS, after adjusting for biomedical and life style factors.

Table 6.3. Multiple regression analysis and Cox' proportional hazards model using backward stepwise procedures for prediction of CD4-slope, CD4 ≤ 200/mm³, SI-variant and the development of AIDS [7,8]

	Outcome Variables			
Predictor Variables	CD4-slope (N=160 β	CD4 ≤ 200/mm³ (N=168) *PH [95%CI]*	SI Variant (N=145) *PH [95% CI]*	Clinical AIDS (N=168) *PH [95% CI]*
Distraction (standard-scores)	0.15*	0.66**[0.50-0.89]	0.72* [0.53-0.99]	-
Age (per 10 years)	– 0.17*	-	-	1.50* [1.03-2.16]
CD4-counts (baseline) (per 100/mm³)	-	0.59**[0.50-0.70]	-	0.80**[0.70-0.91]
p24-antigen (0=neg.; 1=pos.)	– 0.23**	1.86* [1.05-0.27]	2.06*f* [0.97-4.35]	3.02**[1.84-4.95]
Quetelet-index (in kg/(10·m²))	0.22**	-	0.23*f* [0.05-1.03]	0.22* [0.06-0.83]
Adj R^2 = 0.12, $F(5,154)$= 5.4**				
Global Chi-square:		50.7** (df=6)	16.3** (df=5)	41.8** (df=6)

f:p<0.10 *:p<0.05 **:p<0.01; Adj R^2: Adjusted R^2; *PH*: Proportional Hazard; CI: Confidence Interval

[7]Due to missing data for some predictor or dependent variables, the number of subjects in each analysis was not exactly 181.

[8]Only those predictor variables that reached statistical significance (p<0.05) in predicting at least two of the four dependent variables were included in the Table; the original degrees of freedom are given.

Figure 6.1. Survival curve of time between baseline (1986) and development of SI variants in the Amsterdam Cohort Study

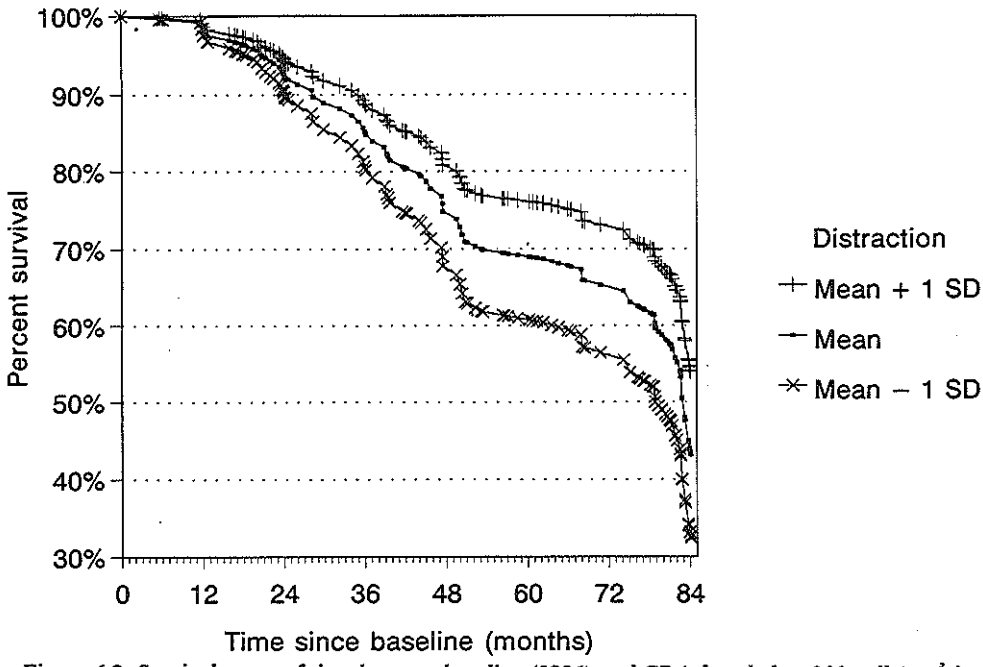
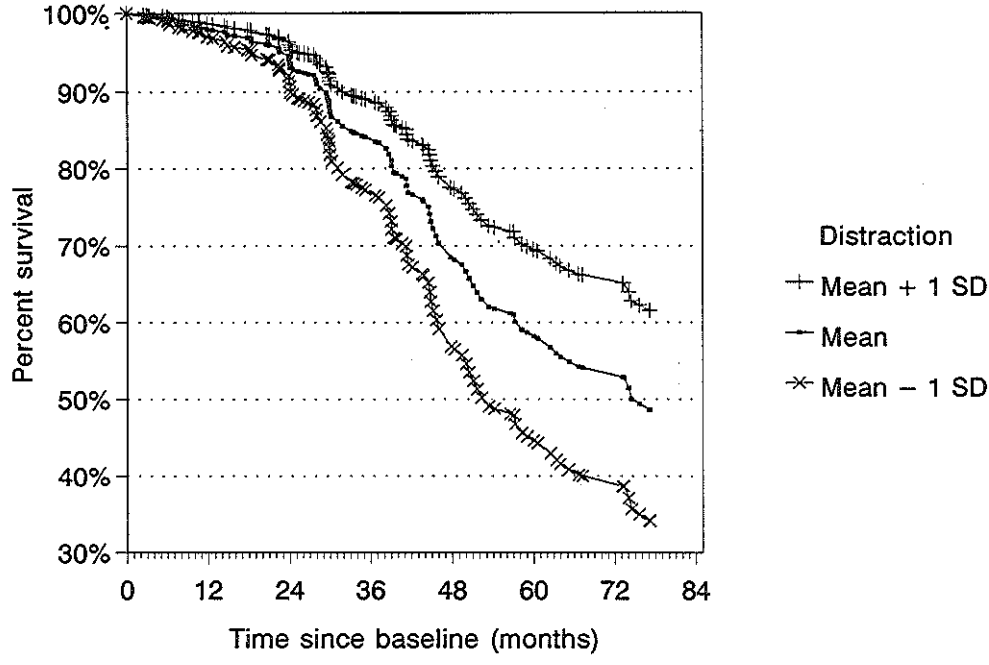


Figure 6.2. Survival curve of time between baseline (1986) and CD4-drop below 200 cells/mm³ in the Amsterdam Cohort Study



Discussion

Biomedical predictors of disease progression. This study confirmed earlier findings of other studies showing that p24 antigenaemia, having less CD4 counts at baseline, and older age confer a greater risk for development of AIDS-defining clinical events (Wolf et al., 1989; Blaxhult et al., 1990; Keet et al., 1993).

Having a lower body-weight proportionate to one's length (Quetelet index) was related to a faster decline in CD4 cells, an earlier development of an SI variant, and development of clinical AIDS. The lower Quetelet may be an indicator of a more advanced disease. However, Quetelet index was not significantly related to any of the biomedical parameters assessed at baseline.

Coping and disease progression. We found that more distraction from problems in general was associated with less decline in CD4 cells, less appearance of SI variants, and less progression to immunologically-defined AIDS (having fewer than 200 CD4 cells/mm^3). The relationships with distraction coping were significant even after taking into account age and a number of biomedical and behavioral factors (e.g., sexual behavior, smoking) that have been previously associated with progression of HIV infection. However, although distraction coping was related to the above mentioned markers for progression of HIV infection, this coping strategy was not significantly related to progression to AIDS-defining clinical events.

At first glance the negative association between distraction and progression of HIV infection is counter-intuitive because it has been assumed that distraction from problems is not an adaptive coping strategy (Schreurs et al., 1984). However, several explanations can be put forward to interpret these associations. Firstly, it may be that subjects who report less distraction as a coping strategy do so because they want to undertake every action possible to slow down progression of HIV infection. These subjects may experience more physical symptoms, and have fewer CD4 cells/mm^3 at the time of filling out the coping questionnaire. These "signs of progression" could be what is motivating them to change their coping strategies in a more active direction. However, there were no significant cross-sectional correlations between distraction coping and biomedical parameters at baseline.

Secondly, it may be that using distraction as a coping style is an adaptive coping style in the case of HIV infection. This leads to the question of how to interpret the distraction factor. It may be that trying to avoid difficult situations, trying to withdraw from them, focusing on other things, and reconciling oneself to the facts are appropriate ways to handle this unescapable life-threatening infection. In fact, in the case of HIV infection, this strategy may provide the necessary optimism to "go on". The ability to distract from problems could help these men in maintaining optimism, even if it is unrealistic, and to preserve a sense of meaning and some aspects of personal control over their lives (Taylor et al., 1992). Remarkably, three items included in the distraction factor (Table 1, items 9, 10 and 16) refer to the tendency to worry about problems. At first glance these items do not fit in with the rest of the items. However, these items may indicate that subjects who try to distract themselves from their problems do so because

they have a tendency to worry about them at the same time. Focusing on other things, for instance, may be a strategy for these individuals not to become overwhelmed by their problems.

Thirdly, the instructions on the coping questionnaire used in the present study refers to coping with problems "in general". Thus, using distraction as a coping strategy "in general", does not necessarily mean that subjects avoid dealing with the medical issues of HIV infection, such as seeking medical care. This supposition is supported by Taylor and colleagues' (1992) findings that unrealistic optimism about the future consequences of their HIV infection -- which may be associated with the use of distraction as a central strategy -- was related to better adjustment and more active coping that did not appear to come at the cost of increased sexual risk behaviors or reduced health maintenance behavior. These findings highlight the need of more research into the nature of coping responses to environmental demands and chronic diseases to unravel the differences and inconsistencies between general and situation-specific coping (Lazarus, 1993).

As stated above, significant associations between distraction coping and markers for progression of HIV infection but not with clinically defined AIDS were found. It may be, however, that other types of statistical analyses, such as path-analyses, are more appropriate for analyzing the associations between coping, development of biological 'risk factors' for progression, and subsequently the development of clinically defined AIDS. For instance, the significant association between distraction coping and CD4-slope on the one hand, and between CD4-slope and the development of clinically defined AIDS on the other hand may suggest an indirect association between distraction coping and the development of clinically defined AIDS. Future studies should further investigate whether these indirect associations exist.

Several studies investigated the associations between a construct often associated with distraction, denial, and the course of other physical illnesses and found a protective effect of denial. In post-heart attack patients, denial has been associated with faster recovery, fewer complications and lower subsequent mortality (Hackett et al., 1968; Lazarus et al., 1973). It may be that there is an optimal level of distraction, which varies across the different stages of the disease as being high enough so that a person is not incapacitated with overwhelming worries, anxieties and negative thinking about the disease, but not so much that the person is avoiding attending to the things that need to be done to keep as healthy as possible (Ironson et al., 1994). The appearance of excessive use of denial strategies in these individuals may be a warning sign that situational stressors have, at least temporarily, overwhelmed an individuals' possibly more "adaptive" distraction strategies. This may be a key point for psychosocial intervention. These interventions may have as a goal that subjects develop ways to distract themselves from their problems in a "healthy way" in order to prevent too much worrying and feelings of hopelessness and depression.

Contrary to what we expected, having a "fighting spirit" was not associated with progression of HIV infection. This finding is in contrast with results of another study that found that having a "fighting spirit", was related to less progression of HIV infection (Solano et al., 1993). In the Solano et al. study subjects were asked to express on a 10

point scale how similar their reactions were with those of the principal character of a story describing a "fighting spirit" reaction of a person who is confronted with the diagnosis of a life threatening disease. This assessment strategy differs from the one used in the present study, in which subjects were asked several questions about coping with problems *in general.*

The results obtained in the present study are also in contrast with the results of Griensven et al. (1990). They found no associations between coping as measured the same questionnaire as used in the present study (UCL) and the development of markers for progression of HIV infection. However, the differences between the study presented here and the Griensven et al. study makes it difficult to compare them. We used other outcome measures, including rate of decline of CD4 cells, and the development of AIDS, as well as a longer follow-up period.

The present study has certain limitations. Coping style was measured at one point in time and only by self-report. Therefore, in order to better understand the results obtained here, it is important to further investigate the associations between distraction coping and HIV progression. These studies should investigate possible changes in these associations over time, and how distraction coping relates to other psychosocial variables including measures of psychological distress. Finally, more studies are needed to investigate possible underlying behavioral and/or psychoneuroimmunological mechanisms before any definite conclusions can be drawn from these findings.

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Chapter 7

Active Confrontational Coping Predicts Decreased Clinical Progression over a One Year Period in HIV-Infected Homosexual Men

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Abstract

The associations between stressful life events, psychiatric symptoms, coping, and social support and HIV disease progression one year later were studied in 51 HIV-infected asymptomatic and early symptomatic homosexual men. Dependent variables were CD4 counts and clinical progression. No associations between the psychosocial parameters and CD4 counts were found. Active confrontation with HIV infection as a coping strategy was predictive of decreased clinical progression at one year follow-up, after taking into account baseline biomedical and behavioral variables. These results show that active coping strategies may have an effect on disease progression, possibly mediated by greater compliance with medical treatments or by psychoneuroimmunological mechanisms.

Introduction

The question of whether psychosocial factors have an influence on the progression of HIV infection has been addressed in several studies. Thus far, contradictory results have been found in studies investigating the associations between stressful life events (Kessler et al., 1991), psychological distress, including depression (Rabkin et al., 1991; Perry et al., 1992; Burack et al., 1993; Lyketsos et al., 1993), and coping styles (Blaney et al., 1992; Ironson et al., 1994), and clinical progression. Burack and colleagues (1993) found a weak but statistically significant association between depressed mood as measured with the Center for Epidemiological Studies Depression scale (CES-D) and decline in CD4 cells over a 66-month follow-up period. CD4 count is currently one of the most important immunologic predictors of the course of HIV infection (Fahey et al., 1990; Philips, 1992). In a different study with 1809 HIV-infected homosexual men, no association was found between CES-D scores and CD4 decline during eight years (Lyketsos et al., 1993). Both studies did find no association between depressed mood and more rapid clinical progression to AIDS or death. Ironson and colleagues (1994) investigated the associations between denial as a coping strategy around the time of serostatus notification and the decline in CD4 cells. They found that denial predicted a decline in CD4 cells one year later and progression to AIDS-defining clinical symptoms two years later. Using a coping strategy characterized as 'fighting spirit' - i.e. an optimistic attitude accompanied by a search for greater information about HIV - was found to be associated with less development of HIV-related symptoms during one year, whereas a denial/repression attitude was associated with more HIV-related symptoms (Solano et al., 1993). Several other studies, however, found that stressful life events and a broad set of psychiatric distress measures were not related to clinical progression of HIV infection (Kessler et al., 1991; Rabkin et al., 1991; Perry et al., 1992)

These conflicting findings may be partly due to differences in psychosocial, immunological, and clinical parameters assessed, as well as the time of follow-up. (Goodkin et al., 1994). Studies using coping assessments tend to yield significant relationships with progression of HIV infection (Solano et al., 1993; Ironson et al., 1994),

whereas studies that measure only stressful life events and/or distress tend to find non-significant relationships (Kessler et al., 1991; Rabkin et al., 1991; Perry et al., 1992; Lyketsos et al., 1993). Differences in psychosocial factors that are hypothesized to be related to progression of HIV infection, as well as in the statistical procedures employed, may be due to the lack of a theoretical rationale interrelating the psychosocial and psychiatric measures assessed (Goodkin et al., 1994).

Goodkin and colleagues (1994) propose a 'stress-coping-social support' model for the effects of psychosocial factors on HIV disease progression. This model postulates direct effects as well as interaction effects of the components of the model on HIV disease progression. Some components of this model, especially coping style, have demonstrated significant relationships with immunological parameters and HIV-disease progression (Goodkin et al., 1992; Ironson et al., 1994).

We tested whether components of the 'stress-coping-social support' model, were related to disease progression in a group of 51 HIV-infected homosexual men during one year. Determining psychosocial factors that are associated with disease progression is important to help identify persons who are at increased risk for disease progression. When such factors can be identified, psychosocial interventions may be of help in deterring the progression of HIV infection.

Subjects and Methods

Subjects. This study took place from July 1991 through December 1993. During this period 51 HIV-infected homosexual men were recruited from two university hospitals, and four smaller hospitals in the Netherlands. Subjects were eligible for the present study if they fulfilled the following entry criteria: (1) being homosexual; (2) age 18-65 years; (3) no IV drug use; (4) no other antiretroviral medication than zidovudine (AZT); (5) no prophylactic treatments except for *Pneumocystis carinii* pneumonia (PCP) prophylaxis; (6) no AIDS-defining diagnoses (CDC, 1987); (7) ability to read and understand the psychological self-report questionnaires. Sociodemographic information on the subjects was obtained about age, education, employment, and monthly income.

Psychosocial assessments. The design of the study was prospective-longitudinal over a one-year period. The presence of psychiatric symptoms was screened with a Dutch translation (Koeter & Ormel, 1991) of the 30-item *General Health Questionnaire* (GHQ-30) (Goldberg, 1972; Goldberg & Miller, 1978). The GHQ-30 does not include somatic symptoms, which supports the selection of this scale for the detection of psychiatric symptoms in patients with a somatic illness (Huppert et al., 1989). Subjects endorsed the occurrence of each symptom experienced during the last four weeks on a 4-point scale. Answers were dichotomized into 'usual and less than usual', and 'more or much more than usual' (Cronbach's alpha=0.93; Goldberg, 1972; Goldberg & Miller, 1978). Validity of the GHQ-30 has been established by Tarnapolsky and colleagues (1978).

Stressful life events were measured with the 'HIV Life Events List', an adaptation

of the Life Experiences Survey (Sarason et al., 1978). This list (49 items, NcGv, 1991) assesses life stressors in the year prior to the assessment with respect to 4 areas: work, family and friends (e.g., illnesses or death of partner/friends), personal circumstances and finance. Subjects rated the events on a 7-point Likert-type scale ranging from -3 (very negative) to +3 (very positive). A total score was calculated by adding the individual item-scores. Stressors related to somatic symptoms were not included in the analyses, to prevent overlap with the presence of clinical symptoms, one of the other predictors.

Coping styles were assessed with the HIV Coping List (HCL, 34 items) (Gremmen et al., in preparation). The HCL measures HIV-specific coping, and was developed from the COPE, originally developed by Carver et al. (1989). Items can be answered on a Likert-type scale ranging from 1 (never) to 4 (always). A second order factor analyses was carried out on the original scales, in order to reduce the redundancy among the predictor variables. Using a Varimax rotation, two factors were generated accounting for 70% of the variance in the scales. Factor 1. consisted of the positive reinterpretation scale and the inverse of the depression reaction pattern scale, and this factor was called optimistic attitude towards HIV (eigenvalue 2.0; 40% of variance explained). Factor 2. consisted of the scales seeking social support, active problem solving, and the inverse of the denial scale, and this factor was called active confrontation with HIV (eigenvalue 1.5; 30% of variance explained).

Social support was assessed with a Dutch self-report questionnaire measuring the respondent's satisfaction with their social support network (Sonderen, 1991). The questionnaire assesses satisfaction in various areas including everyday emotional support, emotional support in stressful situations, appreciation, instrumental support, and informational support (42 items, Cronbach's alpha = 0.96). The total score reflects subjects' satisfaction with his social network. The construct validity of this questionnaire has been established previously (Sonderen, 1991).

Health behavior control variables. Subjects were interviewed about alcohol use, cigarettes smoking, recreational substance use, and physical exercise, because these variables have been shown to be of importance in psychoneuroimmunological research (Kiecolt-Glaser et al., 1988), and may have an effect on progression of HIV infection (Nieman et al., 1993; Laperriere et al., 1990; Goodkin et al., 1994).

Procedures. Patients were invited to join the study by their physicians. After obtaining informed consent, the psychological questionnaires were administered, at either the out-patient clinic setting or, if a subject wanted this, at his home. Psychosocial variables were assessed at baseline.

Follow-up. Subjects were seen by their physicians at baseline, after six months, and after 12 months. Subjects who developed new clinical symptoms or exacerbations of prior symptoms were seen more frequently. Information concerning known duration of seropositive status, use and duration of use of AZT, use of PCP prophylaxis, and the occurrence of clinical symptoms was obtained directly from the subjects, and from their medical records.

Laboratory methods. Sera were tested for the presence of antibodies to HIV-1 using enzyme-linked immunosorbent assays (ELISA; Abbott, Abbott Park, IL; Vironostika Teknika; Organon, Oss, Netherlands), and confirmed with Western Blotting. To determine CD4 cell numbers, peripheral blood mononuclear cells were isolated from heparinized venous blood by density-gradient centrifugation on a Ficoll-Paque gradient. Lymphocyte immunophenotyping was carried out by flow cytometry (Gruters et al., 1991).

Data analyses and statistics. Clinical progression was defined as progression in the CDC staging system from an asymptomatic stage to a symptomatic stage (CDC, 1986) or AIDS (CDC, 1987) or from a symptomatic stage to AIDS. CDC stage II/III will be referred to as asymptomatic stages in this chapter; CDC stage IVA, IVC2, and IVB (peripheral neuropathy) as early symptomatic stages (CDC, 1986). Logistic regression with entering the predictor variables into the equation was used to test whether stressful life events, coping style, social support, and psychiatric symptoms scores could predict clinical progression. The analyses were done in two steps. Firstly, we assessed the predictive value of the biomedical parameters assessed at baseline (age, duration of seropositive status, CD4 counts, presence of symptoms, and use of AZT, and/or PCP prophylaxis), and the behavioral control variables for their association with clinical progression, respectively. Those variables that were associated with clinical progression with a significance level of $p<0.20$ were retained for further analyses. Secondly, we assessed whether psychosocial variables predicted clinical progression significantly, adjusting for the selected biomedical, and behavioral parameters. A comparable procedure was followed with respect to the prediction of CD4 counts by multiple regression analyses. Log transformation of CD4 count was used to normalize its distribution.

Demographic and Biomedical Characteristics (Table 7.1).

Table 7.1. Demographic and biomedical characteristics at baseline

Mean age	38.4 (range 21-55)
Education	19 (37%) : higher level (e.g., university) 20 (39%) : middle level (e.g., high school) 12 (24% : other, lower levels
Occupation	29 (57%) : working 14 (27%) : unable to work due to disability 8 (16%) : unemployed, but not disabled
Mean monthly income	$1313 per month (range 506-5550)
Mean duration of known seropositive status	31 months (range 1-122)
Mean number of CD4 cells/mm^3	380 (sd: 179)
Current use of zidovudine	17 (33%) : yes 34 (67%) : no
Current use of PCP prophylaxis	10 (20%) : yes 41 (80%) : no
Presence of Symptoms	27 (53%) : asymptomatic (stage II/III*) 24 (47%) : symptomatic (stage IV-A, IV-C2, IV-B*)

* See CDC (1986) for specification of staging (CDC-IVB: peripheral neuropathy only).

The sample under investigation consisted of well educated, white homosexual men. Fifty-three percent of the subjects were in an asymptomatic stage of infection. One third of the subjects used AZT at the beginning of and during the study.

Prediction of CD4 counts. None of the psychosocial parameters was associated with CD4 counts at baseline, 6-, or 12-month follow-up, respectively, all p's >0.10. The only parameter that predicted CD4 counts at 6-, and 12-month follow-up was CD4 counts at baseline (Adj. R^2=0.68, and 0.45, respectively, p's<0.001).

Psychosocial parameters and clinical progression. Ten subjects progressed in CDC stage during follow-up. Specifically, five subjects progressed from an asymptomatic stage to a symptomatic stage developing one or more of the following symptoms: oral candidiasis (n=4), oral hairy leukoplakia (n=1), unexplained prolonged fever of more than one month (n=1), and herpes zoster infection including multiple dermatomes (n=1). Five subjects developed AIDS based on one or more of the following diagnoses: PCP (n=1), candidiasis of the esophagus (n=3), extrapulmonary tuberculosis (n=1), and Kaposi's Sarcoma (n=1).

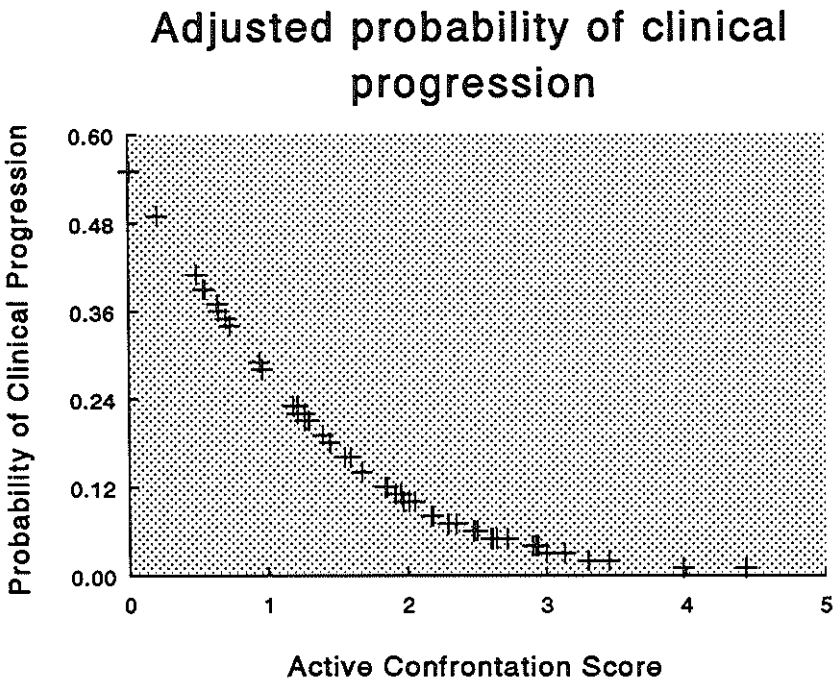
Prediction of clinical progression. Age, the presence of HIV-related symptoms at baseline, and known duration of seropositive status were associated with clinical progression at p-values of less than 0.15. These variables predicted 77% of the clinical progression ($p<0.03$). Use of AZT or PCP prophylaxis at baseline were not associated with clinical progression ($p's>0.20$). None of the behavioral control variables were related to clinical progression, all $p's>0.20$. As for the psychosocial variables, using active confrontation as a coping strategy was associated with less clinical progression, $p<0.06$. Active confrontation alone predicted 81% of clinical progression. Adding active confrontational coping to the model including the biomedical predictor variables increased the prediction of clinical progression significantly ($p<0.02$). The final model including age, the presence of HIV-related symptoms at baseline, known duration of seropositive status and active confrontational coping together predicted 83% of the clinical progression. Thus, after adjusting for the biomedical parameters, active confrontational coping accounted for 26% (6/23) of the variance that remained unexplained using the biomedical parameters alone. The odds ratios of predictors for clinical progression are presented in Table 7.2. Figure 7.1 shows the odds ratio for clinical progression as a function of the active confrontational coping score, adjusted for the biomedical parameters mentioned above.

Table 7.2. Odds ratios of predictors for clinical progression#.

	Odds ratio (95% Confid. Int.)	
Age	0.93	(0.83 - 1.04)
CDC stage at baseline	0.17*f*	(0.02 - 1.25)
Known duration of seropositive status	1.04*	(1.01 - 1.04)
Active Confrontational Coping	0.30*	(0.10 - 0.91)

Each odds ratio is adjusted for the other variables in the model
f = p<0.10 * = p<0.05

Figure 7.1. Probality of clinical progression as a function of the active confrontation coping score, after adjusting for age, CDC stage, and known duration of HIV seropositive status.



Discussion

The present study investigated the associations between psychiatric symptoms, stressful life events, coping styles, social support, and progression of HIV infection over a 12-month period in 51 HIV-infected gay men. Psychosocial, behavioral, and biomedical parameters assessed were not significantly related to CD4 cell counts over a 12-month period, though baseline CD4 counts were significantly related to CD4 counts at follow-up. These results are in line with other studies that also found no association between stressful life events (Kessler et al,. 1991), several measures of distress (Rabkin et al., 1991; Perry et al. (1992), and depression (Lyketsos et al., 1993) and CD4 cell counts over various lengths of follow-up. Taken together, these studies suggest that CD4 counts may not be affected by psychosocial parameters. It may be, however, that this is caused by the high variability in the determination of CD4 counts within and between laboratories (Veugelers et al., submitted). This phenomenon may be especially pronounced when single or relatively few time points are incorporated into the design. The high within-subjects correlations among the different measurements of CD4 counts, however, does suggest that the determination of CD4 counts is reliable. Moreover, the present study did not investigate functional immunological parameters, such as proliferative responses of T cells after stimulation with anti-CD3 monoclonal antibodies (Schellekens et al., 1990) or other mitogens and antigens. It may be that effects of psychosocial factors on functional immunological parameters can be observed, even in the absence of associations with absolute cell counts (Goodkin et al., 1994).

We found that active confrontation with HIV infection predicted less clinical progression of HIV infection, after adjustment for baseline biomedical parameters, and behavioral variables. This result is in line with results of a study conducted by Blaney and colleagues (1992), who found that active coping was associated with the number of total physical symptoms observed (not CDC stage progression). It may be that subjects who use active coping show greater vigilance with respect to the occurrence of physical symptoms, thereby seeking medical intervention earlier, and being more compliant with medical treatments. However, there were no differences in active confrontational coping-scores between subjects who used AZT or PCP prophylaxis and subjects who did not use these medications (results not shown; t-tests, p's>0.40). It may also be that subjects who use more active coping feel less helpless and more in control over the course of the infection. This is line with findings in patients with breast cancer. In these patients, having a 'fighting spirit' and less helplessness has been associated with better disease outcome (Greer et al., 1979; Mulder et al., 1992). In healthy individuals, having an internal locus of control has been related to higher natural killer cell counts and functioning (Brosschot, 1991). Finally, it may be that active confrontational coping with HIV infection is associated with one of the other psychosocial predictor variables, indicating a possible indirect relationship with clinical progression. However, these associations were not statistically significant (results not shown, all p's>0.10).

Clinical progression was defined as developing new HIV-related symptoms. It may be, however, that new symptoms were not reported by the subjects or not recorded by the

physicians. This may have been the case for constitutional symptoms such as fatigue, weight loss, fever, diarrhoea, and night sweats. However, given the subjective nature of these symptoms, and the possible confounding relationship with mood states, we were more circumspect about diagnosing clinical progression defined solely by constitutional symptoms.

The results presented here may be in contrast with the results of another study done by our group. In this study using distraction from problems as a coping strategy with problems *in general* was found to be associated with less CD4 cell decline, less appearance of syncytium-inducing HIV variants (Koot et al., 1993) and less progression to immunologically defined AIDS (CDC, 1993; having fewer than 200 CD4 cells/mm^3) over a 7-year period in 181 homosexual men who were asymptomatic at baseline (Mulder et al., submitted, a). Distraction, however, was not found to be associated with progression to AIDS-defining clinical symptoms (CDC, 1987) in that study. Reasons for divergence may be that the coping questionnaire used in that study was not HIV-specific, and no other psychosocial parameters were obtained from the subjects. Moreover, subjects in the Mulder et al. study were in an asymptomatic stage of the disease at the beginning of the study, whereas approximately half of the men in the present study had HIV-specific symptoms at baseline. It may be that using distraction as a coping strategy is 'healthy' in early stages of infection, but that active coping strategies are more beneficial once HIV-related symptoms develop. Importantly, these discrepant findings highlight the need for more research into the situations where specific coping strategies are most effective (Lazarus, 1993).

We did not find an association between stressful life events, psychiatric symptoms, or positive attitude and clinical progression. Similar findings were reported by others (Kessler et al., 1991; Rabkin et al., 1991; Perry et al., 1992; Burack et al., 1993; Lyketsos et al., 1993). The absence of these associations in the present study may be due to a lack of power, or to the use of a relatively short follow-up period. Taken together, however, the findings in the present study, together with the findings of the studies mentioned above, suggest that there may be no association between life events, psychiatric distress and progression of HIV infection. However, more research is needed, especially regarding the associations between ways of coping with HIV infection and clinical progression. Studies that take into account coping styles indeed have shown relationships with progression of HIV infection (Blaney et al., 1992; Solano et al., 1993; Ironson et al., 1994). Finally, the absence of a relationship between optimistic attitude and clinical progression indicates that the prevalent perception of the lay public that 'positive thinking is good for your health' should be critically evaluated.

The results presented herein may have implications for psychosocial interventions, especially those that attempt to enhance active coping strategies. Such interventions -- coping effectiveness training -- have been described for HIV-infected individuals by Folkman et al. (1991), and individuals who successfully improve their coping skills after such interventions may be at lower risk for clinical progression (Ironson et al., 1994). Finally, despite the fact that no relationships have been found between social support, and optimistic attitude and clinical progression of HIV infection, intervening on these factors

in psychosocial interventions is important, as these variables may preserve or increase psychological well being and quality of life among those living with this disease (Mulder et al., submitted, b; Hays et al., 1992).

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Chapter 8

Psychosocial Group Intervention and the Rate of Decline of Immunological Parameters in Asymptomatic HIV-Infected Homosexual Men

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Abstract

The aim of the study was to determine changes in the rate of decline of immunological parameters after psychosocial group intervention in 26 asymptomatic HIV-infected homosexual men. The interventions consisted of two different 15-week psychosocial group intervention programs: cognitive-behavioral therapy (CBT; n=14), and experiential therapy (ET; n=12). The outcome measures were changes in the decline of CD4 cell counts, and T cell proliferative responses to anti-CD3 monoclonal antibodies from pre- to post-intervention. No significant changes were found in the decline of CD4 cell counts after the intervention. There were no differences in the rate of decline of CD4 cells or T cell responses between the CBT and ET condition. However, those subjects who showed larger decreases in distress over the period from the onset of either intervention program to 9 months follow-up showed less decline in CD4 cell counts over the 2-year period after the intervention. While the rate of decline in T cell responses was significantly less after both interventions, a similar positive change in T cell responses was found in a comparison group of 149 HIV-infected men with similar demographic, psychosocial and immunological characteristics who did not participate in one of the interventions. We conclude that the psychosocial intervention programs tested herein were not causing changes in CD4 cell decline or T cell responses and that decreases in distress were related to increases in CD4 cell counts.

Introduction

Does psychosocial intervention have an effect on immunological parameters in asymptomatic HIV-infected homosexual men? This is a relevant research question because there is some evidence for the effect of psychosocial interventions on immunological parameters in healthy individuals (Kiecolt-Glaser et al., 1992), cancer patients (Fawzy et al., 1990), and homosexual men who were dealing with the initial impact of news of their HIV antibody serostatus (Antoni et al., 1991). Given that the efficacy of the immune system is important for the course of HIV infection (Pantaleo et al., 1993), the possible effects of psychosocial interventions on immunological parameters may have consequences for the progression of HIV infection.

Until now, only a few studies have been published in which the immunological effects of behavioral interventions with HIV-infected people were investigated (Coates et al., 1989; Antoni et al., 1991; Esterling et al., 1992). In one study, 47 healthy gay men were randomly assigned to a 10-week cognitive-behavioral stress management program or to an assessment-only control group (Antoni et al., 1991). Five weeks after entering the study, the men were notified of their HIV antibody serostatus. Two weeks later, the seropositive intervention subjects showed significant increases in CD4 cell counts and NK cell counts after serostatus notification, whereas the control group showed decreases. These findings may be important because the number of CD4 cells is associated with progression of HIV infection and the onset of AIDS (Moss & Bacchetti, 1989; Schellekens

et al., 1992; Pantaleo et al., 1993), while NK cells are involved in the protection against tumors and viral infections (Sirianni et al., 1986). Interestingly, the frequency with which relaxation was practiced at home during the intervention period was positively correlated with post-intervention CD4 and NK cell counts, suggesting the possible importance of individual differences in treatment adherence (Antoni et al., 1991). However, the brief time frame used in this study does not address the effects of such interventions on the longer term declines in the immunological parameters that characterize HIV spectrum disease.

In contrast with the above mentioned positive findings, another study found that an 8-week stress management program with HIV-infected men did not produce changes in immunological parameters, including CD4 cell counts, when compared with a waiting-list control condition (Coates et al., 1989). However, this intervention did not modulate distress levels either.

In the psychosocial intervention studies with HIV-infected individuals conducted to date, few immunological measurements have been tracked, and follow-up measurements have not systematically been obtained. Rate of decline of immunologic parameters may be of more prognostic relevance than are single baseline measures. Therefore, no conclusions can be drawn with respect to long-term potential health effects of such interventions. We assessed whether psychosocial intervention was associated with changes in the rate of decline of immunological parameters. Immunological parameters were collected in the context of a natural history study at three-month intervals beginning after testing HIV seropositive until two years after men were randomized to one of the conditions in the intervention.

Methods

Subjects. All study subjects were recruited from a natural history study conducted at the Municipal Health Service of Amsterdam, The Netherlands, which began in 1984 (Lange et al., 1986; Griensven et al., 1987). Thirty-nine subjects out of a group of 188 HIV seropositive homosexual men followed in the natural history study (20.7%) agreed to participate in the psychosocial intervention study, and filled out an informed consent form. These men were all in CDC stage II or III (i.e., asymptomatic or having lymphadenopathy only; CDC, 1986), and did not use antiretroviral medication at the time they were invited into the present study. Subjects were seen every three months for a physical examination, an interview regarding their medical status, and the collection of blood samples for immunological testing.

The 149 men who did not participate in the psychosocial intervention, but who fulfilled the inclusion criteria, were used as a natural history comparison group. Because the groups were self-selected, the comparison group was not a true control group. However, using the immunological data of this comparison group was thought to be of value in interpreting possible changes observed after psychosocial intervention.

Psychosocial interventions. The 39 men who agreed to participate in the intervention study followed either a cognitive-behavioral group therapy program (CBT) or an experiential group therapy (ET) program, each 15 weeks in duration. Details of these programs have been described in chapter 4. For the purpose of this immunological follow-up study, we combined the subjects assigned to the two interventions, because both interventions showed equal effects on distress, coping, social support, and emotional expression (chapter 4), factors that might contribute to, or mediate immune changes (Mulder et al., 1992).

Drop-outs. Although 39 men agreed to join the intervention study, five men dropped out of the study before the start of the intervention due to practical reasons. During therapy, three men dropped out from the cognitive-behavioral therapy and five men from the experiential therapy groups. Reasons for drop-out included moving into another area, and not feeling comfortable in the intervention group. The data of these drop-outs were not included in the present analyses. Although the deletion of drop-outs may bias the data, the results presented here do not change when drop-outs are included. Thus, immunological effects of the intervention were analyzed for a total of 26 men (CBT: n=14, ET: n=12).

Assessment

Demographic variables. Information was obtained on age, and known duration of HIV seropositive serostatus.

Immunological studies[9]. Immunological parameters (CD4 cells and T cell responses) were assessed at three-month intervals from the time a subject entered into the natural history study and was determined to be HIV seropositive. The immunological outcome measures were chosen because HIV-infected individuals have a progressive decline in the number of CD4 cells (Pantaleo et al., 1993), and T cell responses to antigenic and mitogenic challenge (Schellekens et al., 1990).

Determination of CD4 cell numbers. Peripheral blood mononuclear cells were isolated from heparinized venous blood by density-gradient centrifugation on a Ficoll-Paque gradient. Lymphocyte immunophenotyping was carried out by flow cytometry.

T cell responses. Lymphocyte proliferation was determined by using the whole-blood lymphocyte culture technique, that is described in detail elsewhere (Bloemena et al., 1989). Briefly, heparinized venous blood was diluted 1:10 with Iscove's modified Dulbecco's medium (IMDM) supplemented with antibiotics and 2-mercaptoethanol (5 x $10^{-5}M$). Triplicate cultures were performed in round-bottom microtiter plates, containing 150 mm^3 diluted blood per well. The cells were stimulated with the mAb CD3 CLB T3/4E

[9]Immunological parameters were determined by the Netherlands Red Cross Blood Transfusion Service, and these results were kindly provided for the present study. Unfortunately, the fixed three-month intervals for determining immunological parameters precluded using the waiting list control group, as described in chapter 4, as a control group with respect to the immunological effects of the interventions. Therefore, we assessed changes in the rate of decline of the immunological parameters following randomization to one of the interventions.

(subclass IgE; final dilution, ascites $1:10^4$; Lier et al., 1987). The proliferative response was measured after 4 days of culture by means of [^{3}H]thymidine incorporation added 24 h before harvesting. Reactivity was expressed as counts per minute per 10^3 T cells.

Psychological assessment

Distress changes in the intervention group. We assessed the relationships between changes in affective state and changes in immunological parameters within the intervention group. Distress was measured with validated Dutch adaptations of the Profile of Mood States (POMS) (McNair et al., 1971; Wald & Mellenbergh, 1990) and the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961; Bouman et al., 1985). High POMS scores indicate high levels of mood disturbance for the seven days preceding assessment (alpha of POMS: 0.89). Psychiatric symptoms were screened with the a Dutch translation of the 30-item General Health Questionnaire (GHQ-30; alpha =0.94), a widely used and well validated instrument (Goldberg & Miller, 1978; Koeter & Ormel, 1991). For the purpose of this study, a psychological distress composite score was calculated by using a factor score derived from a factor analyses of the three distress scales (POMS, BDI, GHQ). This strategy was justified by the high intercorrelations among the distress scales (r's=0.80-0.92).

Baseline psychological characteristics in the intervention and comparison group. A screening battery including three items on depression, general anxiety level, and fear about getting AIDS (9-point scale) was administered at baseline to all subjects, allowing us to characterize differences in participants vs. non-participants (Cronbach's alpha = 0.81). HIV-related coping behavior was also assessed at baseline by 10 items selected from a Dutch version (chapter 4) of part of the situational version of the COPE, originally developed by Carver et al. (1989). The items were selected from two scales, measuring active coping (5 items; Cronbach's alpha = 0.64) and seeking social support (5 items; Cronbach's alpha = 0.79). No differences were found among the subjects in the intervention vs. the natural history comparison group with respect to baseline affective state and HIV-related coping behavior (all p's>0.10).

Procedures. Psychological data collected immediately before, and six months after the intervention were used for the present study. The intervention started in early 1991. The immunological data collected through April 1993 were used for the present study.

Statistical analyses. To evaluate changes in the decline of immunological parameters, we used the Summary Statistic Method for analyzing laboratory marker changes in AIDS clinical trials (Dawson et al., 1991). Specifically, rate of change in immunological parameters was operationalized by calculating the slopes of the least-squares regression lines fit through each subject's immunological data collected at 3-month intervals during both the pre-intervention period (beginning at the time a subject was tested HIV seropositive in the natural history study), and continuing over a 24-month post-intervention period, respectively. Only subjects who had 3 or more data points during each of the pre-

and post-intervention periods, respectively, were included in the analyses, as meaningful rates of change could not be calculated in subjects who had only 2 data points for a period. No subjects in the intervention group, and only ten subjects in the comparison group were excluded from the analyses on these criteria. Ten subjects in the intervention group, and 49 subjects in the comparison group started to use zidovudine (AZT) during the follow-up period (Chi-square, $p>0.4$). These subjects were *not* excluded from the analyses. The mean number of times that subjects had their CD4 counts, and T cell responses recorded in the pre- and post-intervention periods is described in Table 2.

The within group changes in the slopes of the immunological parameters were analyzed using Wilcoxon Matched-pairs Signed-rank tests. Associations between changes in distress (from pre-intervention to 6-month follow-up) and changes in the decline of immunological parameters from the pre-intervention period as compared to the post-intervention period (until 24-month follow-up) were calculated using Spearman rank-order correlations. The slopes of the intervention and comparison group were compared using Mann-Whitney tests.

Results

Demographic, psychological, and immunological characteristics at baseline (Table 8.1) The demographic, psychological, and immunological characteristics at baseline are reported in Table 8.1. There were no differences on demographic, psychological and immunological variables assessed among the subjects in the intervention and comparison group (all p's>0.10).

Table 8.1. Demographic, psychological, and immunological characteristics at baseline (SD).

	Intervention Group	Comparison Group
Age (years)	40.4 (range 26-60)	38.4 (range 21-61)
Known duration of seropositive Status (years)	5 (range 1-7)	4.6 (range 1-6)
Distress score	3.7 (1.7)	3.8 (1.9)
Seeking social support	2.3 (0.8)	2.1 (0.8)
Active coping	3.2 (2.2)	2.6 (2)
CD4 cells/mm^3	390 (200)	469 (241)
T cell reactivity to anti-CD3 mAb per 1000 CD3 cells in cpm*	127 (162)	102 (115)

*cpm = counts per minute

Within intervention group changes in rates of decline of immunological parameters. The rate of decline of CD4 cells did not change from the pre- to the post-intervention period, both within the intervention group, as well as within the comparison group (Table 8.2). The slopes of T cell responses reversed during the 24-month post-intervention period as compared to the pre-intervention period, both within the intervention and comparison group (Wilcoxon Matched-pairs Signed-ranks tests, both p's<0.002).

Table 8.2. Median of slopes of immunological parameters (25 and 75 percentiles) and the mean number of immunological tests on which the calculation of the slopes was based [..] for subjects in the intervention group (n=26) vs. the subjects in the comparison group (n=139)

	Slope from first HIV positive visit to start intervention	Slope from beginning intervention/comparison to 24 months follow-up
	Slope of CD4 cell counts*	
Comparison Group	-4.5 (-8.3 to -2.1) [16]	-4.6 (-9.2 to -1.3) [9]
Intervention Group	-4.7 (-9.8 to -1.4) [18]	-3.4 (-6.6 to -0.3) [10]
	Slope of T cell responses after stimulation with CD3 mAbs**	
Comparison Group	-1.5 (-3.5 to 0.2) [10]	1.8 (0.3 to 4.6) [9]
Intervention Group	-1.7 (-3.8 to -0.3) [12]	1.1 (-0.5 to 4.9) [10]

* Slope: Change in CD4 cells per mm^3 per month
** Slope: Change in counts per minute per 1000 T cells per month

Distress-immune change score correlations. Changes in psychological distress from pre-intervention to 6-month follow-up within the intervention group were significantly correlated with changes in the slope of the immunological parameters from pre-intervention to 24 months follow-up: r=-0.39, p<0.03. This finding suggested that to some extent men with the largest reduction in psychological distress showed less decline in CD4 cells in the post-intervention period. However, there was no significant correlation between changes in psychological distress and the changes in the slope of the T cell responses over these periods (p>0.40).

Differences between intervention and comparison group in rates of decline of immunological parameters (Table 8.2). There were no significant differences in rates of decline of the CD4 cell numbers and T cell responses after stimulation with CD3 mAb between the intervention and comparison group during 24-month follow-up after the intervention (Mann-Whitney tests, p-levels >0.20).

Discussion

We found no changes in the rate of decline of CD4 cells in HIV-infected homosexual men after participation in a psychosocial intervention program. However, the men with the largest reduction in psychological distress showed less decline in CD4 cells. There were no differences in the rate of decline of CD4 cells and decline of T cell responses to anti-CD3 mAbs between subjects participating in the intervention as compared to a group of subjects who did not want to participate. Several problems remain, however, in the interpretation of these findings.

The design of this study precludes a true comparison between the intervention and comparison group, because the comparison group was 'self-selected' and not randomly assigned. We do not know what the reasons were why the subjects in the comparison group decided not to participate in the psychosocial intervention programs. Although we did not find statistically significant differences between the intervention and comparison group in a number of demographic, psychosocial and immunological variables at baseline, it may be that the groups varied with respect to other characteristics. For instance, the subjects in the comparison group could have been less motivated to participate because of having less difficulties in adjusting to HIV infection, may have been participating in other group support programs, or may have had a more satisfactory social network.

The size of the intervention group was relatively small, which may have prevented the detection of immunological changes. Although we followed the subjects in the present study over a 2-year period, this may not have been long enough to detect a significant change. Burack and colleagues (1993) found a predictive effect of depression on CD4 cell decline over a 6-year period. Finally, it may be that psychosocial group intervention does not change these specific immunological parameters in HIV-infected individuals, as was also found by Coates and his colleagues, in their study using an 8-week intervention program (Coates et al., 1989).

A study using a randomized experimental design and a larger number of participants is needed to address the above mentioned problems. In such a randomized study, not only immunological effects should be investigated, but also long-term clinical effects. Until now, no results have been reported of studies that investigated these clinical effects in HIV-infected individuals.

The mean known duration of HIV seropositive status in the intervention group was five years. It may be that HIV-infected individuals with a shorter known duration of HIV seropositive status, and consequently more preserved immune functioning, may be better candidates for testing the immunological effects of a psychosocial intervention, as was shown by Antoni et al. (1991). Although highly speculative, it may be that in HIV-infected individuals immunological parameters such as T cell responses become refractory to psychosocial interventions over time, via muted reactivity to neuroendocrine changes following distress reductions after psychological interventions (Antoni et al., 1990).

Within both the intervention as well as in the comparison group we did find a significantly lower rate of decline of T cell responses during the 24-month post-intervention period as compared to the pre-intervention period. This is probably due to a

floor effect because their proliferative responses were already at 50% of the level of non-HIV-infected controls at the beginning of the intervention period (oral communication, M.Roos, Department of Immunology and Virolgy, CLB, Amsterdam). Therefore, this finding is unlikely to reflect an actual improvement of T cell functioning.

The correlation between changes in CD4 counts and changes in distress might be explained in several ways. It may be that the men who showed a decrease in distress did so because they knew -- based on the communications from their physicians -- that they had stabilizing CD4 counts during the intervention and psychological follow-up. Alternatively, it may be that the reduction of distress during the intervention and follow-up period influenced the stabilization of the CD4 cell decline through psychoneuroimmunological mechanisms (Antoni et al., 1990; Stein et al., 1991; Mulder et al., 1992). The absence of a correlation between changes in distress and changes in the slopes of T cell responses to anti-CD3 mAbs stimulation, however, does not support this last hypothesis. Future randomized experimental studies will be necessary to test the above mentioned hypotheses.

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Chapter 9

General Discussion

General Discussion

The studies presented in this thesis focus on which factors are associated with distress levels (Part I) and progression of HIV infection (Part II) in homosexual men in early stages of infection.

Specifically, the following research questions were addressed:

(1) What is the level of psychiatric symptoms and what are the associations between stressful life events, coping, and social support and psychiatric symptoms (chapter 3 and 4)?

(2) What are the effects of cognitive-behavioral vs. experiential group psychotherapy on the level of psychological distress, coping styles, social support, and emotional expression (chapter 4)?

(3) What are the associations between psychosocial parameters and progression of HIV infection (chapter 5, 6 and 7)?

(4) What are the effects of cognitive-behavioral and experiential group psychotherapy on immunological parameters (chapter 8)?

Part I

Discussion of Determinants of Psychological Distress

Levels of psychiatric symptoms. One quarter of the fifty-seven subjects who participated in the study presented in chapter 3 (Determinants of psychiatric symptoms during one year) received a psychiatric diagnosis on the Present State Examination. These subjects were recruited in six out-patient medical clinics in the Netherlands. Using the General Health Questionnaire (GHQ) as a screening instrument for psychiatric disorders, the same percentage of psychiatric cases was found using a cut-off score of 10/11 (Hemert et al., submitted). A similar percentage of GHQ-defined cases (26%) were found in the thirty-nine subjects who were recruited at the Amsterdam Municipal Health Center for participation in the intervention study (chapter 4; results not shown). Thus, in two studies with different groups of HIV-infected homosexual men (total n=96), one quarter of the sample did have psychiatric problems. In an earlier study in the Netherlands investigating distress levels using the SCL-90 (Derogatis, 1983) in 119 symptomatic HIV-infected men visiting the Amsterdam Medical Center, 77%, scored high on the depression subscale, and 57% scored high on the anxiety subscale (Beuzekom, 1991). Together, these results indicate that a substantial number of HIV-infected homosexual men in the Netherlands have serious psychiatric problems, and may be in need of psychosocial interventions.

Determinants of psychiatric symptoms. In order to provide interventions which are effective in decreasing psychiatric symptoms, we investigated which factors are important in influencing symptoms (chapter 3). We found that stressful life events including bereavement, job loss, financial problems etc., and satisfaction with the social network were significantly associated with the level of psychiatric symptoms. These findings are in line with other studies (Blaney et al., 1991; Hays et al., 1992; Leserman et al., 1992; Kelly et al., 1993a), and confirm the importance of life events and social support for the level of experienced psychiatric symptoms. However, the study presented in chapter 3 has certain limitations. First, the sample size was fairly small. Secondly, several variables were not assessed that were of potential relevance in determining symptom-levels. These variables include, for instance, the presence of personality disorders, and prominent defense mechanisms. As shown by Perkins and colleagues (1993), HIV-infected subjects with a personality disorder may have higher rates of Axis I disorders as compared to subjects without personality disorders. Thus, it is important in future studies to assess Axis II disorders, as well as their associations with psychiatric symptoms, coping and social support.

The effect of denial on reported levels of distress has only rarely been studied in HIV-infected individuals. We found that using active confrontation with HIV infection, including less denial, was associated with higher levels of psychiatric symptoms in relation to stressful life events (chapter 3). However, this study did not assess the precise association between denial and psychiatric symptom levels. In general, conflicting findings have been reported with respect to the association between denial and distress. One study found that HIV-infected subjects who use less denial around the time of serostatus notification, as measured by the COPE (Carver et al., 1989), reported lower levels of distress three weeks and one year later (Antoni et al., 1991). Another study reported that the use of denial by end stage renal disease patients was associated with *lower* SCL-90 scores (Fricchione et al., 1992), or lower anxiety in patients with myocardial infarction (Gentry et al., 1972). Studying the associations between denial and distress levels is important to gain more knowledge about the ways psychosocial interventions should be designed and evaluated. For instance, it may be that in some subjects denial decreases by participating in a psychosocial intervention program. This may lead to the experience of more distress, and to drop out from the intervention (oral communication, H. Siemens). It may be that for some persons an increase in distress because of less denial is a normal step in the processing of being HIV-infected (Fricchione et al., 1992). However, other persons may need denial to be able to cope with the infection, and for them a decrease in denial may lead to long lasting hopelessness, and despair. Future studies need to further investigate the importance of denial in relation to distress, and changes in the associations between denial and distress during different stages of HIV infection. It may be that using denial is an adaptive strategy in early stages, but becomes a maladaptive strategy when HIV-related symptoms develop. Finally, more research is needed to investigate the associations between denial, seeking medical treatment, and medication compliance.

On the basis of these findings we concluded that psychosocial interventions can be effective in reducing distress levels when addressing coping with stressful life events, and

aiming at improving the social network. These interventions could be provided in a group format, in order to provide social support as part of the psychotherapeutic process.

Effects of psychosocial interventions. We implemented a study with a randomized experimental design to investigate the effectiveness of two forms of group psychotherapy for 39 asymptomatic HIV-infected homosexual men: a cognitive-behavioral group psychotherapy program (CBT) and an experiential group psychotherapy (ET) program (chapter 4). We found that psychosocial intervention, independent of the therapeutic orientation, decreased distress significantly, as compared to a waiting-list control group (WCG). Kelly and colleagues (1993b) reported on the results of a similar study. They compared the outcomes of cognitive-behavioral group program (CBGP) to a social support group program (SSGP). The SSGP was based on the expressive-supportive group therapy program as described by Spiegel et al. (1991), and somewhat similar to our ET program. The Kelly et al. interventions consisted of eight weekly sessions of 90-minutes duration. Both interventions produced reductions in scores on SCL-90 subscales measuring depressive symptoms, hostility and somatization. Tests for clinical significance of change, however, underscored benefits of the SSGP. However, the drop-out rate in the SSGP group was very high (64%), whereas the drop-out rate in the CBGP group was only 28%. Thus, the results of this study may have been biased because of the differential drop-out.

The findings obtained in our study (chapter 4) and the Kelly et al. (1993b) studies suggest that non-specific group and therapist qualities may have caused the equality in effects of the interventions. These include group support, therapist support, and opportunity for emotional expression (Stiles et al., 1986). However, there may be differences between various intervention strategies that remain undetected due the assessment batteries' limitations. For example, when measuring the effect of an experiential therapy program, an observer scale such as the Experiencing Scale (Klein et al., 1969) may be a more sensitive measure to detect intervention-related changes in subtle cognitive and emotional processes, as compared to self-report questionnaires tapping outward distress levels.

Both the study presented in chapter 4 and the study of Kelly et al. (1993b) did not investigate individual differences in benefits from either program. It may be that some subjects benefit more from one program than another. Lutgendorf and colleagues (1991), for instance, investigated the associations between personality styles and benefits from a cognitive-behavioral stress management program for HIV-infected gay men. They found that personality styles as measured with the Millon Behavioral Health Inventory (MBHI), were associated with changes in POMS-depression scores after the intervention. Specifically, those subjects that scored high on the MBHI sensitive scale, an interpersonal style characterizing freely expressive individuals, showed decreased depression scores, in contrast to subjects who scored high on the introversive subscale (detached-passive, emotionally flat), who did not show significant changes in depression scores. However, these findings need to be interpreted cautiously, because possible differences in baseline depression scores were not reported. The effectiveness of a psychosocial intervention may not only depend on personality characteristics, but also on baseline levels of distress,

introspective qualities of the subject, possible environmental stressors (e.g., death of the partner) that a person experiences during the intervention period, and the relationship with the therapist (Stiles et al., 1986). Thus, future studies investigating the effectiveness of different psychosocial intervention programs should investigate the importance of non-specific therapeutic elements including group support, and therapist-client relationship, and individual characteristics for treatment outcome.

Although we did find a significant effect of the CBT and ET programs on psychological distress, no significant changes in coping and social support were observed after either intervention (chapter 4). Because the therapists were convinced that changes in coping and social support took place (oral communication), the lack of changes found may have been due to the type of self-report questionnaires used. It may be that more sensitive assessments are needed than the ones described in chapter 4. These may include self report questionnaires such as the Utrecht Coping List (Schreurs et al., 1987), Sarason's social support questionnaire (Sarason et al., 1983), or using interviews.

There is a need to study the optimal duration of psychosocial interventions. The optimal duration may vary with the stage of infection. Short-term interventions can be beneficial shortly after receiving an HIV seropositive diagnosis (Antoni et al., 1991) or during the asymptomatic stage in order to assist subjects in dealing with the knowledge of being HIV-infected (chapter 4). Long-term interventions may be needed when HIV-related symptoms develop to help subjects in coping with the physical consequences of the infection and when existential issues may come up more frequently and intensively (Spiegel et al., 1991).

Another topic which may be important to address in future psychosocial intervention studies includes addressing safe sex practices. Including issues related to safer sex practices is important because, at least in some studies in the Netherlands, a recent trend towards an increase in unsafe sex practices has been observed among homosexual men (Wit et al., 1992). Beyond potentially contributing to the spread of the infection this behavior may increase the likelihood of disease progression by re-exposing the individual to the same or different strains of HIV-1 as well as other sexually transmitted pathogens (e.g., HSV-2), potentially associated with HIV-1 reactivation (Griensven et al., 1990). Providing these interventions in a group format is of utmost utility for discussing ethical and moral dilemmas regarding sexual activities. The participants can function as each other's role models and as a resource for self-restraint and altruism. Other infected persons may be listened to and trusted where no therapist can hope to intervene. The effects of interventions on reducing high risk sexual behaviors were investigated in several studies (Coates, 1990). A 12-week group program for gay men, for instance, that provided AIDS risk education, cognitive-behavioral self management training, sexual assertion training, and attention to the development of steady social support, decreased the frequency of high risk sexual practices (Kelly et al., 1989). Likewise, the number of the men's sexual partners decreased after a 10-week stress management program (Coates et al., 1989). Whether or not the spread of the infection or rate of disease progression was influenced by these interventions, remains to be investigated.

Part II

Discussion of Associations between Psychosocial Factors, Immunological Parameters and HIV Disease Progression

In the first study (chapter 6), it was found that distraction from problems in general was associated with less decline in CD4 cells, less appearance of syncytium-inducing HIV variants, less progression to immunologically-defined AIDS, but not with progression to clinical AIDS. In the second study (chapter 7) we found that using an active confrontational strategy to cope with HIV infection was associated with decreased clinical progression, but not with CD4 cell counts, during one year. In the third study, psychosocial intervention did not alter immunological parameters, although we found an association between within-subjects changes in distress and changes in CD4 counts.

Coping and progression of HIV infection. The results described in chapter 6 and 7 appear contradictory, because distraction coping seems opposite to active confrontational coping. However, before discussing these findings further, data can be presented showing the correlations between the two coping styles, and other psychosocial variables. These data have been collected on part of the subjects that participated in the correlational study presented in chapter 7. The Pearson correlation coefficients are presented in Table 9.1. As can be seen, the correlation between the coping factor active confrontation and distraction is not significant.

Table 9.1. Pearson correlation coefficients between HCL and UCL factor scores, and other psychosocial variables (n=37).

	Distraction	Fighting Spirit
Active confrontation	0.06	0.05
Optimistic attitude	-0.43*	0.67*
General health quest.	0.31*f*	-0.36*
Life events	-0.07	0.21
Social support	-0.06	-0.09

f : $p < 0.10$ *: $p < 0.05$

In line with the results presented in chapter 6, the direction of the association between distraction and log CD4 counts at one year follow-up was positive, while adjusting for baseline log CD4 counts (data were obtained from the subjects participating in the study presented in chapter 7; $r=0.24$, $p<0.18$; n=36). Taken together, these results show that using distraction as a coping strategy, indeed may not be 'bad for your CD4 counts'.

Using distraction from problems in general may have a different effect in different stages of the disease. In the study done at the Municipal Health Center (chapter 6), predominantly asymptomatic subjects participated, whereas a good number of subjects in the other study (chapter 7) were symptomatic (47%). It may be that using the coping style distraction is beneficial in early stages, and may in fact provide the necessary optimism to 'go on'. However, this hypothesis is not supported by the data, as shown by the negative correlation between distraction coping and optimistic attitude presented in Table 9.1. Unfortunately, changes in coping over time were not assessed in the study presented in chapter 6. Another hypothesis is that, from a cognitive viewpoint, the subjects with low distraction will focus on their deficits and problems, leading to feelings of distress and anxiety, which in turn may have a negative effect on immunological parameters (Antoni et al., 1990; Fricchione et al., 1992; Burack et al., 1993). However, this hypothesis is also not supported by the data, because we found a trend for a positive correlation between distraction and psychiatric symptoms (Table 9.1). Finally, one could speculate that subjects who are overwhelmed by problems have higher GHQ scores and need to distract themselves from these problems in order to be able to cope with it. To investigate this further, it is important that future studies investigate how coping styles such as distraction relate to other psychosocial measures such as stressful life events, psychiatric symptoms, and biomedical parameters over time during different stages of infection.

Taken together, distraction coping and active confrontational coping do not seem to be mutually exclusive; in fact, subjects may use both coping styles at the same time. Although highly speculative, using distraction as a coping strategy may serve as a way of regulating tension levels, leading to less tension-induced changes in the central nervous system with possible concomitant neuroendocrine and immunological changes. Moreover, as mentioned earlier, subjects showing HIV specific active confrontational coping may show more vigilance to physical symptoms and/or have better compliance with medical treatments. Thus, distraction coping as well as active confrontational coping may have beneficial effects on HIV disease progression, although more studies are needed to confirm the findings obtained in chapter 6 and 7, and to investigate how distraction and active confrontational coping relate to each other. These studies should also investigate the behavioral and psychoneuroimmunological mechanisms by which these associations may be mediated.

Immunological effects of psychosocial interventions (chapter 8). No associations were found between participation in a psychosocial intervention program and changes in the decline of CD4 counts or T cell responses to anti-CD3 mAbs. However, this study has several limitations. First the design precluded establishing causal effects. Because of the fixed three-month intervals for determining immunological parameters in the natural history study from which subjects were drawn, it was impossible to synchronize the beginning and end of the 15-week intervention with these immunologic measurement points. Thus, it was not possible to use subjects assigned to the waiting-list group as an immunological control group (chapter 4), nor to determine immunological changes directly after the intervention. Thus, only longer term changes in the rate of decline following the intervention could be examined.

Secondly, the immunological measurements obtained may not have been sensitive enough for detecting immunological changes after psychosocial interventions. It may be that other functional immunological tests such as natural killer cell activity (NKCA) are more sensitive than responses to anti-CD3 mAbs to possible neuroendocrine or autonomic changes following psychosocial intervention. Psychosocial interventions have been shown to increase NKCA in HIV-infected individuals (Antoni et al., 1991), as well as in patients with melanoma (Fawzy et al., 1990). However, the associations between antigen specific T cell responses and NKCA and progression of HIV infection are not well established (Sirianni et al., 1990).

Thirdly, another reason for not detecting a change in the rate of immunological decline may be that the intervention did not show a significant effect on coping styles. Because two studies by our group (chapter 6 and 7), as well as others (Goodkin et al., submitted; Solano et al., 1993; Ironson, 1994), found that coping strategies were associated with (markers of) progression of HIV infection, it may be that significant changes in coping styles after intervention are necessary in order to obtain significant immunological effects. This can be illustrated by a study of Antoni et al. (1991), who found significant positive changes in coping styles together with significant increases in CD4 cells after a cognitive-behavioral stress management intervention. Thus, it may be important for future

interventions to more directly aim at altering coping strategies, as is described by Folkman et al. (1991) in their 'coping effectiveness training'.

When investigating the effects of psychosocial interventions on immunological parameters and HIV disease progression in future studies, several factors have to be taken into account. Randomization between intervention and a no-treatment or minimal treatment control group is necessary to prevent self selection. The effects of biomedical parameters such as age, known duration of HIV infection, baseline immune status, disease stage, use of medication, and possible genetic factors on disease progression need to be controlled for, either by stratification procedures or post-hoc analyses. The effects of the intervention on compliance with medical treatment, and health behaviors need to be investigated to unravel the effects of these factors on health outcomes. Long-term follow-up is needed to determine clinical effects. Sensitive immunological parameters may be needed for picking-up small effects of the intervention, such as T cell responses to anti-CD3 mAbs or specific antigens such as candida (Teeuwsen et al., 1990). These parameters should be investigated at multiple time points to enhance reliability. When these issues are taken care off, psychosocial interventions may be demonstrated to be effective, not only in reducing distress levels, but also in reducing disease progression, as was shown previously in patients with metastatic breast cancer (Spiegel et al., 1989) and malignant melanoma (Fawzy et al., 1993).

Representativeness of the Samples

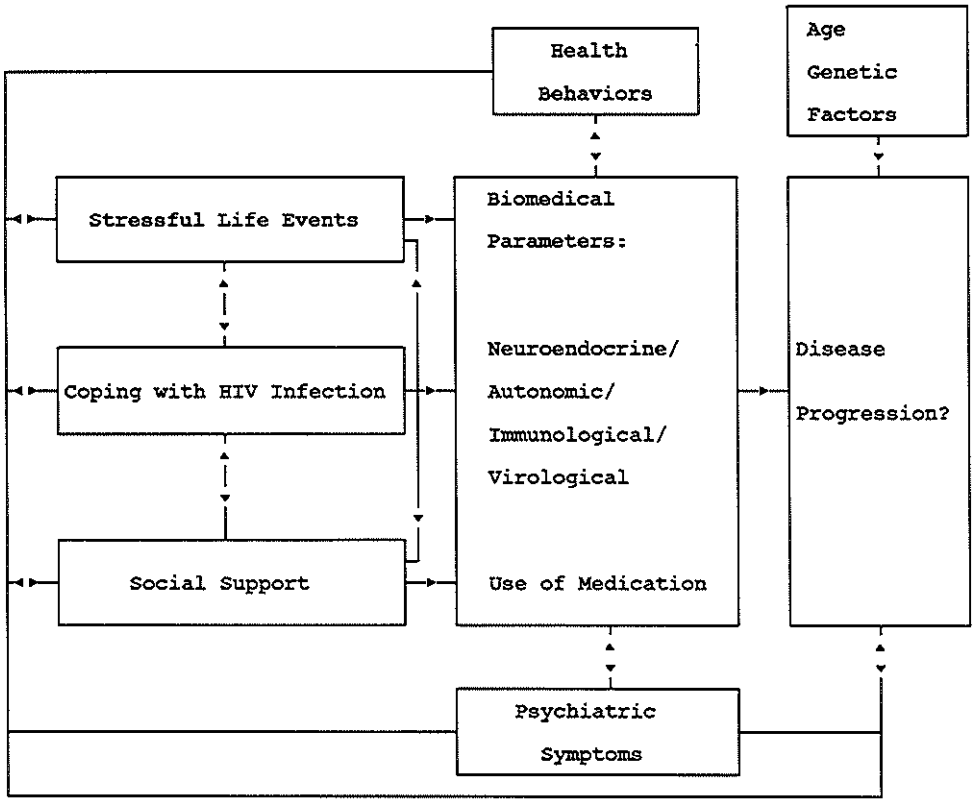
The studies described herein used white gay men in early stages of HIV infection. It is unknown whether the results are generalizable to HIV patients with AIDS, hemophilia, or who are heterosexual, female, non-white or intravenous drug users. It is likely that some findings are generalizable while others are not. For instance the negative effects of low social support and stressful life events on distress measures may be generalizable to other populations, as shown in a study with patients with hemophilia (Dew et al., 1990). However, psychoneuroimmunological findings may be more difficult to compare across different populations or different stages of HIV infection. For instance, having AIDS-defining infections or cancers, intravenous drug use, frequent blood transfusions in hemophiliacs, and hormonal fluctuations in women may all have their specific psychoneuroimmunological effects (chapter 5). Thus, in order to unravel possible psychoneuroimmunological relationships, studies should restrict themselves to relatively homogeneous populations.

Theoretical Considerations

The studies presented here referred to the 'stress-moderator' model (chapter 3) as proposed by Blaney and colleagues (1991) or to the 'stress-coping-social support' model (chapter 7; Goodkin et al., 1994). The difference between the first and the second model is that in the

first model coping and social support modify the effect of stressful life events on distress or disease progression, respectively, whereas in the second model direct effects as well as interaction effects of all the components of the model are hypothesized. Using the components of this model was useful in predicting distress, and, to some degree, in predicting clinical progression. Below, we present a drawing of the 'stress-coping-social support' model (Figure 9.1). The studies presented in this thesis did not explicitly aim at testing this model. The model was used to select relevant psychological dimensions and to guide the statistical analyses.

Figure 9.1. Putative conceptual model for the prediction of distress and disease progression in HIV infection.



The study presented in chapter 3 confirmed the relevance of the components of the model in predicting the level of psychiatric symptoms. However, with respect to disease progression, only the coping style factor was a significant predictor (chapter 7). It may be that stressful life events and social support are indirectly related to disease progression, through correlations with coping. However, the zero order correlations between life events and social support and active confrontational coping, respectively, were non-significant (results not shown). Thus, the relevance of this model in predicting HIV disease progression needs to be investigated further. The conceptual model presented in figure 9.1 is a working model, and is not complete, and other factors may be important in determining disease progression. In testing this conceptual model, several qualitative aspects of different model components have to be taken into account. These include the intensity, chronicity, controllability, and predictability of stressors (Steptoe, 1991), as well as differences between situational vs. general measures of coping (Lazarus, 1993) and

social support (Green, 1993). Finally, there may be changes in the relative importance of the ingredients of the model over time and during different stages of HIV infection.

A similar model is proposed by Steptoe, and is called the 'psychobiological stress response'. The psychobiological stress response is a loosely coupled system involving adjustments in affective, cognitive and behavioral levels, together with associated changes in neuroendocrine, autonomic and immune function (Steptoe, 1990; Steptoe, 1991). The psychobiological response is determined by an interaction between 'resources' and 'demands'. Resources are the internal as well as external powers that individuals have at their disposal to deal with demands (stressors). In the 'stress-coping-social support' model, coping and social support are viewed as resources. However, resources as defined by Steptoe (1991) also include prior experiences, and personality characteristics (which may include coping style).

Building a theoretical model for the influence of psychosocial factors on HIV disease progression is hampered because only a few studies have been done, and these studies yielded contradictory findings so far (chapter 5). However, the working model described by Goodkin et al. (1994) seems promising in describing associations between psychosocial factors, immunological parameters and disease progression.

Finally, only through experimental studies in which components of the model are manipulated through behavioral interventions can the causality underlying these associations be established.

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Summary

Infection with Human Immunodeficiency Virus (HIV) is associated with a graduate decline in the function of the immune system. After 8-10 years, 50 to 75% of HIV-infected gay men develop life-threatening infections, cancers, or AIDS-dementia, resulting in a diagnosis of Acquired Immunodeficiency Syndrome (AIDS). No definite medical cure is available that prevents progression of HIV infection. Therefore, living with an HIV-positive serostatus puts a heavy burden on one's coping capabilities and causes HIV-infected subjects to suffer from symptoms of depression and anxiety, at least periodically.

The length of the period until the development of AIDS varies considerably among individuals. It has been suggested that some of the variation is due to psychosocial factors, including stressful life events, psychological distress, ways of coping with HIV infection, and the quality of the social network. Whether this is so, however, is still a matter of debate given the contradictory results of studies in this area. The lack of consensus may be due in part to the failure of most studies to employ a theoretical rationale which interrelates the broad set of psychosocial and psychiatric measures assessed and drives the statistical hypotheses.

We studied the associations between psychosocial factors, immunological parameters and disease progression, using the 'stress-coping-social support' model. Moreover, we studied the immunological effects of psychosocial interventions. Identifying possible psychosocial 'risk factors' for disease progression is of clinical relevance. In the event that such factors can be found, psychosocial interventions may slow down disease progression and enhance the effects of medical treatments.

The thesis is divided into two parts. Part I focuses on the detection of psychosocial factors that predict the occurrence of psychiatric symptoms. Part II focuses on the detection of psychosocial factors that predict rate of decline of immunological parameters and HIV disease progression in homosexual men in early stages of infection.

Part I begins with an overview of the psychosocial consequences of HIV infection and the implications of this knowledge for psychotherapy (chapter 2). We conclude from the literature that therapists need to take several factors into account when providing psychosocial counseling. These include the subject's stage of infection, social circumstances, personality characteristics, and cognitive functioning. Providing group support and education can help in reducing distress and increasing social support, as was shown in several intervention studies using different types of short-term group interventions.

In chapter three we described the occurrence of psychiatric illness during one year in 57 HIV-infected asymptomatic and early symptomatic homosexual men. At baseline, 14 subjects (26%) were defined as having a psychiatric diagnosis according to the Present State Examination. We found that the most significant predictor for psychiatric symptom-scores during follow-up was the symptom-score at baseline. Stressful life events which were not related to the somatic course of the disease, and social support showed significant associations with psychiatric symptom-scores at follow-up. These associations

were significant even after adjusting for psychiatric symptom-scores and the presence of HIV-related symptoms at baseline. We adjusted for the presence of HIV-related symptoms as these were associated with distress in previous studies. Coping styles were not directly related to the occurrence of psychiatric symptoms during follow-up, after adjusting for symptom-scores at baseline. However, subjects who used active confrontation as a way to cope with HIV infection showed higher levels of psychiatric symptoms in relation to the experience of stressful life events, whereas having an optimistic attitude was associated with lower levels, though these moderator effects were only evident for the mean GHQ scores for active confrontational coping, and the 3-month follow-up GHQ scores for optimism. One may conclude from this study that it is important for psychosocial interventions to focus on improving the quality of the social network, and to teach individuals how to deal with stressors which are not necessarily related to their disease.

In the study presented in chapter four, we applied a randomized experimental design to investigate the effects of a cognitive-behavioral group psychotherapy (CBT) and an experiential group psychotherapy (ET) program for 39 asymptomatic HIV-infected homosexual men. Both therapies consisted of 17 sessions over a 15-week period. The major finding of this study was that psychosocial intervention, independent of the therapeutic orientation, decreased distress significantly, as compared to a waiting-list control group (WCG). There were no significant changes in the intervention groups as compared to the WCG in coping styles, social support, and emotional expression. Finally, CBT and ET did not differ in their effects on psychological distress or on the other psychosocial variables measured in this study. We hypothesized that the equality of both interventions was due to non-specific therapeutic factors including group support and attention from therapists.

Part II begins with a review of psychoneuroimmunological studies in HIV-infected individuals (chapter 5). We concluded from the results of studies conducted until now that there is not conclusive evidence for the impact of psychosocial parameters on the course of HIV infection.

Chapter six described the associations between coping styles and progression of HIV infection over a seven year period in 181 homosexual men who were asymptomatic at the beginning of the study. Using a coping style characterized by distraction from problems in general was found to be associated with a lower rate of decline in CD4 cells, less progression to immunologically defined AIDS (dropping under 200 CD4 cells/mm^3) and less appearance of syncytium-inducing HIV variants. Distraction coping was not related to the development of AIDS-defining clinical symptoms. Coping characterized by having a 'fighting spirit' was not related to these outcome measures.

In the study presented in chapter seven, we investigated the associations between stressful life events, psychiatric symptoms, coping, and social support, and HIV disease progression one year later in 51 HIV-infected asymptomatic and early symptomatic homosexual men. These psychosocial variables were selected on the basis of a 'stress-coping-social support' model. We found no associations between the psychosocial parameters and CD4 counts. Active confrontation with HIV infection as a coping strategy

was found to be predictive of less disease progression at one year follow-up, after taking into account baseline biomedical and behavioral variables. This association may be mediated by greater compliance with medical treatments in men who cope actively or by psychoneuroimmunological mechanisms. However, these results need to be interpreted cautiously because of the small number of subjects participating in this study.

Finally, we determined (chapter 8) changes in the rate of decline of immunological parameters before and after the psychosocial group interventions described above in chapter 4. No significant changes were found in the slopes of CD4 cell counts before and after the intervention, but there was a significant positive change in the rate of decline of T cell responses. However, these changes in T cell responses were also found in a similar group of 139 HIV-infected homosexual men from the Amsterdam cohort, who were not participating in one of the interventions. There were no differences in the rate of decline of CD4 cells or T cell responses between the CBT and ET condition. Finally, those subjects who showed larger decreases in distress over the period from the onset of either intervention program to 6 months after the intervention showed less decline in CD4 cell counts over the 2-year period after the start of the intervention. We concluded that the psychosocial intervention programs tested herein were not associated with changes in CD4 cell decline or T cell responses and that increases in CD4 cell counts were related to decreases in distress.

In chapter nine the findings of all studies are discussed. The results in chapter six and seven seemed to be contradictory at first glance: distraction from problems in general was associated with less decline in CD4 cells, and less occurrence of syncytium-inducing HIV variants (chapter 6), whereas using active confrontation with HIV infection as a coping style was associated with less clinical progression (chapter 7). However, the association between both coping styles was not significant. This may mean that both coping scales do not measure two ends of the continuum active-passive coping and that they seem to measure two different psychological constructs. We concluded that more research is needed to investigate how coping styles such as distraction relate to other psychosocial measures such as stressful life events, psychiatric symptoms, and biomedical parameters over time during different stages of infection. Finally, a theoretical working model --the 'stress-coping-social support' model-- is described.

In the studies described above investigating the associations between psychosocial factors and immunological parameters or clinical progression, the designs that were used did not allow causal relationships to be examined. Future studies can do this by investigating the biomedical effects of psychosocial interventions which aim at optimizing the components of the 'stress-coping-social support' model. However, even if no effect of psychosocial interventions on clinical progression can be demonstrated, providing psychosocial counseling services for HIV-infected individuals remains of great importance, given the demonstrated benefits it has for psychological functioning.

Samenvatting

Weten drager te zijn van het Humaan Immunodeficiëntie Virus (HIV) betekent leren omgaan met een levensbedreigende infectie. Het HIV-virus veroorzaakt een verstoring van de werking van het immuunsysteem en dit kan op den duur leiden tot het 'Acquired Immunodeficiency Syndrome' (AIDS), gekenmerkt door o.a. levensbedreigende infecties, bepaalde soorten kanker zoals Kaposi's sarcoom of dementie. Gemiddeld duurt het 8-10 jaar voordat iemand die drager is van het HIV-virus AIDS krijgt. Nadat eenmaal de diagnose AIDS is gesteld is de levensverwachting ongeveer 1-2 jaar. Er is vooruitgang geboekt in het bestrijden van de gevolgen van de HIV-infectie maar er bestaat nog geen afdoende geneesmiddel.

Sommige mensen leren om te gaan met de gevolgen van de HIV-infectie, terwijl anderen dit niet lukt en last hebben van gevoelens van angst en somberheid. Welke factoren ertoe bijdragen dat de één zich psychisch redelijk voelt en de ander niet was het onderwerp van het eerste deel van dit proefschrift.

De tijdsduur tot aan het manifest worden van AIDS is per persoon verschillend. Het is mogelijk dat psychosociale factoren een deel van deze individuele variatie verklaren. Om dat te onderzoeken zijn de studies verricht die in het tweede deel van dit proefschrift staan beschreven. De psychosociale factoren waar het in deze onderzoeken om gaat zijn bijvoorbeeld het meemaken van stressvolle gebeurtenissen, het hebben van psychische klachten, de manier van omgaan met de HIV-infectie en de kwaliteit van sociale relaties. Eerdere onderzoeken op dit gebied leverden niet eenduidige resultaten op. Dit komt voor een deel omdat er geen algemeen geaccepteerd theoretisch kader is wat het onderzoek stuurt.

Wij hebben het verband tussen psychosociale factoren, immunologische parameters en ziekteprogressie onderzocht bij HIV-geïnfecteerde homosexuele mannen. Voor het kiezen van de te bestuderen psychosociale variabelen en de statistische analyses hebben we gebruik gemaakt van het 'stress-coping-sociale steun' model. Daarnaast zijn de effecten van psychosociale interventies op immunologische parameters onderzocht.

Het uiteindelijke doel van dit soort onderzoek is om 'psychosociale risicofactoren' voor ziekteprogressie te vinden. Wanneer zulke 'risicofactoren' worden gevonden, kan met behulp van psychosociale interventies geprobeerd worden om het beloop van de ziekte te vertragen en het effect van geneesmiddelen te ondersteunen.

Deel één van het proefschrift begint met een overzicht van de psychosociale gevolgen van de HIV-infectie en de implicaties voor psychotherapie (hoofdstuk 2). Uit eerdere studies bleek dat het voor psychotherapeuten belangrijk is rekening te houden met het stadium van de infectie, de sociale omstandigheden, persoonlijkheidskenmerken, en cognitief functioneren. Verschillende studies hebben uitgewezen dat kortdurende individuele of groepsbegeleiding kan helpen in het verminderen van psychische klachten en het verbeteren van de kwaliteit van het sociale netwerk.

In hoofdstuk 3 wordt het voorkomen van psychiatrische symptomen beschreven bij 57 HIV-geïnfecteerde homosexuele mannen, die bij de start van het onderzoek geen of

slechts lichte lichamelijke symptomen van de HIV-infectie hadden. Deze mannen zijn gedurende een jaar gevolgd met betrekking tot het optreden van psychiatrische symptomen, coping-stijlen, sociale steun en stressvolle gebeurtenissen. Bij de start van de studie hadden 14 mannen (26%) een psychiatrische diagnose volgens de Present State Examination. De meest significante voorspeller van het optreden van psychiatrische symptomen tijdens de follow-up periode was het aantal reeds aanwezige symptomen bij de start van de studie. Stressvolle gebeurtenissen, welke geen verband hadden met het lichamelijk beloop van de HIV-infectie (zoals bijvoorbeeld het hebben van problemen op het werk) en de mate van ervaren sociale steun, voorspelden significant het aantal psychiatrische symptomen tijdens de follow-up periode. Er was geen verband tussen het optreden van HIV-gerelateerde aandoeningen en het aantal psychiatrische symptomen. Er was ook geen direct verband tussen coping-stijl en het aantal psychiatrische symptomen tijdens follow-up, na correctie voor het aantal symptomen bij de start van het onderzoek. Mannen die geneigd waren de problemen rondom de HIV-infectie actief te benaderen, of die een minder optimistische houding hadden, rapporteerden meer psychiatrische symptomen wanneer zij stressvolle gebeurtenissen meemaakten. Het contra-intuïtieve verband tussen actief coping en meer psychiatrische symptomen in relatie tot het meemaken van stressvolle gebeurtenissen wordt mogelijk veroorzaakt doordat mannen met een actieve coping-stijl minder geneigd zijn om hun problemen te ontkennen en er dus mogelijk ook meer last van hebben. Deze resultaten wijzen erop dat psychosociale interventies die gericht zijn op het verbeteren van het sociale netwerk en het leren omgaan met stressoren die niet direct te maken hebben met het lichamelijke beloop van de HIV-infectie, mogelijk effectief zijn in het verminderen van het aantal psychiatrische symptomen.

In hoofdstuk 4 is een gerandomiseerd onderzoek beschreven naar de effectiviteit van cognitieve-gedragstherapie (CGT) en ervaringsgerichte therapie (ET). Aan dit onderzoek deden 39 asymptomatische HIV-geïnfecteerde homosexuele mannen mee. Beide therapieën bestonden uit 17 groepsbijeenkomsten van ieder 2,5 uur gedurende 15 weken. De belangrijkste uitkomst van deze studie was dat psychosociale begeleiding, onafhankelijk van de therapeutische richting, de mate van psychische klachten deed verminderen in vergelijking met een wachtlijst-controlegroep (WCG). Er waren geen significante veranderingen in coping-stijlen, sociale steun en emotionele expressie na afloop van beide vormen van begeleiding in vergelijking met de WCG. CGT en ET verschilden niet in hun effecten op de gemeten psychosociale variabelen. Onze verklaring voor het ontbreken van verschillen tussen beide vormen van psychosociale interventie is dat aspecifieke factoren, zoals groepssteun en aandacht van de therapeuten, een belangrijke bijdrage hebben geleverd aan het tot stand komen van het effect.

Deel twee begint met een overzicht van onderzoeken naar het verband tussen psychosociale factoren en het beloop van de HIV-infectie (hoofdstuk 5). Tot nu toe zijn tegenstrijdige resultaten gevonden. Vergelijking tussen studies wordt bemoeilijkt door verschillen in onderzoeksmethoden. Deze verschillen worden mede veroorzaakt doordat er geen geaccepteerd theoretisch kader is dat het onderzoek stuurt.

In dit proefschrift werden een drietal studies beschreven naar het verband tussen psychosociale factoren en het beloop van de HIV-infectie. In één studie werden de verbanden onderzocht tussen coping-stijlen en progressie van de HIV-infectie gedurende zeven jaar (hoofdstuk 6). Dit onderzoek is verricht bij 181 homosexuele mannen, die asymptomatisch waren bij het begin van de studie. We vonden dat het afleiding zoeken in het geval van problemen in het algemeen een geringere daling van het aantal CD4-cellen voorspelde, het minder vaak optreden van een daling tot onder de 200 CD4-cellen/mm^3 en het minder optreden van syncytium-inducerende HIV-varianten. Afleiding zoeken was niet gerelateerd aan het optreden van ziektebeelden die passen bij de diagnose AIDS. Het hebben van een 'fighting spirit' kon het beloop van de HIV-infectie niet voorspellen.

In de tweede studie zijn de verbanden onderzocht tussen het meemaken van stressvolle gebeurtenissen, psychiatrische symptomen, coping, en sociale steun en progressie van de HIV-infectie (hoofdstuk 7). Deze factoren zijn gekozen op basis van het 'stress-coping-sociale steun' model. Een groep van 51 HIV-geïnfecteerde homosexuele mannen, die bij de start van het onderzoek geen of slechts lichte lichamelijke symptomen van de HIV-infectie hadden, werd gedurende één jaar gevolgd. Er zijn geen verbanden gevonden tussen de gemeten psychosociale parameters en het aantal CD4-cellen. Wel werd gevonden dat het actief benaderen van problemen rondom de HIV-infectie geassocieerd was met minder ziekteprogressie. Dit verband wordt mogelijk veroorzaakt door een betere therapietrouw met medische behandelingen bij mannen met een actieve coping-stijl of door psychoneuroimmunologische mechanismen. De resultaten van deze studie dienen echter met voorzichtigheid te worden geïnterpreteerd, gezien het kleine aantal deelnemers.

Ten slotte is onderzocht in hoeverre de psychosociale interventies die beschreven zijn in hoofdstuk 4 het beloop van het aantal CD4-cellen en de delingsactiviteit van T-cellen na stimulatie met anti-CD3 monoclonale antilichamen konden beïnvloeden (hoofdstuk 8). Er werden geen significante veranderingen gevonden in de mate van daling van het aantal CD4-cellen na afloop van de interventies. De daling van de T-cel testwaarden was weliswaar minder na afloop van de begeleiding, maar dit was ook het geval in een groep van 139 vergelijkbare HIV-geïnfecteerde mannen uit het Amsterdamse cohort die niet aan de begeleiding hadden meegedaan. Er waren geen verschillen in het beloop van de immunologische parameters tussen de CGT en ET. Wel bleek dat mannen die minder psychische klachten rapporteerden 9 maanden na de start van de begeleiding (zowel CGT als ET) een geringere daling van het aantal CD4-cellen hadden tot twee jaar na de start van het programma. Het 'kip en ei' probleem maakt de interpretatie van dit verband echter moeilijk. De conclusies uit dit onderzoek waren dat de onderzochte vormen van psychosociale begeleiding niet geassocieerd waren met veranderingen in de gemeten immunologische waarden, maar dat veranderingen in het aantal CD4-cellen samenhingen met veranderingen in psychische klachten.

In hoofdstuk 9 worden de resultaten van de verschillende studies besproken. De resultaten beschreven in hoofdstuk 6 en 7 lijken op het eerste gezicht tegenstrijdig: het afleiding zoeken in het geval van problemen in het algemeen voorspelde een geringere daling van het aantal CD4-cellen en het minder optreden van syncytium-inducerende HIV-varianten (hoofdstuk 6), terwijl het actief benaderen van problemen rondom de HIV-

infectie geassocieerd was met minder ziekteprogressie (hoofdstuk 7). Er bleek echter uit nader onderzoek dat beide vormen van coping niet twee uitersten van de glijdende schaal actief-passief coping vertegenwoordigden. Beide coping-schalen meten dus waarschijnlijk verschillende soorten coping-stijlen. Meer onderzoek is echter nodig om het precieze verband tussen coping-stijl en ziekteprogressie vast te stellen. Daarbij is het van belang dat eveneens onderzocht wordt wat het verband is tussen coping en andere psychosociale factoren zoals stressvolle gebeurtenissen, psychiatrische symptomen en biomedische parameters door de tijd heen. Tenslotte werd ingegaan op theoretische aspecten en werd het 'stress-coping-sociale steun' model toegelicht.

In de bovengenoemde studies waarin de verbanden tussen psychosociale factoren en immunologische en klinische parameters werden onderzocht konden oorzakelijke verbanden niet worden getoetst. In toekomstig onderzoek kan dit gebeuren door de effecten van psychosociale begeleiding op de progressie van HIV-infectie te onderzoeken. Een dergelijk onderzoek is in 1994 gestart. Maar ook wanneer zou blijken dat psychosociale begeleiding geen effect heeft op het lichamelijk beloop van de ziekte, dan blijft een goede opvang en begeleiding voor mensen met HIV-infectie toch gewenst.

Dankwoord

Als eerste wil ik professor Marco de Vries bedanken, die aan de wieg stond van dit onderzoek. Zijn creatieve ideeën bij het opzetten van het onderzoek, het scheppen van de mogelijkheden om het onderzoek uit te voeren en de inspirerende en steunende begeleiding zijn voor mij van grote waarde geweest. Onze samenwerking is voor mij een genoegen. Professor Paul Emmelkamp ben ik erkentelijk voor zijn kritische adviezen en de efficiënte en plezierige begeleiding. Ondanks de geografische afstand kon ik gemakkelijk bij hem terecht. Dr. Frans van den Boom, dr. Frits van Griensven, drs. Peter van Rooijen en dr. Theo Sandfort waren behulpzaam bij de opzet van het interventie-onderzoek. Zonder hun kennis van het psychosociale AIDS-onderzoek, enthousiasme, steun en geloof in de uitvoerbaarheid was het mij niet gelukt om het onderzoek op te zetten. Mijn dank gaat ook uit naar mw. Nel Albrecht-van Lent, drs. René Keet, Ir. Paul Veugelers, drs. Jan Willem Mulder en de andere medewerkers van de AIDS-afdeling van de GG&GD te Amsterdam voor hun inzet bij het uitvoeren van het interventie-onderzoek. Veel van de HIV-geïnfecteerde deelnemers aan het onderzoek hebben baat gehad bij de psychosociale begeleiding en dat is mede te danken aan de psychotherapeuten die de groepen hebben begeleid: Jan Andreae, Harm Siemens, David Stein en Rob Teunissen.

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Bert Garssen en Adriaan Visser hebben vele nuttige commentaren gegeven op het

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Vanzelfsprekend gaat mijn erkentelijkheid uit naar de leden van de beoordelingscommissie: prof.dr. R.E. Ballieux, prof.dr. A.D.M.E. Osterhaus, prof.dr. J. Passchier en prof.dr. L. Pepplinkhuizen.

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Rotterdam, juli 1994

Curriculum Vitae

Niels Mulder werd geboren op 20 april 1959 te Rotterdam. Hij behaalde in 1977 het diploma Gymnasium ß aan het St. Maartenscollege te Haren (Groningen). In 1986 werd het artsexamen behaald aan de Rijksuniversiteit Groningen. Naast de geneeskunde studie volgde hij een antroposofische artsencursus te Arlesheim, Zwitserland en enkele stages in de antroposofische geneeskunde. De geneeskunde studie werd afgesloten met een (deel)onderzoek op de afdeling klinische immunologie van het Academisch Ziekenhuis Groningen (AZG) (Prof.dr. T.H. The). Na een half jaar als arts-assistent op de afdeling interne geneeskunde van het AZG te hebben gewerkt kwam hij in dienst als arts-onderzoeker op het Nederlands Kanker Instituut te Amsterdam, afd. tumorbiologie. Daar verrichtte hij onderzoek naar de klinische toepassingen van radioactief gelabelde monoclonale antilichamen voor het opsporen van tumor-metastasen (dr.Ir. J. Hilkens, dr. P.F. Bruning). In 1989 maakte hij de overstap naar het Helen Dowling Instituut voor Biopsychosociale Geneeskunde te Rotterdam. Hier startte hij, onder leiding van prof.dr. M.J. de Vries, met het onderzoek wat geleid heeft tot dit proefschrift. Het onderzoek werd gefinancierd door het Ministerie van Welzijn, Volksgezondheid en Cultuur (projectnummer 90063A) en het Helen Dowling Instituut. Vanaf 1 oktober 1994 gaat hij in opleiding tot psychiater aan het Academisch Ziekenhuis Dijkzigt te Rotterdam.

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