Effects of cognitive behavioral stress management on HIV-1 RNA, CD4 cell counts and psychosocial parameters of HIV-infected persons

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Objective: To determine the effects of cognitive–behavioral stress management (CBSM) training on clinical and psychosocial markers in HIV-infected persons.

Methods: A randomized controlled trial in four HIV outpatient clinics of 104 HIV-infected persons taking combination antiretroviral therapy (cART), measuring HIV-1 surrogate markers, adherence to therapy and well-being 12 months after 12 group sessions of 2 h CBSM training.

Results: Intent-to-treat analyses showed no effects on HIV-1 surrogate markers in the CBSM group compared with the control group: HIV-1 RNA < 50 copies/ml in 81.1% [95% confidence interval (CI), 68.0–90.6] and 74.5% (95% CI, 60.4–85.7), respectively ($P = 0.34$), and mean CD4 cell change from baseline of 53.0 cells/μl (95% CI, 4.1–101.8) and 15.5 cells/μl (95% CI, −34.3 to 65.4), respectively ($P = 0.29$). Self-reported adherence to therapy did not differ between groups at baseline ($P = 0.53$) or at 12 month's post-intervention ($P = 0.47$). Significant benefits of CBSM over no intervention were observed in mean change of quality of life scores: physical health 2.9 (95% CI, 0.7–5.1) and −0.2 (95% CI, −2.1 to 1.8), respectively ($P = 0.05$); mental health 4.8 (95% CI, 1.8–7.3) and −0.5 (95% CI, −3.3 to 2.2) ($P = 0.02$); anxiety −2.1 (95% CI, −3.6 to −1.0) and 0.3 (95% CI, −0.7 to 1.4), respectively ($P = 0.002$); and depression −2.1 (95% CI, −3.2 to −0.9) and 0.02 (95% CI, −1.0 to 1.1), respectively ($P = 0.001$). Alleviation of depression and anxiety symptoms were most pronounced among participants with high psychological distress at baseline.

Conclusion: CBSM training of HIV-infected persons taking on cART does not improve clinical outcome but has lasting effects on quality of life and psychological well-being.

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Introduction

Morbidity and mortality outcomes among HIV-infected persons with access to combination antiretroviral therapy (cART) have dramatically improved but still remain substantial owing to therapeutic failure, late initiation of cART, interruption or refusal of cART, incomplete adherence, drug resistance, chronic hepatitis C and B viral infections, use of alcohol or illicit drugs, and toxicities of cART. In addition, psychosocial factors, including depression, depressive symptoms and stress [1,2], as well as psychological resources [3] and social support [4] have been shown to influence the course of HIV infection, probably through both physiological [5] processes and behavioral processes such as drug adherence [6] or delay in accepting initiation of cART [7]. In addition, an increased prevalence of suicidal behavior has been reported, especially in HIV-infected persons with psychiatric comorbidity [8].

The prevalence of psychiatric disorders and emotional distress in HIV-infected persons is high, with 30–50% screening positive for any psychiatric disorder [1,9,10], nearly twice the rate of major depression seen in noninfected individuals [11], and an increased prevalence of emotional distress [12].

Treatment of psychiatric morbidity and strengthening of psychosocial resources in HIV-infected persons may improve their well-being and delay the progression of HIV infection. Randomized controlled trials have suggested that cognitive–behavioral stress management (CBSM) can have beneficial effects on different aspects of psychological well-being and possibly on neuroendocrine and immunological parameters, which may influence the course of HIV infection [13–25]. However, the majority of CBSM trials were performed before the availability of cART.

This paper describes a multicenter randomized controlled trial of CBSM group training in HIV-infected persons taking cART to investigate the effect of such training on virological, immunological and psychological parameters over a 12-month study period.

Methods

Participants and study design

This randomized, open-label multicenter controlled trial compared the effects of standard medical care versus standard medical care plus CBSM group training (ClinicalTrials.gov Identifier: NCT00436085). Ethics committee approval was obtained and each participant gave written informed consent.

Recruitment began in December 2003 and ended in August 2004. All participants were recruited through routine biannual Swiss HIV Cohort Study (SHCS) visits at HIV outpatient clinics in Berne, Basel, St Gallen and Zurich, Switzerland. Invitation followed written instructions and included information leaflets for HIV-infected persons and their care providers about the background and design of the study. The SHCS comprised 6177 persons during the recruitment period, of whom approximately 4000 (65%) were seen at the participating German-speaking study sites.

Adults between 18 and 65 years of age were considered for inclusion if they had sufficient German-speaking abilities to participate in group therapy, had received cART within the 3 months prior to screening, had a CD4 lymphocyte count >100 cells/μl, and had no active opportunistic infection at baseline. Furthermore, participants were only included if they had not received formal psychotherapy within the previous 3 months, were neither intravenous drug users nor on stable methadone maintenance, and had no current major psychiatric disorder (bipolar affective disorder, psychotic disorders, major depression with melancholia) or diagnosis of antisocial and borderline personality disorders at baseline, as determined by standardized interview [26].

Randomization

Participants were stratified according to CD4 lymphocyte nadir (0–50, 51–200, >200 cells/μl) assuming that this was the most important surrogate for severity of current or previous HIV-related illness. Allocation sequences included randomly permuted block sizes of two and four and were generated using the computer program RANCODE V3.0 (IDV Datenanalyse und Versuchsplanung, Gauting, Germany). Individual assignment codes were properly concealed between black sheets, stored in sequentially numbered envelopes and opened in the presence of study participants. After randomization, participants received a set of questionnaires (see below), which were to be completed and sent back to the study nurses by the participants.

Data collection and outcome measures

Data on baseline and follow-up clinical and laboratory characteristics were extracted from the SHCS database. Psychological data were collected at regular SHCS cohort visits using standardized clinical research forms including the questionnaires described below.

Primary endpoints were changes of CD4 lymphocyte cell count and HIV-1 RNA from baseline to the follow-up at 12 months. Secondary outcome measures were scores on (i) the HIV Medical Outcome Study (MOS-HIV) questionnaire, which measures health-related quality of life with two self-report mental and physical health summary scores [27]; (ii) the Hospital Anxiety and

Depression Scale (HADS), which assesses levels of general anxiety and depression over the preceding 4 weeks based on self-report [28]; and (iii) the Simplified Medication Adherence Questionnaire (SMAQ), which contains six items to detect nonadherence (defined as answering yes to any qualitative question, more than two doses missed in the past week, or more than two days of total nonmedication in the last 3 months) [29]. All dependent variables were assessed at baseline and at 1, 6 and 12 months after termination of CBSM training in the intervention group.

Intervention

Standard medical care was provided by fellow physicians, who were supervised by staff physicians specializing in infectious diseases, at the HIV outpatient clinics of the participating SHCS centers. A visit lasted, on average, approximately 30 min; the enrolment visit was longer.

CBSM training consisted of 12 weekly group sessions lasting 2 h and provided during a 12 week period for each group. They were administered between December 2004 and August 2005 for all study groups. Sessions were moderated by one cognitive–behavioral psychotherapist (university degree and formal training in cognitive–behavioral training) and one postgraduate psychotherapy trainee (university degree and second year in cognitive–behavioral training). Group sizes ranged between four and 10 participants. The rationale of the intervention utilized a manual-based multicomponent approach, including HIV-relevant topics and psychotherapeutic techniques (Table 1).

With the exception of the first (introduction) and last (discussion) session, each session was dedicated to a particular topic (e.g. stress, depression, work, etc.). CBSM training groups started when a sufficient number of HIV-infected persons were randomized into the intervention arm; therefore, time intervals between randomization and treatment differed for participants in the intervention group.

Statistical analysis

The intention was to recruit a total of 100 HIV-infected persons in order to provide 90% power ($\alpha = 0.05$) to detect an effect size of $d = 0.6$, which is equivalent to a 30% change in CD4 cell count, a 15% change in the proportion of persons with HIV-1 RNA < 50 copies/ml, a change of 2.5 points in HADS subscale scores, or 6 points in MOS-HIV score. The actual sample size of the randomized sample (104) and the on-treatment sample (77) provided 92% and 83% power, respectively, to detect these effects. SPSS 11 statistical software (SPSS, Chicago, Illinois, USA) for Apple OS X was used for all statistical analyses. Analysis of variance or Pearson's χ^2 tests were used to examine demographic and clinical variables at baseline. Mann–Whitney U tests were performed to analyze treatment effects on the logarithm of HIV-1 RNA, and Pearson's χ^2 tests were used to analyze group differences in the number of persons with HIV-1 RNA > 50 copies/ml at each assessment. A time $\times$ intervention analysis of variance (for CD4 cell counts) and a time $\times$ intervention $\times$ scale multivariate analysis of variance (for MOS-HIV and HADS data) with subsequent time $\times$ intervention univariate analysis of variance for single scales was used to investigate differences between groups in terms of treatment effects. For significant results, within-group effect sizes were calculated using the Cohen d formula [30]. Mean differences between groups in changes from baseline were analyzed with univariate analysis of variance with difference contrasts.

All analyses were performed according to the principle of intention to treat, with last observations carried forward when follow-up data were missing.

Results

Trial profile

The inclusion criteria were met by 104 persons who also signed the informed consent and were randomized (Fig. 1). Twenty-three declined to participate after

Table 1. Overview of treatment modules included in the cognitive–behavioral stress management.

Technique	Description
Psycho-education	Each topic is described and discussed in terms of its relevance to HIV; participants also receive written material including summaries on recent scientific findings and 'to do' lists
Group dynamic exercises	Empathy, respect, trust and cohesion within the group are encouraged and practiced with short and defined ice-breaker, e.g., sharing personal information, and trust-building, e.g., establishment of group rules, exercises
Homework	Each topic is accompanied by homework, which encompasses either the assessment of problematic/helpful aspects or the transfer and practice of techniques learned to everyday life
Cognitive strategies	The objective is to identify and acknowledge cognitions as major determinants of feelings and behavior and, if necessary, to modify them; alternative self-instructions are then practiced in role-plays and real life
Progressive muscle relaxation (PMR)	The objective is to train participants to recognize muscular tension and to self-induce relaxation; in the first five sessions, PMR techniques are taught by the psychotherapist, whereas in the remaining sessions, participants act as PMR trainers for the group; participants also receive written and spoken (CD) PMR instructions

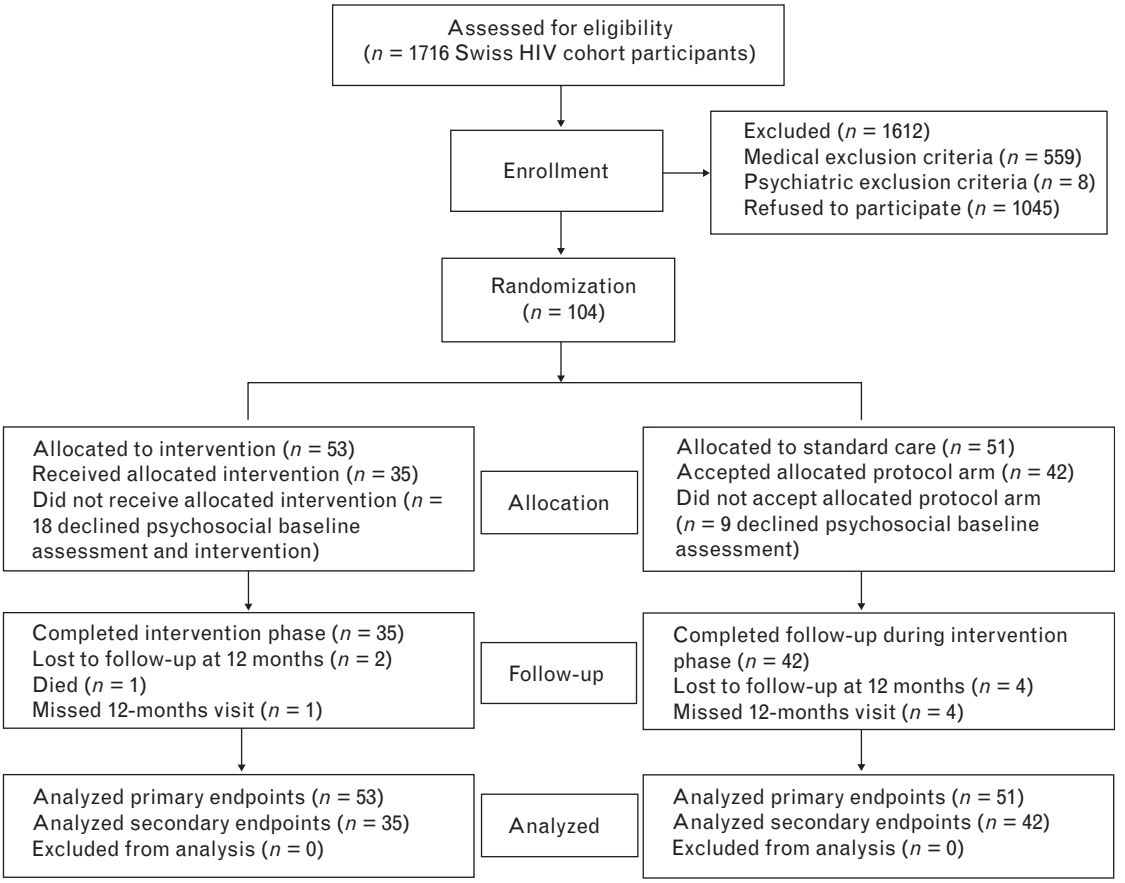

Fig. 1. Trial profile. The trial intervention was cognitive–behavioral stress management as described in the Methods. The primary endpoints were CD4 lymphocyte count and HIV-1 RNA; the secondary endpoints were psychosocial questionnaires.

randomization and did not return baseline psychometric questionnaires; the reasons given were 'no time' (15), 'no longer interested' (1), 'no longer need training' (2), and 'no reason' (5). Two sets of intent-to-treat analyses were run, with analysis of CD4 cell and HIV RNA data in all randomized participants and an on-treatment analysis of CD4 cell and HIV RNA as well-as psychometric data.

Baseline characteristics

No significant demographic, clinical, or laboratory differences were found between the intervention versus the control group at baseline (Table 2). Both groups had been treated with antiretroviral drugs for a median of approximately 7.4 years, of which a median of 6.6 years consisted of cART. The median since first HIV-1 RNA was measured below level of detection was 5.8 years. The mean baseline CD4 cell count was 503 cells/μl, and 76% of the participants had a baseline viral load < 50 copies/ml.

No statistical differences in psychosocial baseline measurements and psychiatric history were found between study groups (Table 2). A total of 30 (28.8%) participants had a history of at least one psychiatric disorder, while 19 (18.3%) had a current diagnosis of at least one psychiatric disorder. A comparison of available baseline characteristics between the 27 subjects refusing to participate after randomization and the 77 study completers indicated that the groups did not differ with regard to age, sex, education, mode of infection, previous AIDS diagnoses, baseline and nadir CD4 cell counts, baseline adherence to cART, and psychiatric diagnoses (data not shown). Nadir CD4 cell count did not have a significant influence on any of the reported results of primary endpoints (data not shown).

Adherence to intervention and effects of intervention on HIV infection

Mean attendance of CBSM sessions was 9.6 out of 12 sessions (range, 4–12) and did not differ between study sites.

No clinical progression of HIV infection was observed; one patient in the intervention arm died from pneumonia and sepsis. CBSM training had no effect on primary endpoints including CD4 cell count, viral load (Fig. 2) and adherence to cART at any time point of assessment or at study end (Table 3). Similar nonsignificant differences in results were obtained in the on-treatment analysis (data not shown). Intent-to-treat analyses showed that more participants in the CBSM arm were still taking cART at

Table 2. Baseline characteristics of study participants.

	Intervention (CBSM)	Control
Randomized [No. (%)]	53 (100)	51 (100)
Female	8 (15.1)	7 (13.7)
Median age [years (range)]	44.5 (25–64)	43.4 (25–63)
HIV acquisition [No. (%)]		
Homosexual	34 (64.2)	28 (54.9)
Heterosexual	10 (18.9)	13 (25.5)
Intravenous drug use	2 (3.8)	5 (9.8)
Other or unknown	7 (13.2)	5 (9.8)
Education [No. (%)][a]		
Mandatory school only	5 (9.4)	8 (15.7)
Finished apprenticeship	31 (58.5)	27 (52.9)
Higher education	15 (28.3)	14 (27.5)
Earn their living [No. (%)]		
Professional work	34 (64.2)	37 (72.5)
Insurances, excluding insurances for unemployment	19 (35.8)	12 (23.5)
Savings or other sources	0 (0)	2 (3.9)
Clinical characteristics		
Prior AIDS [No. (%)]	17 (32.1)	12 (23.5)
Baseline median CD4 cell count [cells/μl (range)]	400 (101–1541)	506 (168–1240)
Median nadir CD4 cell count [cells/μl (range)]	136.0 (1–663)	162.5 (3–508)
Baseline median HIV-1 RNA [copies/ml (range)]	5 (bld-73 400)	bld (bld-114 000)
Baseline HIV-1 RNA < 50 copies/ml [No. (%)]	42 (79.2)	37 (72.5)
Median peak HIV-1 RNA [copies/ml (range)]	120 361 (16–10 000 000)	118 870 (0–2 779 744)
Median time since first HIV-1 RNA < 50 copies/ml [years (range)]	5.84 (0.05–7.90)	5.71 (0.02–7.76)
Median time on ART [years (range)]	7.33 (0.01–13.08)	7.40 (0.20–12.07)
Median time on cART [years (range)]	6.49 (0.01–8.75)	6.69 (0.20–8.86)
Never initiated cART (No.)	1	0
Median Karnofsky score (range)	94.5 (70–100)	100 (70–100)
Psychiatric morbidity [No. (%)]		
Lifetime, all diagnoses[b]	15 (28.3)	15 (29.4)
Mental disorder owing to physical disease	0	1 (2.0)
Disorders resulting from psychoactive substance use	10 (18.9)	12 (23.5)
Affective disorders	12 (22.6)	10 (19.6)
Somatoform disorders	1 (1.9)	0
Current, all diagnoses[b]	10 (18.9)	9 (17.6)
Affective disorders	6 (11.3)	6 (11.8)
Phobic anxiety disorder	5 (9.4)	5 (9.8)
Somatoform disorder	1 (1.9)	0 (0)

CBSM, cognitive–behavioral stress management; ART, antiretroviral therapy; cART, combination antiretroviral therapy; bld, below limit of detection.
[a]Data not available for four participants.
[b]Multiple diagnoses possible.

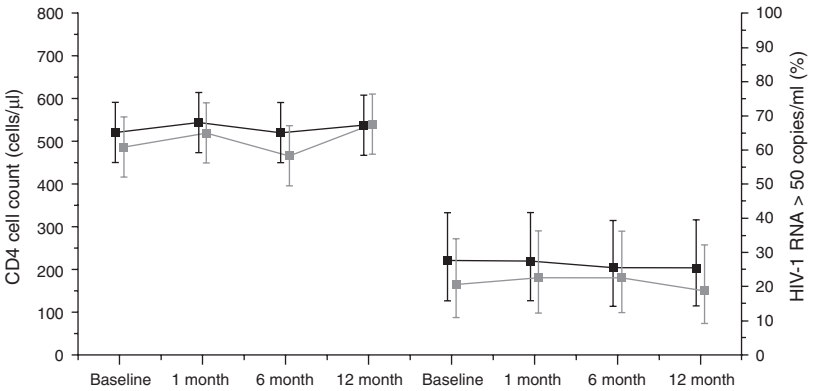

Fig. 2. Mean CD4 cell count and percentage with HIV-1 RNA > 50 copies/ml by treatment group. Cognitive–behavioural stress management (grey symbols) and controls (black symbols) with 95% confidence intervals. All study participants were taking combination antiretroviral therapy.

Table 3. Outcome at 12-month follow-up.

	Intervention (CBSM)	Control	*P* value
Randomized [No. (%)]	53 (100)	51 (100)	
HIV-1 RNA < 50 copies/ml [No. (%)]	43 (81.1)	38 (74.5)	0.34
CD4 cell change from baseline [cells/μl (95% CI)]	53.0 (4.1–101.8)	15.5 (−34.3–65.4)	0.29
ART [No. (%)]			
On therapy at 12 months	52 (98.1)	44 (86.3)	0.03
Ceased treatment during study	0 (0)	5 (9.8)	0.03
Interrupted treatment during study	3 (5.7)	3 (5.9)	0.64
Changed treatment during study	20 (37.7)	17 (33.3)	0.40
No information at 12 months	0 (0)	2 (3.9)	0.29
Died	1 (1.9)	0 (0)	0.51
Mean adherence to ART[a,b] (95% CI)			
Self-reported adherence at baseline	20 (57.1)	21 (50.0)	0.53
Self-reported adherence at 12 months	22 (62.9)	23 (54.8)	0.47
Mean MOS-HIV[b,c] (95% CI)			
Physical health summary score at baseline	48.0 (44.3–51.8)	53.0 (49.6–56.5)	0.06
Change from baseline at 12 months	2.9 (0.7–5.1)	−0.2 (−2.1–1.8)	0.05[d]
Mean differences between groups in changes from baseline at 12 months	3.1 (−0.2–6.0)		0.04[e]
Mental health summary score at baseline	45.2 (41.5–48.9)	49.7 (46.3–53.1)	0.08
Change from baseline at 12 months	4.8 (1.8–7.3)	−0.5 (−3.3–2.2)	0.023[d]
Mean differences between groups in changes from baseline at 12 months	5.3 (1.3–9.4)		0.01[e]
Mean HADS[b,f] (95% CI)			
Anxiety, baseline	7.5 (6.0–9.0)	6.1 (4.7–7.2)	0.16
Change from baseline at 12 months	−2.1 (−3.6– −1.0)	0.3 (−0.7–1.4)	0.002[d]
Mean differences between groups in changes from baseline at 12 months	−2.4 (−4.0– −0.9)		0.003[e]
Depression, baseline	6.5 (5.0–7.9)	4.5 (3.2–5.8)	0.06
Change from baseline at 12 months	−2.1 (−3.2– −0.9)	0.02 (−1.0–1.1)	0.001[d]
Mean differences between groups in changes from baseline at 12 months[e]	−2.1 (−3.6– −0.5)		0.009[e]

CBSM, cognitive–behavioral stress management; ART, antiretroviral therapy; CI, confidence interval; MOS-HIV, Medical Outcome Survey-HIV; HADS, Hospital Anxiety and Depression Scale.
[a]Definition of adherence in Methods.
[b]Based on 77 participants.
[c]Larger positive values indicate greater treatment effects of the intervention.
[d]Significant time by treatment–interaction effect.
[e]Significant treatment effect.
[f]Larger negative values indicate greater treatment effects of the intervention.

study end ($P = 0.03$) (Table 3). The five persons in the control arm who stopped cART during the study had CD4 cell counts of 212, 411, 971, 900, and 445/μl at time of cessation; viral replication was completely suppressed at time of cessation in three of the five participants, and the reported reasons for cessation were 'patient's wish' (2), 'not specified' (1), 'structured treatment interruption' (1) and 'toxicity' (1), respectively.

Effect of intervention on psychometric measures

MOS-HIV summary scores differed between groups over time ($P = 0.04$), with persisting increases in physical and mental health summary scores, respectively, in the CBSM group at months 1, 6 and 12 ($P = 0.05$ and $P = 0.02$; Fig. 3 and Table 3). Effect sizes (*d* values) for differences between baseline and 12-month follow-up scores were small (physical health summary score, 0.26) and medium (mental health summary score, 0.48) in the CBSM group, whereas effect sizes approached zero in controls. HADS scores differed between groups over time ($P = 0.006$), with significant improvement in both HADS scales in the CBSM group (anxiety, $P = 0.002$; depression, $P = 0.001$; Fig. 3 and Table 3). Effect sizes (*d* values) for differences between baseline and 12-month follow-up HADS scores were moderate in the CBSM group (anxiety, 0.52; depression, 0.54), but negligible in controls. Mean differences in changes from baseline of MOS-HIV and HADS scores differed significantly between groups for all comparisons between baseline and the 12-month assessment (Table 3).

Analyzing HADS data for two different participant strata (baseline scores above versus below the cut-off separating normal and pathological values) indicated that significant CBSM training effects were only observable in subjects above the cut-off score (Fig. 3). Effect sizes (*d* values) for differences between baseline and 12-month follow-up scores indicated a significant benefit for the CBSM group above the respective cut-off score (HADS anxiety, 1.2; HADS depression, 1.5), whereas effect size scores were all $d < 0.2$ in controls and in the CBSM group below cut-off.

Discussion

We found no effects of CBSM training on morbidity, viral load and CD4 cell counts, and adherence to cART compared with standard medical care. However, we did

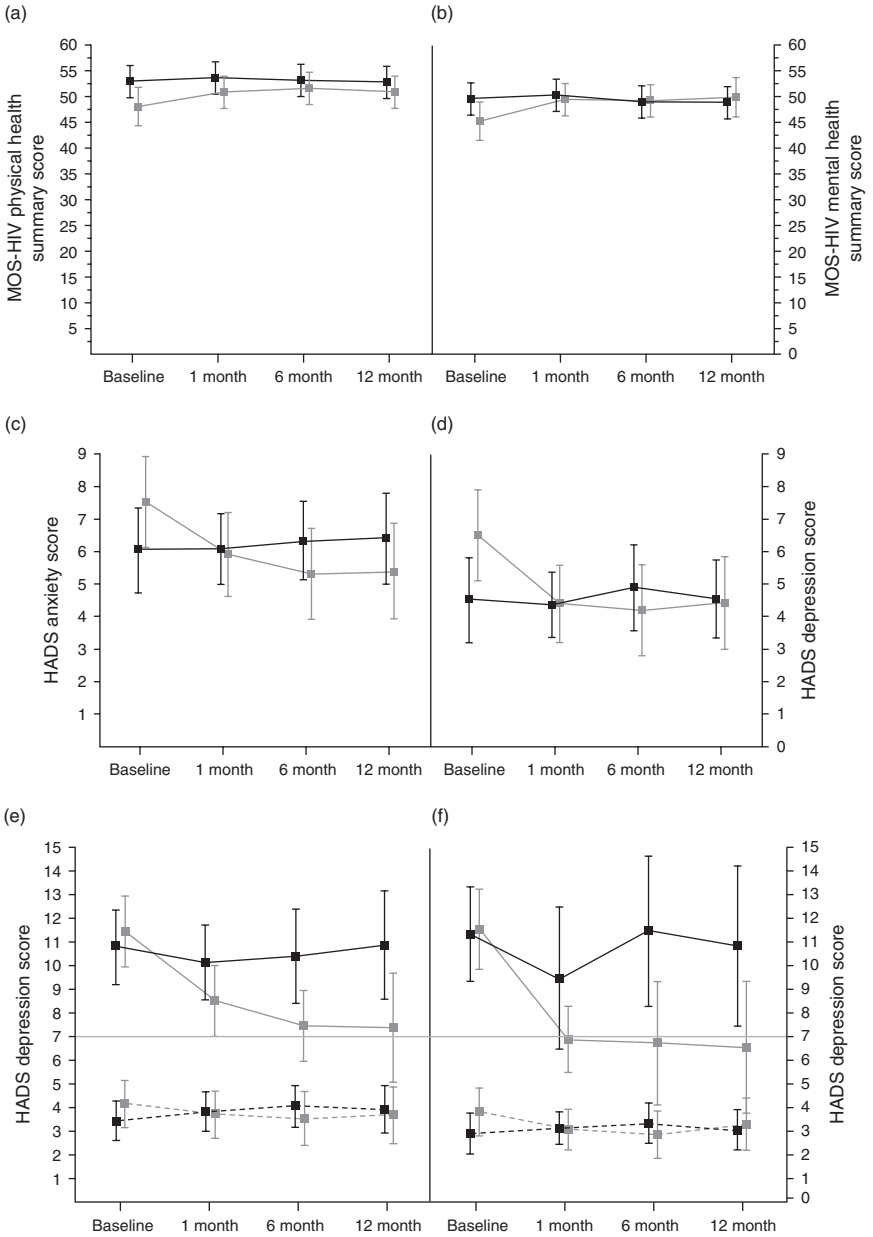

Fig. 3. Mean scores on the HIV Medical Outcome Study (MOS-HIV; a,b) and Hospital Anxiety and Depression Scale (HADS; c–f) by treatment group: cognitive–behavioural stress management (CBSM, open symbols) and controls (black symbols). (e,f) HADS subscale results for participants below and above the baseline cut-off scores; the horizontal line indicates the cut-off score separating normal from clinically conspicuous values. (e) Anxiety subscale in study participants by treatment group (below cut-off score, 19 in the CBSM group and 27 in the control group; above cut-off score, 15 in the CBSM group and 16 in the control group). (e) Depression subscale in study participants by treatment group (below cut-off score, 23 in the CBSM group and 34 in the control group; above cut-off score, 12 in the CBSM group and 8 in the control group). Bars give 95% confidence intervals.

observe benefits of CBSM training on quality of life and psychological distress. Notably, significant improvements in distress were only observable in individuals with high distress at baseline.

A strength of this trial was the inclusion of a group of HIV-infected persons from a routine practice clinical setting who were taking stable antiretroviral therapy and had restored cellular immunity. Further strengths include the longitudinal assessment of the clinically relevant markers of HIV infection, the use of an intervention according to a manual, and the recruitment at multiple study centers. Limitations are that the mode of group training might have affected the acceptability of the intervention, which would explain the fact that only a small proportion (6.1%) of eligible individuals actually

agreed to participate. Other routes of administration with known efficacy, such as individual psychotherapy, might prove to be more accessible to HIV-infected persons who are unwilling to participate in group therapy sessions [31,32].

Our findings endorse previous reports on the efficacy of CBSM training in reducing psychological distress and enhancing quality of life in HIV-infected individuals [19,23], extending these findings to persons receiving cART. However, we were unable to find evidence for beneficial short- or long-term CBSM training effects on surrogate markers of HIV infection as previously reported by others [16,33,34]. These discrepancies between earlier studies and our controlled trial are unlikely to result from differences in the efficacy of the employed CBSM training, since effect sizes in the psychosocial outcome parameters were comparable. Although not directly comparable to our viral load effect size estimate, Antoni *et al.* [34] reported a 0.56 $\log_{10}$ copies/ml decrease in HIV viral load over 15 months in a CBSM training group after controlling for HIV medication adherence. However, these results were obtained in persons with substantial morbidity, including 54% with previous AIDS and 77.6% with detectable plasma HIV levels at baseline, who were on heterogeneous and nonsuppressive antiretroviral regimens.

The absence of an effect of CBSM on clinical markers may be explained by the relatively small contribution of psychosocial factors to HIV progression among persons on cART with complete viral suppression and restored immune function. Since a negative impact of psychological distress on HIV disease progression has been demonstrated in prospective studies with a follow-up of up to 9 years [1,2], effects of CBSM training on the clinical status might be observed in the long-term observation of HIV-infected individuals with high levels of psychological distress.

Our results indicate that CBSM group training is an efficacious and effective intervention for enhancing quality of life and psychological well-being in HIV-infected persons taking stable antiretroviral therapy with restored immunity and little somatic morbidity. Its beneficial effects are particularly observed among persons who present with depression and anxiety scores at baseline, which indicate high psychological distress. Therefore, screening for psychological distress [35] and referral to individually acceptable psychotherapeutic interventions should be integral to HIV management, if not all somatic diseases [36].

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