Objectives:

1. Discuss how maladaptive coping patterns, such as Type C, influence immune regulatory processes among women.
2. Describe at least one way the interrelationships among stress, coping and immune processes affect regulatory processes.
3. Describe one way that maladaptive coping patterns, such as Type C, can contribute to enhanced production of pro-inflammatory cytokines that may negatively affect disease progression of HIV among women.
4. Describe how maladaptive coping patterns, such as Type C, can contribute to dysregulation of cytokines and beta-chemokines that influence disease progression.
Theoretical Considerations

- Parallels between multisystem (immune, ANS, CNS) dysregulation and aberrant activation are characteristic of both HIV infection and stress/coping failure, suggesting possible synergy and/or common mechanisms. (Temoshok, 2000)

- Accumulating evidence for bi-directional immune system-to-brain signaling in the field of psychoneuroimmunology.

- Acute stress and pathogens produce similar behavioral and physiological responses. Evidence for cross-sensitization between infection and stressors. Shared circuitry? Shared signaling mechanisms? Stressors another form of infection?

- Chronic stress/distress dysregulates diurnal rhythms, and is associated with increased immunopathology, and multisystem dysregulation. Key: the coherence across systems.
Type C Coping

- Type C is characterized by a failure to recognize internal physical or emotional cues, lack of emotional expression, focus on needs and feelings of others at the expense of self, façade of normalcy and mental health, underlying depression.

- This maladaptive coping pattern keeps the individual in a chronic state of stress with concomitant dysregulation of homeostatic responses, including inappropriate responses to stressors, i.e., increased physiological reactivity, and decreased recovery (e.g., Temoshok, 2004).

- The Type C coping style has been found to be robust and reproducible across different study populations, cultures (USA, Italy), diseases studied (melanoma, HIV), and measurement strategies (videotape rating, vignettes).
Adaptive Coping Response

Stressor (physical, environmental, social) → Physiological state of stress (HR & BP, cortisol) → Cognitive appraisal of the situation (identify, classify, analyze problem) → Action/adaptation (problem solving: escape from, cope with, or remedy stressor) → Emotional response (fear, anger, sadness, etc. amplifies stress signal)
Abnormal Type C Stress Response

Stressor
(physical, environmental, social)

Physiological state of stress
( > HR & BP, > cortisol)

Emotional response
(fear, anger, sadness, etc.
unrecognized and unexpressed -- no emotional amplification of stress signal)

State of stress perpetuated
(chronic induction of stress response, with negative effects on cardiovascular and immune systems)

No cues to prompt cognitive appraisal, action
In an Italian cohort (N = 200), Type C coping style significantly predicted HIV progression (from CDC-A2 to any more advanced stage) at 6 month ($\beta = .32; R = .20; p < .01$) and 12 month ($\beta = .23; R = .17; p < .02$) follow-up assessments.

In 28 patients with AIDS, heart rate response (to describing 5 emotional situations over the past week) which better approximated the inverted-U shaped curve of normal homeostasis significantly predicted months survival.* The other 3 hypothetically maladaptive patterns had significantly shorter survival.


*controlling for initial CD4+ cell count and months since diagnosis. No participants were on AZT.
Chemokines and HIV

- Chemokines (*chemoattractant cytokines*) are specialized cytokines produced by activated primary T cells which function primarily to mobilize inflammatory and white cells.

- The beta-chemokines MIP-1α and MIP-1β are of special interest in HIV because they bind to the CCR5 co-receptor, which, in addition to the CD4+ receptor, is required for (macrophage-tropic) HIV to enter CD4+ cells.

- Chemokines specific for the CCR5 co-receptor suppress infection by macrophage-tropic strains of HIV. *(Cocci et al. Science 1995; 270; 1811-1815).*

- MIP-1α and MIP-1β production are correlated with more favorable clinical status in persons with HIV, hypothetically by blocking viral entry. *(Garzino-Demo et al. PNAS 1999; 96: 11986-91)*
Chemokines and CCR5 Receptor Binding

MIP-1α and MIP-1β (red blob) block CCR5 co-receptor, preventing HIV entry.

Recent work suggests that stress can enhance production of proinflammatory cytokines, notably interleukin-6 (IL-6), which has been linked to several diseases including cardiovascular disease, osteoporosis, diabetes, and cancer.

Dysregulation of the pro- and anti-inflammatory balance has been implicated in immune activation and HIV pathogenesis.

Crystal structure of IL-6
Image source: Protein Data Bank
Current Study Overview

5-year NIH grant (R01HD048154) to identify, in a longitudinal study, the complex mechanisms by which coping and interrelated psychosocial variables may interact with immunological factors and physiological response patterns to affect HIV progression in 200 HIV+ persons.

- **Hypothesis 1:** The previously documented effect of Type C coping on HIV progression is mediated by decreased production of HIV- inhibiting β-chemokines (MIP-1α/β).

- **Hypothesis 2:** Adjacent constructs to Type C, specifically alexithymia, may also contribute to HIV progression via relationships with HIV- inhibiting β-chemokines (MIP-1α/β).

- **Hypothesis 3:** Dysregulated cardiovascular reactivity may mediate or moderate the relationships between Type C coping, immune function, and disease progression.

- **Hypothesis 4:** Type C coping will be associated with overproduction of the inflammatory cytokines IL-6 and IL-10, and decreased production of the Th1 cytokine IFN-γ.
Alexithymia

- A personality construct that denotes a deficit in the cognitive processing and regulation of emotion.
- This deficit may result in an undifferentiated, diffuse psychological distress (model of Taylor et al.), which fosters a hypervigilance toward somatic sensations and increased report of somatic complaints.
- Associated with a number of psychosocial problems in our studies: depressive symptoms, clinician-rated stress severity, UCLA Loneliness Scale, and less disclosure of HIV status.
Participants

- Participants are 200 HIV+ adults, assessed every 6 months for 3 years.
  - Mean age 44.5 (range 29-61).
  - 92% African-American, 7.5% Caucasian.
  - 49% male, 51% female.

- All had CD4+ counts above 200 at study entry, but many have previously been AIDS-defined.

- Antiretroviral therapy (ART) status at baseline:
  - 17% treatment naïve
  - 69% currently prescribed ART
  - 14% had previously taken ART

- Medications for comorbid conditions are common:
  - 25% on cardiovascular medications, primarily for high blood pressure
  - 34% on psychiatric medications, primarily antidepressants
  - 17% on methadone maintenance
Psychosocial Methods

- Type C, Distressed, and Adaptive Coping assessed by Vignette Similarity Rating Method (e.g., Temoshok in Fernandez-Ballesteros, 2003; in A. Christensen, 2004).

- Alexithymia assessed by Toronto Alexithymia Scale (TAS-20). Stable 3-factor structure for subscales:
  - Difficulty identifying feelings and distinguishing between feelings and bodily sensations
  - Difficulty defining feelings
  - Externally oriented thinking

- Other theoretically relevant constructs:
  - Stress: Perceived Stress Scale, Interviewer’s rating
  - UCLA Loneliness Scale
  - Depressive symptoms
  - Hardiness
Peripheral blood samples were drawn approximately one week before the psychophysiology tasks.

*In vitro* production of beta-chemokines MIP-1α and MIP-1β was measured in response to three antigens: Candida, PHA, and p24 (HIV core protein)

- Chemokines measured by ELISA
- Supernatants collected on days 3 and 6

Assays for MIP-1α and MIP-1β performed by ELISA.

Stimulation Index (SI): Antigen-induced chemokine production compared to unstimulated background controls.
Participants complete two emotion-induction tasks approximately one week after each blood draw.

Each 3-minute task is preceded by a 5-minute resting baseline and followed by a 5-minute resting recovery period.

Heart rate and blood pressure are monitored at 90-second intervals.

Variables of interest include reactivity during the test period and return to baseline during the recovery period.
Emotion Induction Tasks

- **Anger recall:** Participants are asked to recall and describe an incident in the prior two weeks in which they were angry. The experimenter’s responses support the expression of anger.

- **Role play:** Participants role play complaining to their landlord about uncompleted repairs. Playing the landlord, the experimenter is rude, brusque, and dismissive. (e.g., “What are you complaining about now?”)
Baseline regression analyses of Type C and alexithymia to IL-6 and MIP-1α production (controlling for CD4+ count and age; N = 171)

- **Type C Coping:** significantly related to higher IL-6 production *(progression factor)* when stimulated by Candida and PHA, approaching significance for p24.

- **Alexithymia:** significantly related to lower MIP-1α production *(protective factor)* when stimulated by p24.

- Type C Coping and Alexithymia are not significantly correlated and have independent effects on these immune factors.
Baseline regression analyses of heart rate reactivity/ recovery to MIP-1α production* (adjusted for CD4+ count, age, CV meds, methadone use,)

*N = 140

- **Heart rate reactivity:** significantly related to lower MIP-1α production (protective factor) when stimulated by p24.

- **Longer Heart rate recovery:** significantly related to lower MIP-1α production (protective factor) when stimulated by p24.

- **Alexithymia:** significantly and independently related to lower MIP-1α production (protective factor) when stimulated by p24.
Another way to look at this

Current study

Depicts combination of 2 different regression analyses: baseline to test and test to recovery, contrasting the 10th (low) percentile and 90th (high) percentiles for MIP-1β.

Temoshok et al. 1987

Current results are strikingly similar to HR results in 1987 study of long-term survival in men with AIDS.
Baseline HR Reactivity and Recovery Predict IL-6 Production at 12 months (N = 79)
(adj... the Role Play Task at baseline predicted greater IL-6 production \((\text{progression factor})\) when stimulated by the p24 and PHA antigens.

- Greater SBP reactivity during the Role Play Task, and poorer SBP recovery after the Anger Recall Task at baseline, predicted greater IL-6 production \((\text{progression factor})\) to the p24 antigen.
Summary Thus Far

- The chronic exposure to stress sustained as a result of emotional dysregulation (Type C coping, alexithymia) appears to result in immune dysregulation, allowing enhanced IL-6 production with corresponding restraints on MIP-1α production. This combination may promote HIV progression.

- These findings suggest that a chronic pattern of autonomic dysregulation, along with emotional dysregulation, may contribute to HIV progression via persistent suppression of anti-HIV B-chemokine production combined with the immune activating effects of chronically increased IL-6 production.
Future Directions: Develop and Test Interventions

- To identify psychogenic factors to incorporate into psychosocial interventions intended to influence more salutary HIV medical outcomes.
- To test these interventions for their ability to (a) increase protective factors, and (b) decrease immune dysregulation which, hypothetically, sensitizes inflammatory responses, resulting in amplified inflammatory cytokine production that contributes to HIV replication, and (c) decrease—ultimately—HIV progression.
Psychogenicity

- Parallel to the term “immunogenicity” in vaccine research, “psychogenicity” refers to the demonstrated ability of an intervention to produce hypothesized psychological changes that have been demonstrated to be associated with more favorable biomedical outcomes or mechanisms.

- One cannot reasonably conclude that an intervention “caused” a favorable outcome, even in a RCT, unless one can demonstrate that the intervention reliably modified immune or other mechanisms shown to affect clinical outcomes.
Stress Management

- Stress activates innate inflammation signaling pathways.
- Cognitive-Behavioral Therapy (CBT) used by Antoni et al. in Miami (manualized) for HIV and cancer patients.
  - Optimal disease adjustment (QOL) often characterized by lower distress, greater positive life experiences.
  - Interventions such as relaxation, CBT, interpersonal skills training can help patients cope better with stressors of disease and treatment.
  - Optimal psychosocial adjustment may affect physical health via stress pathways that influence disease pathogenesis.
Mental Mechanisms

- Replace self-conscious rumination with mindfulness as non-evaluative attention to and awareness of the present.
- Increase reflection as seeking to understand.
- Decrease fear of negative evaluation (assess with Trier Social Stress Test).
- Important implications for recovery from threat (decrease reactivation of physiological responses, decrease intrusive thoughts).
Biofeedback

- May produce similar physiological results to meditation, even if it is a different process in the brain.
- Aims to decrease reactivity.
- Aims to promote restorative physiological state.
- In those with a relatively high chronic level of activation and a constant state of vigilance and alertness, aims to normalize this tonic level of activation (parallel to negative effects of chronic peripheral inflammation and continual activation of brain cytokine signaling).
- Cf. Temoshok’s (2003) emphasis on contextual and response system appropriateness as parallel to immune response specificity, in contrast to the “promiscuous” (dysregulated) immune responses in early HIV; “junk” Natural Killer cell numbers vs. functional cytotoxicity.
Emotion Regulation Training

- Developed by Paul Ekman, Ph.D., UCSF
- Aims to reduce emotional responses that have negative consequences for self and others.
- Helps person learn about emotions in self and others.
- Because emotions linked to physiological responses, HPA axis, training may modify this activity.
Recommended Best Practices

- We have shown that maladaptive coping patterns, specifically Type C and the emotional dysregulation characteristic of alexithymia, are associated with immune (cytokine / chemokine) factors that influence HIV progression.

- At the physiological level, maladaptive physiological stress responses (exaggerated reactivity and decreased recovery) are also associated with these same immune factors.

- Cognitive Behavior Therapy to reduce stress, mindfulness training, biofeedback, and Emotion Regulation Training have been successfully used with HIV, cancer, and/or other medical patients to address maladaptive coping patterns and increase quality of life.

- Clinical research is underway to evaluate the psychogenicity and efficacy of these promising interventions to influence immune factors mediating HIV progression.