Immune-Compromised Patients: HIV and Organ Transplantation

29

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Contents

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29.1 Introduction

The consultation-liaison psychiatrist has no greater opportunity and obligation to contribute to patient care, practitioner training and research than in advancing the work with immune-compromised patients. This area of health care has grown enormously in the past quarter century with the global emergence of the AIDS epidemic. New case numbers continue to rise in the established geography of the disease and AIDS continues to enter areas heretofore untouched by the condition. Current projections suggest that by the year 2030, AIDS will take more lives than were lost in any of the other great plagues of humanity (Global AIDS Epidemic Report, UNAIDS 2006).

In contrast to the viral assault on the immune system associated with HIV disease, the compromise of immune regulation and response associated with transplantation medicine is induced by the interventions developed by the field. Success in expanding the organ types and their post-transplant longevity has increased the number of potential beneficiaries and the population of living organ transplant recipients.

The AIDS and organ recipient patient populations will grow and increasingly reflect the clinical

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challenges of caring for the chronically ill. As such, the consultation psychiatrist provides expertise regarding the psychosocial aspects of illness experience and coping, transplant candidacy and care, and health behaviors, including treatment adherence. The psychiatrist also plays a critical role in the assessment, referral and ongoing treatment of pre-existing or newly developing mental and substance use disorders. This is a special need in immune-compromised patients, given the nature of the high-risk groups for AIDS and organ failure. Psychiatric treatments are considered and provided in a behaviorally and medically complex context. In providing effective treatment of co-existing mental disorders and dysfunctional health behaviors, the consultation psychiatrist may alter quality of life, impact treatment decisions, and extend patient longevity.

As the scale and dimensions of mental health care for the immunocompromised patient have grown, the research field of psychoneuroimmunology has emerged. This rapidly growing area of investigation provides sound evidence that psychosocial and behavioral factors can modulate immune function (Glaser 2005). Observation and intervention studies are advancing our understanding and creating a framework for the optimal provision of clinical evaluation and treatment of the patient with immune dysregulation.

29.2 HIV Patients

29.2.1 Vignette

J.K. is a 33-year-old man referred by his internist for psychiatric assessment after an initial medical evaluation revealed that he was infected with HIV. The patient had brought himself for medical evaluation, knowing that his sexual and drug use habits had significantly increased his risk of infection. Recently, he'd met someone, hoped to begin a new romantic relationship and was encouraged by this individual to clarify his HIV status. With the disclosure of the positive HIV test result by the internist, the young man became intensely overwrought—he seemed both surprised and exquisitely apprehensive. Summoning all the advantages of his lengthy experience working with HIV-infected patients, the physician tried to calm, reassure, and support the patient in his first response to the test results. As the patient's distress remained largely refractory to the physician's approach, the internist decided to refer the patient for psychiatric consultation.

Days later, the patient met with the consulting psychiatrist and expressed fear of a decline in his health, rejection by others, especially by his new found friend, and a sense of terror, reflective of his having received a 'deadly' diagnosis. J.K. reported experiencing shortened, restless sleep, general nervousness admixed with waves of discouragement and behavioral withdrawal. He admitted special difficulty refraining from drug use since his meeting with the internist. He sketched out a history of occasional days-long episodes of mild depressive symptoms that cleared without special action or intervention, but otherwise denied a significant personal or family history of psychiatric disorder.

The consultant understood the episode as subsyndromal depression or, perhaps adjustment disorder with mixed emotional features. The primary care provider was advised to continue to emphasize in subsequent appointments with the patient, the elements of the medical monitoring and treatment plan and their potential positive impact on J.K.'s quality of life and longevity. It was suggested that monitoring includes checks on the patient's mood and affect, attitude about his illness and prognosis, and screening for elements of suicidal ideation or impulse. The psychiatrist underlined the need for psychosocial screening in the event of missed medical appointments or deteriorating adherence to treatment.

The patient met twice more with the psychiatrist—sessions in which added sources of apprehension were identified and addressed. Special emphasis was placed on effectively managing the disturbing effects of disclosure of HIV status on key relationships. Recognizing the increased risk of major depression in those with subsyndromal depression, the psychiatrist and the patient considered beginning an antidepressant medication trial. However, J.K.'s dysphoria subsided and the antidepressant trial was not undertaken.

Over the next 9 months, the patient saw his internist three times, apparently content with the care he was receiving. At the third of the visits, his

internist revealed that the patient's CD4 cell count had fallen below 350, raising the need to begin antiretroviral treatment. The patient became obviously apprehensive and very dispirited with this news. The need for specific HIV treatment represented a fearful downturn and confirmation of the relentless progression of his condition. Both the patient and the practitioner agreed that further consultation with the psychiatrist was indicated.

The psychiatrist met with the patient 10 days later. By then, J.K. was despondent and apprehensive on a daily basis. He was experiencing sleep-onset difficulties, compromised energy to carry out daily activities and considerable withdrawal from contacts with others. The patient's presentation suggested the leading edge of a probable major depressive episode. Despite some reluctance, the patient agreed to a trial of fluoxetine.

Over the next 3 months and three visits to the psychiatrist, the patient experienced a gradual improvement in mood, energy, behavior, and sleep quality. The visits provided a setting for J.K. to identify sources of pathological fear and despair and reduce their influences. During the same period, the patient and his internist were able to review and prepare for the challenges and complexities of initiating three-drug antiretroviral treatment. Over the following 6 months, J.K. managed to effectively integrate the antiretroviral protocol, the antidepressant regimen and his response to a new phase of his illness and its treatment into his ongoing perspective and activities.

29.2.2 Introduction

The HIV illness experience is unique for each infected individual, yet there are common issues and themes across the various illness phases. In the first subsection, we explore aspects of illness experience and response, illness narratives, and psychosocial treatment considerations relevant to the CL psychiatrist. As meaning of illness, social support and adaptive coping have been associated with improved psychological and physical outcomes in HIV-illness (Farber et al. 2003), we look at specific interventions that address these areas.

Patients with psychiatric disorders, including personality disorder (especially borderline and antisocial personality disorders), are at higher risk of HIV infection (Perkins et al. 1993). For infected individuals, psychiatric disorder can impact the subjective experience of infection, as well as the treatment of HIV and related illness. Therefore, appropriate assessment and effective treatment of psychiatric conditions is of paramount importance. The diagnosis and treatment of certain psychiatric disorders can be similar to that in non-infected individuals—there are also unique diagnostic and treatment considerations in the setting of HIV-infection. Finally, there are unique neuropsychiatric manifestations of HIV/AIDS and related medical sequelae. We will address these issues related to psychiatric and neuropsychiatric illness in the second subsection.

29.2.3 Psychosocial Issues and Treatment Considerations

There are common intrapsychic and interpersonal conflicts and issues that are illness-phase specific. Some familiarity with these themes affords us a better understanding of our HIV-infected patients and allows for more appropriate psychosocial treatment. Sensitivity to these dynamics can guide therapeutic contacts, which can provide support and be powerful facilitators of growth and healing. In addition, during longer hospitalizations there can be a role for more structured, brief psychotherapy. Themes that are identified during this work can be further explored and addressed in subsequent outpatient psychotherapy.

29.2.3.1 New Diagnosis

A patient's response to HIV diagnosis can depend on their awareness of pre-testing risk behaviors. For those unaware of their high risk, there may be disbelief or concerns that the results are inaccurate. Once a patient tests positive, there may be periods of denial and also significant anxiety related to issues of mortality, impact on life dreams, uncertain disease course and treatment, and uncertain response from family and loved ones (including feared rejection). There may be guilt related to high-risk behaviors and feelings

of shame in relation to social stigma. Patients and their loved ones can also exhibit other symptoms associated with loss, including guilt, sadness, anger, bargaining, and acceptance (Cohen 1990).

Once diagnosed, patients must also deal with the issue of whether or not to inform friends and family. Sometimes this involves acknowledging sexual or drug-related lifestyles that were previously undisclosed. Sexual partners current and past need to be informed by the patient—the patient should be encouraged to do this, once they have processed the diagnosis adequately themselves. Some states require this disclosure to intimate relations. At the appropriate time, patients must also be counseled on safe-sex practice to decrease their likelihood of transmitting the virus and contributing to the epidemic.

Suicidality should be evaluated—the suicide rate in patients with AIDS has been reported as 36 times that of the general population (Cohen 1990). This rate has decreased with the introduction of highly active antiretroviral therapy (HAART), but continues to be higher in patients with HIV infection and AIDS (Jia et al. 2012). Patients without prior history of suicidal ideations may talk of suicide when they are overwhelmed and trying to manage feelings of despair, loss of control, helplessness, and fear of the future—the major intervention here is to help the individual manage and work through the overwhelming anxiety. As well, lowered self-esteem, impact on sense of identity, alienation from friends and family can also contribute to suicidal ideations—crisis intervention, communication, and support are important here (Cohen 1990). Patients with pre-infection history of depression, anxiety, personality disorder, and suicide attempts can be at much higher risk for suicide and need to be managed appropriately (Sheridan and Sheridan 1988).

29.2.3.2 Early Illness

After being diagnosed, the patient struggles to integrate the diagnosis and its treatment into their life. Here it becomes important to explore the meaning of illness, including illness-related fears. Fears of unknown illness and treatment, lack of cure, and the possibility of premature death can lead to significant anxiety (Cohen 1990). Complexes related to earlier interpersonal loss can become constellated, especially when these losses have not been adequately worked through. There can be significant anxiety and anticipatory mourning regarding the potential impact of HIV-infection on previously held dreams and ambitions. It is important to create a safe space for these painful feelings to be expressed—both allowing for mourning, while also providing hope.

Patients also often struggle with larger existential questions such as, "Why did this happen to me?" Even in the time-limited setting of consultation psychiatry, it can be invaluable to create a safe space to begin gentle exploration and engagement with these questions. If the consultant is not comfortable with transpersonal and existential themes, and if it seems appropriate, pastoral, spiritual, or religious support can be recruited.

Patients often have misconceptions regarding HIV infection and treatment—many are unaware that modern antiretroviral treatment has transformed HIV-infection from a death sentence to a chronic illness. It can be important to provide education regarding this, or to facilitate the exchange of this information via the primary team and hospital educational resources.

The psychiatric consultant can also facilitate linkage with community resources and support groups. It is important to be aware of medical clinics or providers in the community who are comfortable with or specialize in work with HIV-positive individuals. Social work can often assist with educating the patient and making referrals to resources that can help with insurance issues, legal aid, and other HIV-related services.

29.2.3.3 Chronic Illness

There are other themes that are common and may need to be explored and addressed when relevant. These can include dealing with social stigma and the interpersonal response to their infection, the need for chronic medical care and medical morbidities, the worsening of medical condition when it occurs, AIDS-related cognitive changes, and processing the impact of HIV/AIDS on

educational and vocational pursuits. For some of these issues it becomes important to draw from grief work and both mourn the loss as well as facilitate and co-construct new meanings and life goals with the patient. Again, the psychological and physical interpenetrate—recent research shows that patients who experience maladaptive grief show more rapid loss of CD4 T-cells over time, even when controlling for age, health status, use of antiretrovirals, and illicit drug abuse (Goforth et al. 2009). In addition to these themes, HIV-related symptom onset and an increase in symptoms can be key triggers for hopelessness and demoralization, which need to be addressed.

29.2.3.4 Terminal Illness

There is significant existential anxiety around death in American culture, which often leads to avoidance in caregivers who are uncomfortable with emotional engagement with the dying patient. At the time the patient needs human contact the most, the opposite often happens. This can be especially true in busy public hospital settings, with indigent and often homeless populations who have limited, if any, social network. When these networks exist, even if in the form of case managers, they should be recruited and attended to. When these networks don't exist, the psychiatric consultant is often the primary source of human contact (in teaching hospitals, medical students can be valuable allies). It is critical to engage with the dying patient in a sincere and compassionate way. The consultant can work with the primary team in addressing treatable issues, such as poorly managed pain. The consultant can help facilitate communication with relationships that have been strained or broken. Often times, the patient needs help in thinking through those people he or she wishes to contact, with what needs to be expressed, and with problem-solving in making these connections. In this modern age, the Internet can be invaluable for locating phone numbers and other information.

It can be crucial to explore the patient's spiritual beliefs, especially perspectives on the afterlife, and engage with this in appropriate ways. For patients with significant guilt, forgiveness and self-compassion work can be crucial for a less tormented and anxious passing. For spiritually inclined patients, culturally syntonic rituals can be co-constructed and engaged in. Appropriate spiritual bibliotherapy can be carefully integrated in some instances. For those patients who identify with specific religious belief systems, texts from those belief systems can be requested or spiritual figures from respective churches, mosques, synagogues, or temples can be incorporated into the care. Finally, when a patient dies, the consultant must tend to his/her own emotional responses. Ideally, the consultant has engaged with this inevitable existential reality beforehand. It is important to take time, even in the busy workday to mourn the loss of a person, to find ways to take care of one's own grief response and find ways to restore one's own energy, and then move forward (Sheridan and Sheridan 1988).

29.2.3.5 Special Issues: Adherence to Antiretroviral Treatment

Compliance with Highly Active Antiretroviral Therapy (HAART) can be challenging even independent of any psychiatric diagnoses or significant psychological distress. Often there are many pills to take at once. The medications often have multiple dosing times each day. Therefore, the complicated dosing regimens often impact other life involvements. HAART often has significant side effects that can be distressing and also have other psychosocial impact. For some, the medications are a reminder of having a disease they would rather forget. There can also be anxiety that people will find out and discriminate against them if the medications are seen, which can also negatively impact medication compliance. Thus, compliance with HAART requires a serious commitment from even the most well compensated patient.

Major depression can further reduce adherence (Singh et al. 1996). Depressed patients often have decreased interest in self-care and may ignore medical symptoms and problems. They may be too withdrawn to present for care and medical follow-up. Depression can interfere with problem solving which is important to negotiate complex medication regimens and approach issues such as medication side effects.

With a sense of hopelessness and negative thinking, some patients may doubt the potential benefits of treatment. In HIV-positive patients with depressed mood, one group found that a single-session that targeted the rehearsal of adherence-related behaviors led to enhanced HAART adherence (Safren et al. 2001). In addition to interventions that specifically address medication non-adherence it becomes crucial to treat major depression, as there are studies that show antidepressant treatment increases viral suppression, likely due to improved adherence (Tsai et al. 2010).

29.2.3.6 Special Issues: The Role of Spirituality

Spirituality is a potentially important component and dimension at every level and phase of care. There is some literature that looks at spirituality and religiosity in the setting of HIV-infection. Nelson et al. (2002) studied 162 patients with terminal illness, 78 patients of whom had terminal AIDS—spirituality, religiosity, and depression were assessed in these patients. There was a strong negative association between spiritual well-being and depression (i.e., higher spirituality was associated with lower depression)—especially the (existential) subscale that looked at meaning and depression. The authors recommended existential or spirituality-based interventions for terminally ill individuals with HIV. A more recent study (Ironson and Kremer 2009), spoke of spiritual transformation as occurring in up to 39 % of individuals with HIV, and in looking at 147 people with HIV, found that spiritual transformation was associated with better treatment success (undetectable viral loads, higher CD4 counts), better medication adherence, fewer symptoms, less distress, more positive coping, different life attitudes (i.e., existential transcendence, meaning in life, optimism, death acceptance), and substance abuse recovery. Notably, survival up to 5 years was 5.35 times more likely in these individuals.

29.2.3.7 Illness Narratives

"Narrative is a fundamental human way of giving meaning to experience. In both telling and interpreting experiences, narrative mediates between an inner world of thought-feeling and an outer world of observable actions and states of affairs…" (Garro and Mattingly 2000, p. 1). Telling stories allows the patient/author to represent and understand their experience, and to expand and reshape concepts and values—creating a personal narrative that is more cohesive, enriching, and more meaningful. These revised stories create new understandings of self and other that can reshape one's experience of the past, present, and anticipated future.

In telling stories, certain parts are left out because of attentional biases. As a person's story is explored, neglected, and forgotten aspects, as well as new perspectives and lines of inquiry can allow for new stories to be created. "Patient and doctor together reconstruct the meaning of events in a shared mythopoesis … Once things fall into place; once experience and interpretation appear to coincide, once the patient has a coherent "explanation" which leaves him no longer feeling the victim of the inexplicable and the uncontrollable, the symptoms are, usually, exorcised" (Eisenberg 1981).

Farber et al. (2000) looked at resilience factors associated with adaptation to HIV disease, focusing on the construct of hardiness. They describe hardiness as having three dimensions: (1) commitment, which relates to one's sense of meaningful and purposeful engagement with life, (2) challenge, which relates to ones sense that change is fundamental and can allow for growth, and (3) control, the sense that one can influence the life course as it unfolds. In their study of 200 patients with symptomatic HIV, they demonstrated that high hardiness was associated with lower psychological distress, higher perceived quality of life in physical health, mental health and overall functioning domains, and more positive personal beliefs.

In a subsequent study, Farber et al. (2003) looked at 203 symptomatic patients with HIV and AIDS, measuring meaning of illness, problem-focused coping, social support, psychological well-being, and depressed mood. Positive meaning was associated with a higher level of psychological well-being and a lower level

of depressed mood. This contribution of positive meaning of illness was over and above the contributions of problem-focused coping and social support. The authors suggest the use of psychotherapy that supports problem-focused coping when appropriate, but also pays attention to HIV-related meaning can help decrease distress and increase psychological well-being. Therapy interventions that focus on meaning and purpose and focus on the articulation of meaning and purpose may reduce distress, facilitate coping, and increase positive adaptation.

29.2.3.8 Psychosocial Treatments Relevant for CL Psychiatry

Narrative Therapy

Much of psychotherapy can be considered as a form of narrative work—whether this is schema-focused work in cognitive behavioral traditions or an implicit orientation guiding Jungian psychoanalysis. "… Narrative therapy is characterized by telling one's story; examining the roots of that story; seeking aspects of that story previously overlooked; exploring how incorporating new aspects of the story changes the meaning attributed to different events; anticipating how self-image, priorities and relationships change as a result of the new meanings; and finding an appreciative audience for the new growth" (Petersen et al. 2005).

Words can contain and transform difficult affects and self-states, yet both the verbal and non-verbal aspects of the relational experience between clinician and patient are important. This includes the tonal and rhythmic dimensions that carry the dialogue—this is the intuitive music, or art of our work (Singh 2013). Within this dynamic relational field, "telling the story desensitizes patients to threatening cues that trigger anxiety, decreasing fear and avoidant behavior" (Petersen et al. 2005). Yet, "while retelling provides some comfort and momentary relief, the story must change in order to add therapeutic advantage" (Petersen et al. 2005). Appraisals are labeling of experience that shape emotional and behavioral response. Positive reappraisal results in assigning new meaning to the event, integrating confusing aspects into a coherent conceptualization, which can then lead to emotional and cognitive resolution (Petersen et al. 2005). Again, positive meaning of illness is associated with decreased depression and improved psychological well-being in individuals with HIV and AIDS (Farber et al. 2003).

This co-creation of a more adaptive and meaningful narrative can be engaged via questioning in a way that promotes contemplation of potential growth or lessons learned through the illness process. The idea of transformative suffering can be brought up, including the Jungian concept of the "wounded healer." Sometimes amplification can be attempted with fairy-tales and myth, for example, using the mythological tale of Chiron, who drew his strength from a poisoned arrow inflicted upon him by Zeus. Patients can find it interesting and useful to hear that in shamanic cultures, the healer often gained their power through an encounter with severe suffering. These can provide cognitive models that can shape the appraisal of illness experience in more adaptive ways. Not only can one find new areas of strength through the illness experience, but one also has an opportunity to offer something back to other individuals in the community. The important skill or art is to not disavow the pain or suffering as well, as this can be an important part of the grieving and mourning process. If these feelings are prematurely, or superficially dealt with, they often return in a variety of ways including delayed grief reactions, projections and projective identifications, or psychosomatic responses. As Edwards (1993) reminds us: "Countertransference from our own fear or pain may prompt us to get ahead of the patient by focusing on empowerment or hardiness. Anger and sorrow must be expressed and relieved before natural restitutive urges appear. There is a natural rhythm to grieving …" He goes on to say, "After patients have expressed and worked through their intense diagnosis-related feelings, they are often intrigued and mobilized by the suggestion that, although they cannot change the fact that they are HIV-positive, they do have control over their response to the disease."

29.2.3.9 Addressing Relational Deficits and Conflicts

The lack of perceived social support is associated with low self-esteem, depression, and poor quality of life (Safren et al. 2002). It is therefore important to explore and address this when possible. The consulting psychiatric team can provide an important relationship. Supportive visits can be very powerful—even when there are constraints on provider time, as long as one conveys to the patient that he/she is cared for and being listened to. It is also important to assess for community relationships that can be integrated—friends, family members, and case managers. Sometimes problem-solving or work targeting suspended or damaged relationships can be helpful (and followed through in subsequent outpatient psychotherapy). The consulting psychiatrist can attempt to arrange family meetings—sometimes it is possible to involve families even after many years of separation. "The support from family and loved ones can make the difference between dying with despair and dying with dignity and love. The fact that this does not always work is never a reason not to try" (Cohen 1990). Depending on the patient's unique needs, referrals can be made to outpatient mental health programs, to individual psychotherapy or counseling, to religious or spiritual groups, to 12-step groups or to HIV-specific resources—all of which can provide therapeutic relationships.

29.2.3.10 Adaptive Coping Techniques

Coping refers to mechanisms that regulate distress and there are three categories described (Clarke and Kissane 2002): problem-focused (e.g., information-seeking, problem-solving, direct action), emotion-focused (e.g., escape and avoidance, seeking social support, cognitive reframing, behavioral interventions including mindfulness and affect regulation techniques), and meaning-focused. Active and adaptive coping styles are associated with improved outcomes, including decreased depression (Safren et al. 2002). Maladaptive coping is associated with worsened physical health in HIV-positive individuals (Armon and Lichtenstein 2012). Thus, it is important for the psychiatric consultant to evaluate the patient's coping repertoire, expanding it when needed. Important work that addresses coping skills can be initiated even in time-limited consultations. The patient can further develop this after discharge, sometimes with the support of community resources (meditation centers, stress management groups) or in individual psychotherapy.

It is first helpful to question patients about what has helped them cope with difficulty in the past, including prior experience with mindfulness and relaxation exercises. Often, exploration of approaches appraised as "not helpful" reveal that they weren't tried for long enough or that normal responses (e.g., the mind wandering repeatedly during meditation) were labeled as signs of ineffectiveness or failure. Here it can be useful to provide corrective information, since that particular technique may be valuable to revisit.

Some specific approaches that can be powerful include mindfulness and acceptance-based work. Mindfulness is a form of practice that cultivates a gentle attention in the present and looks at arising thoughts and sensations as fleeting events in the mind to be neither attached to nor averse to, but to simply "be with" as they rise and fall. There is a substantial literature on the use of mindfulness in a spectrum of conditions, including anxiety, depression, chronic pain, substance use disorders, borderline personality disorder, and psychosis. Acceptance-based work has various shades, including cultivating self-acceptance, as well as acceptance of one's experience in the moment. Basic exercises utilizing these approaches are not difficult to learn, but to be most effectively utilized, do require additional training and personal practice by the provider.

There are other relaxation techniques, different from mindfulness, which can be taught in single sessions and assigned as "homework" between sessions. This often shifts the locus of control into the patient and strengthens their sense of agency, which can be crucial for patients who are struggling with bodies and medical courses that may seem out of control. Some relaxation techniques include deep, diaphragmatic breathing; visualization and guided imagery exercises; the use of relaxing music or

ambient sounds; and yoga or other physical movement.

Having people list their concerns and needs can help break things down, making them more manageable in times that otherwise seem overwhelming. Utilizing written cognitive behavioral therapy handouts on problem-solving can be a concrete intervention that allows goals to be broken down into a series of steps, sometimes with pros and cons for branch points. This allows patients more active involvement and can break through the frozen paralysis of overwhelming states. The tactful use of these active approaches can counter the emotional weight of ambiguity inherent in medical care. Sometimes patients need the gentle and active coaching style encouraged in cognitive behavioral approaches, even when one is also simultaneously attending to deeper psychodynamic conflicts and themes, to transference-countertransference process and to dreams and other symbolic material. As always, one needs to be mindful of giving room for the expression of feeling and to one's own potential resistance to the raw human experience of the suffering other.

Finally, music and expressive arts modalities can be effective. Non-verbal communication and expression can allow access and processing of material that is otherwise threatening and defended against. It is also a way to give shape to and digest as of yet unformulated emotion and psychic material. As Aldridge (1993) states, "By painting, singing, dancing, acting or making music together we can bring the emotion of suffering into the world in concrete form. Suffering made external as expression and brought into form as art gives the individual the chance to grapple with the meaning of that suffering and thereby to bring about change." Artistic involvement can also provide refuge, and a place where creativity and play are nourished.

29.2.3.11 Brief Psychotherapy and Additional Considerations

We often have a limited number of sessions available with our patients—especially in this age of managed care, which pushes for short hospital stays. Despite this, patients are sometimes hospitalized for longer time periods. In this case more formal brief psychotherapies can be attempted. The narrative approaches we've discussed can be expanded into these longer courses. There are also brief psychodynamic, interpersonal, and cognitive behavioral approaches that can be helpful and which often explore and address previously mentioned themes. If there are specific psychiatric disorders, one can utilize evidence-based psychotherapeutic approaches. Sometimes grief work can be engaged. Some patients with HIV have significant punishment beliefs for which techniques such as positive affirmations or cognitive restructuring can be attempted—as well, we slowly shift these and other internalized, relational models and self-understandings through new relational experiences with the clinician. If there are particular skill deficits, skill-building work can be attempted (for example, the skills utilized in dialectical behavior therapy for borderline personality disorder, including distress tolerance, interpersonal effectiveness, and mindfulness skills). Antiretroviral medication adherence issues can be targeted in brief therapy.

29.2.4 Specific Psychiatric Syndromes in HIV Patients

29.2.4.1 Mood Disorders

Depression is the most common psychiatric disorder for which HIV-positive individuals seek treatment and there is evidence that mood disorders are more prevalent in HIV-positive individuals. In part this reflects higher rates of mood disorder in the main risk groups—intravenous drug users and homosexual men.

Depression: Diagnostic Considerations

Diagnosis and treatment of Depression in HIV infection can be complicated by somatic symptoms shared by both disorders—these include attention and concentration difficulties, sleep disturbance, appetite disturbance, and fatigue. Co-morbid substance abuse can also complicate the diagnosis. It is also imperative to differentiate demoralization and adjustment disorder from

other forms of depression, as the treatment approach can be quite different, with more focus on psychotherapeutic intervention. Especially with demoralization, it becomes important to not pathologize what can be considered a normal response to intense circumstance. In addition, once must also consider unresolved grief issues, dysthymic disorder, major depression, and bipolar depression.

Demoralization and Adjustment Disorder

In demoralization, patients have sadness that is often specifically related to a particular event or circumstance. Sometimes, this can be difficult to differentiate from major depression. Unlike in major depression, the patients often report feeling fairly normal when they are distracted from thinking about the event or circumstance causing their distress (Angelino and Treisman 2001) and this sadness ameliorates if the event or circumstance achieves some resolution or improvement. In one HIV Clinic, the distinction between depression and demoralization was explored and approximately half of the patients with depressive complaints were felt to have major depression, whereas the other half experienced demoralization (Lyketsos et al. 1994).

At the heart of demoralization is a breakdown in coping—when these mechanisms are insufficient, distress and helplessness ensue (Clarke and Kissane 2002). Breakdowns in hope and meaning are also important contributors to demoralization—a breakdown in one's assumptive world, with loss of meaning, can happen in response to events such as major illness or bereavement (Clarke and Kissane 2002). When demoralization is due to illness, it will abate as the patient's health improves—even when there is a terminal illness, demoralization will improve if the physician understands their concerns and addresses them (Slavney 1999). Demoralization may also be common in the context of addiction, when during periods of sobriety the person struggling with addiction faces losses and also from a sense of powerlessness over the drug craving (Angelino and Treisman 2001).

An important distinction between major depression and demoralization is that the former is characterized particularly by anhedonia, whereas the latter is characterized by a subjective feeling of incompetence. "A depressed person has lost the ability to experience pleasure generally, whereas a demoralized person, while being unable to look forward with pleasant anticipation, may laugh and enjoy the present moment. The demoralized feel inhibited in action by not knowing what to do, feeling helpless and incompetent; the depressed have lost motivation and drive even when an appropriate course of action is known" (Clarke and Kissane 2002).

It has been argued that demoralization is a normal response under certain circumstances; though people differ in their vulnerability to it, even the most resilient have their breaking point (Slavney 1999); others argue that this minimizes the importance of demoralization and that though it can at times be understandable, it is always abnormal (Clarke and Kissane 2002). Patients who are estranged from family and friends, and patients with physicians who are distant or condescending may be more vulnerable to demoralization (Slavney 1999).

Demoralization, when diagnosed, needs to be explained and validated to both the patient and their physician as a normal response to a difficult situation. Sometimes physicians are uncomfortable with emotional distress and want the psychiatrist to recommend an antidepressant—there is a great opportunity for psychoeducation here and it should be made clear that they are not suffering from a psychiatric disorder (Slavney 1999). Adjustment disorder, on the other hand, is diagnosed when marked distress that is in excess of what would be expected given the nature of the stressor, or by significant impairment in social or occupational (academic) functioning is present. For billing purposes for Demoralization Syndrome, the ICD-9 code V71.09 ("Other suspected mental condition") can be used (Slavney 1999).

Clarke and Kissane (2002) describe some important therapeutic tasks in demoralization: (1) symptomatic relief of physical and mental symptoms; (2) cognitive work that includes information and reassurance, reality-testing, problem-solving, exploring appraisals and meanings, identifying and challenging cognitive distortions, looking at meaning and purpose; (3) a behavioral component that links the exploration of meaning and purpose

with goal setting and scheduling of positive activities, which can assist in redeveloping a sense of mastery and control, re-engagement in relationships, enjoyment of pleasurable activities; and (4) providing an empathic understanding of the patient, which reduces alienation and reinforces their value as a person.

Secondary Depression

This includes depression secondary to medical conditions, medication-induced depressive symptoms, and substance-induced depression. Careful history taking, physical exam, and appropriate medical work-up are important to investigate these etiologies of depressive symptoms. In addition to the usual organic workup, testosterone deficiency should be considered and antiretroviral medications with potential mood effects should be assessed for (e.g., efavirenz (Sustiva)). When there is significant substance abuse, clear diagnosis can be challenging. It can be helpful to inquire about periods of sobriety and assess the presence of mood symptoms during these periods. It can also be helpful to inquire about the temporal sequence—i.e., did the depressive symptoms predate the substance abuse or vice-versa.

Testosterone deficiency, present in up to 50 % of men with HIV, is a specific medical condition that is associated with HIV-infection, which can lead to depressive symptomology. Symptoms of hypogonadism can include depressed mood, fatigue, diminished libido, decreased appetite, and loss of body mass. Evaluation includes testing for serum testosterone (below 300–400 ng/day is abnormal) and treatment is testosterone. Depot testosterone (400 mg IM biweekly) has been shown to improve mood in HIV-positive men with major depression in a double-blind placebo-controlled study. Transdermal testosterone replacement can also be considered and may offer a more physiologic pharmacokinetic profile (Colibazzi et al. 2006).

Mania: Diagnostic Considerations and Differential

As with manic-like states in non-HIV patients, substance-induced (e.g., psychostimulants) etiologies need to be considered, as well as medication-induced etiologies (e.g., corticosteroids, androgens, zidovudine, didanosine, efavirenz) (Colibazzi et al. 2006). In primary mania, there is often a preexisting bipolar disorder or at least family history of a mood disorder. In secondary mania, there is less association with family history, but more association with progression of underlying HIV disease and CNS involvement. The symptomology of secondary mania is different and may include more irritability, less pressured speech, more psychomotor slowing, and more cognitive impairment (Ferrando and Wapenyi 2002).

Mood Disorders: Treatment Considerations

Depression

In addition to improving the general quality of life, in HIV-positive individuals, treatment of clinical depression has been shown to increase health-related quality of life and increase antiretroviral adherence (Elliot and Roy-Byrne 2002). There is now growing data to support the pharmacologic and psychotherapeutic treatment of major depression in the setting of HIV-infection.

TCAs (imipramine) have been shown to be effective in HIV-depression, but significant side effects lead to frequent discontinuation. Coupled with potential lethality in overdose, TCAs have become second-line agents (Ferrando and Wapenyi 2002). SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram) have been shown to be effective in HIV, across HIV illness stages, in both open label and double-blind, placebo-controlled trials—they have been shown to be as effective as TCAs, but with more tolerable side effect profiles. The response rates and adverse effects do not vary as a function of CD4 count (Ferrando and Wapenyi 2002). There is some evidence that HIV-positive patients receiving antiretroviral treatment and SSRI treatment may be at increased risk for developing serotonin syndrome (DeSilva et al. 2001). Mirtazapine, venlafaxine, bupropion have been studied in small, open label trials with major depression and HIV with favorable response rates (>70 %) and few adverse effects (Ferrando and Wapenyi 2002).

For augmentation in partial response, one can consider lithium, thyroid hormone, buproprion, antipsychotic medications, or methylphenidate (Angelino and Treisman 2001). There are open

label and placebo-controlled studies that support the use of psychostimulants in advanced HIV, demonstrating quick response and good tolerability. Caution should be used with substance abusers, given abuse potential though there are no published reports of abuse of prescription psychostimulants in HIV patients under medical supervision (Ferrando and Wapenyi 2002). Recent RCTs have demonstrated the benefit of modafinil (Rabkin et al. 2010) and armodafinil (Rabkin et al. 2011) for HIV-related fatigue, and may provide benefit for patients with depression in which anergia predominates.

Regarding Complementary and Alternative Medicine (CAM), St. John's Wort is not recommended as it may decrease levels of protease inhibitors. Overall, research into CAM interventions for clinical depression in HIV-positive individuals is lacking and an area for further research.

Aerobic exercise has been shown to be safe and potentially beneficial for those living with HIV/AIDS (O'Brien et al. 2010) and as beneficial in depression. There are intriguing, emerging perspectives that look at neuroimmunomodulatory effects of physical activity on the brain in depression, with evidence suggesting that exercise can enhance the beneficial and reduce the detrimental effects of the neuroimmune system (Eyre et al. 2013). Extending this research to reflect on the relation of exercise to the immune system in the HIV/AIDS context may provide a more compelling basis for this intervention with the depressed HIV patient. One study of psychotherapy and HIV compared interpersonal psychotherapy, cognitive behavioral therapy, supportive therapy plus imipramine, and supportive therapy alone—interpersonal therapy and supportive therapy plus imipramine were superior to the other treatments (Markowitz et al. 1998). Interpersonal therapy works with four themes: role transition, interpersonal deficit, interpersonal conflict, and grief/loss. When the major depression is treated, there are often other issues that can still benefit from psychotherapy.

Mania

Practice guidelines recommend lithium, valproic acid, or carbamazepine. Lithium has been shown to be effective in HIV-positive individuals, but it has a low therapeutic index and can be neurotoxic and poorly tolerated in HIV-positive individuals. Valproic acid has been the best studied with one study using doses up to 1,750 mg/day and serum levels >50 μg/L and another study finding efficacy at levels between 90 and 100 μg/L (Ferrando and Wapenyi 2002). There is some in vitro evidence of increased HIV replication, but this has not been shown in vivo, including an in vivo trial that showed valproic acid does not affect viral load in patients on antiretroviral therapy (Maggi and Halman 2001). Newer data have shown that valproic acid may ameliorate neurotoxicity associated with AIDS Dementia Complex (ADC) (Schifitto et al. 2006). In addition to anticonvulsants, atypical antipsychotics, including risperidone, olanzapine, and quetiapine, can be effective mood stabilizers. One needs to be mindful of potential metabolic side effects, especially with olanzapine and clozapine. Finally, benzodiazepines can be a useful short term adjunct—there is a case report using clonazepam 2 mg PO TID with success in controlling HIV-related manic symptoms (Ferrando and Wapenyi 2002).

29.2.4.2 Anxiety Disorders

Patients at various illness phases can have significant anxiety relating to HIV-infection and sequelae. Current anxiety symptoms are present in up to 11 % of HIV patients (Sewell et al. 2000). Somatic etiologies need to be considered—e.g., substance intoxication and withdrawal states, medication side effects (e.g., interferon, petamidine, AZT, 3TC), opportunistic illness-related anxiety symptoms, and other medical conditions such as anemia, hypoxia, and various metabolic disturbances. Anxiety and agitation can frequently be seen in the setting of delirium and ADC. In addition to anxiety secondary to somatic etiologies, the differential includes adjustment disorder with anxious features and other anxiety disorders, including social phobia, generalized anxiety disorder, post-traumatic stress disorder, panic disorder, and obsessive-compulsive disorder. There has been recent interest in PTSD resulting from illness and also in caregivers for

the ill and dying, with PTSD quite common in these contexts. In addition to subjective distress, PTSD has been shown to negatively affect medical outcome. Special attention should be paid to evaluating for illness-related PTSD symptoms.

Anxiety Disorders: Treatment Considerations

SSRIs are first line agents for generalized anxiety disorder, social phobia, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder. Mirtazapine (Remeron) and venlafaxine (Effexor) are also good options. Other options include gabapentin (Neurontin) and buspirone (Buspar). Atypical antipsychotics such as quetiapine can be considered (Buoli et al. 2013), but potential metabolic side effects and drug interactions need to be considered (Pollack et al. 2009).

Patients often seek benzodiazepines because of immediate relief—yet safety concerns, cognitive side effects, and abuse potential need to be addressed. For patients who request benzodiazepines, but who are at high risk of negative consequence (e.g., patients with substance abuse or dependence), it is important to express an intention to treat their anxiety, but to also set gentle but firm limits. For non-high risk patients, benzodiazepines can be considered for short-term use, or as a time-limited agent to bridge the gap before antidepressant effect has taken place. Lorazepam, oxazepam, and temazepam are the agents of choice for patients taking protease inhibitors.

Relaxation and meditation techniques can be effectively taught to patients in the hospital setting and can be powerful, non-pharmacological anxiety-management tools. For patients with longer anticipated hospital stays, cognitive behavioral material specific to their anxiety disorder can be incorporated. The advantage of these non-pharmacological approaches is that they can allow the patient a sense of internal control, helpful in countering demoralization, and there are usually no side effects to deal with. Music can be a useful relaxation tool as well and other expressive arts modalities should also be considered.

29.2.4.3 Psychotic Disorders

Psychotic Disorders: Diagnostic Considerations

Psychosis in HIV can have multiple etiologies, including substance intoxication or withdrawal states, medication-induced, opportunistic infection-related, or secondary to other organic etiologies. HIV-patients with delirium or dementia can have psychotic symptoms. Given the higher prevalence of antisocial personality disorder in HIV-positive populations, malingering also needs to be considered.

It is important to rule out substance-induced and organic etiologies before making a primary psychiatric diagnosis. Primary psychiatric disorders that can involve psychotic symptoms include mood disorder with psychotic features, schizoaffective disorder, schizophrenia, as well as certain personality disorders—mainly borderline-personality disorder.

Psychotic Disorders: Treatment Considerations

HIV-positive patients can be more susceptible to extrapyramidal side effects (EPS) as a consequence of HIV-induced neuronal damage to the basal ganglia (Work Group on HIV/AIDS 2000). Also, movement disorders such as acute dystonias and Parkinsonism can be seen in advanced HIV in the absence of neuroleptic treatment (Ferrando and Wapenyi 2002). With regard to typical antipsychotics, haloperidol has been shown to be effective in HIV-positive patients with schizophrenia, but with high EPS incidence. With regard to atypical antipsychotics, both clozapine and risperidone have been shown to be safe and effective in HIV-positive patients (Lera and Zirulnik 1999; Singh et al. 1997). Overall, atypical antipsychotics are preferable given the lower rate of EPS. However, there are limited data for antipsychotics and larger, controlled studies are needed to expand our knowledge on the appropriate use of second-generation antipsychotics in HIV-infected patients (Hill and Lee 2013). Finally, there is evidence to support the use of cognitive behavioral therapy in psychotic disorders such as schizophrenia (Rector et al. 2012),

and limited data examining CBT in the HIV treatment setting (Goldberg et al. 2011).

29.2.4.4 Substance Abuse/ Dependence Disorders

In substance use disorders, substance use often impairs judgment and leads to impulsivity and high-risk sexual behaviors. Certain substances such as cocaine and methamphetamine can increase sexual desire and lead to high-risk situations. In the context of intravenous drug use, the sharing of contaminated needles is a major risk factor for HIV infection. Substance abuse and dependence can increase the risk of infection and also decreases compliance with HIV treatment. Substance intoxication and withdrawal states can also complicate the diagnosis of psychiatric disorders.

Substance Disorders: Treatment Considerations

This can be similar to treatment in non HIV-positive substance abusers. Motivational enhancement techniques can be especially valuable for ambivalent patients. Patients should be educated that longevity is now possible with properly treated HIV, and that this also involves treating chemical dependency. For patients who previously viewed HIV-diagnosis as a death sentence, this corrective information can partially address feelings of illness-related hopelessness and thus affect their motivation towards treatment.

The overall treatment can be seen as consisting of four steps: detoxification, rehabilitation, treatment of co-morbid conditions, and relapse prevention. Referral to 12-step groups can be helpful, especially trying to link the patient with a sponsor. Education on safe-sex behavior (condom use) and high-risk drug behaviors (needle-sharing) to decrease the risk of spread is important. Finally, vocational rehabilitation, social rehabilitation, and the creation of a drug-free environment are essential to preventing relapse (Angelino and Treisman 2001).

29.2.4.5 Personality Disorders

Patients with personality disorder, especially borderline and antisocial personality disorder, are more likely to contract HIV due to impulsivity and increased high-risk behavior. Once infected, personality disorder affects all aspects of HIV-infection and its treatment. Intrapsychic issues such as meaning of illness, behavioral response including coping, and interpersonal dynamics including those between patients and care providers are all affected. A thorough examination of this topic is beyond the scope of this section and can be found elsewhere.

In the hospital, the "difficult patient" is a common cause for psychiatric consultation. There are interventions that can be implemented with both patient and providers. For providers, including ward staff, it is often important to create a space for angry and hostile feelings arising in providers to be voiced, minimizing the chance that they will be disowned and projected completely onto the patient. As well, it becomes important to frame the patient as a wounded individual deserving of compassion, as well as needing limits. Gentle, strict, but non-punitive limits need to be set on inappropriate patient behavior and sometimes formal contracts need to be constructed. There is often room for direct skills-building work with the patient. If some relationship can be established with the patient, distress tolerance and interpersonal communication skills can be worked on. Mindfulness and stress-management techniques can be introduced to deal with distress and affective dysregulation, and thus decrease acting out behaviors. Through chain analysis and therapeutic conversation, patient behaviors that detract from receiving deserved care can be addressed and new avenues of getting needs met can be explored.

Sometimes, patients who are otherwise higher functioning can regress in hospital settings and appear personality disordered. Other times, history-taking, including dialogue with collateral sources, clarifies a longer-standing pattern of frank personality disorder. In this case, it is critical to make referral to psychotherapy and to consider referral to HIV-specialty clinics where there is psychiatry and psychology presence—this is critical since the personality disorder will undoubtedly surface in areas of medication and treatment compliance, provider interactions, and also in high-risk behaviors which are risks for further spread of HIV in the community.

29.2.4.6 Cognitive Disorders: Delirium and Dementia

Delirium

When the HIV-positive patient presents with altered mental status, special attention should be paid to ruling out organic processes associated with HIV-infection—these include direct HIV-infection of the CNS, opportunistic infections associated with HIV, other disorders related to HIV, as well as neuropsychiatric side effects of HIV treatment. As well, when a patient with unknown status (but high risk) has altered mental status of unclear etiology, HIV-testing should be done, as positive status necessitates additional evaluation.

Delirium is one of the most common diagnoses in HIV-positive patients evaluated by consultation psychiatry. HIV-positive patients have less cognitive reserve and are more likely to develop delirium. Delirium is characterized by rapid onset of fluctuating level of consciousness, markedly poor attention, disorientation, as well as perceptual disturbances. This diagnosis needs to be suspected even in patients with pre-existing psychiatric diagnoses. Practitioners often focus on more obvious phenomenon such as delusional content or hallucinations, deeming the etiology as psychiatric—disorientation and waxing/waning consciousness are not typical of a primary psychiatric illness and should be a tip-off to delirium. There is often a significant role for the consultant to provide education regarding delirium and its medical nature, despite neuropsychiatric and behavioral phenomenon.

As with non HIV-positive patients, the etiology is often multifactorial and the differential can include withdrawal/intoxication states, medication effects (especially anticholinergic medications, benzodiazepines, and narcotic analgesics), metabolic disturbances (e.g., hypoxia), electrolyte imbalances (hyponatremia, hypercalcemia), liver and renal failure, infection and sepsis (in HIV, one needs to consider HSV, VZV, CMV, and HIV encephalitis; as well as cerebral cryptococcus and toxoplasmosis), cerebral hypoperfusion (e.g., from shock and severe hypotension), postictal states and other CNS events (e.g., ischemic and hemorrhagic stroke).

The workup should include careful gathering of history from friends, family, case managers, and care providers in the community, to establish a better baseline and course of cognitive decline. A careful physical examination should be performed, including detailed neurological exam. Lab testing should be done and include evaluation of electrolytes, renal and hepatic function, syphilis serology, vitamin B12 level, and toxicology screen. Head imaging and unless contraindicated, lumbar puncture should also be performed. Review of current medications and evaluation of recreational drugs and alcohol consumption are also important. Electroencephalogram can be helpful if epileptiform activity is suspected, and diffuse slowing is consistent with delirium.

Lumbar puncture in HIV-positive individuals is complicated by frequent non-specific findings (e.g., mild elevations in white blood cell count, mild elevations in protein, mild decrease in glucose). Regardless, lumbar puncture can be critical for detecting treatable CNS diseases, including cryptococcal, syphilitic, tuberculous, or lymphomatous meningitis. CSF PCR for TB, varicella zoster virus (VZV), herpes simplex virus (HSV), cytomegalovirus (CMV), and JC virus (in progressive multifocal leukoencephalopathy, PML) can be useful tools when available.

Regarding imaging, MRI is more sensitive than CT, but CT with double-dose contrast can be a good alternative. Diffuse white-matter abnormalities can be suggestive of PML or HIV encephalitis. Periventricular contrast enhancement is sometimes seen with CMV or varicella zoster virus. Focal cerebral lesions are often abscesses (e.g., toxoplasmosis) or primary CNS lymphoma.

Treatment Considerations

Of course, attempts need to be made to treat the underlying disease(s) and other potentially exacerbating factors. Pharmacologic approaches can be useful for managing the delirium, especially the use of atypical antipsychotics, which have a lower risk of EPS. Haloperidol and chlorpromazine in small doses have also been shown to be effective in HIV/AIDS delirium without much EPS (Breitbart et al. 1996). Non-pharmacologic

approaches are also useful, including providing frequent reorientation, avoiding sensory overstimulation or deprivation, providing soothing music, and having friends, family members or community providers providing contact and presence. Once the delirium has cleared, it is important to process the experience of delirium with the patient, who can often experience it as intensely frightening and sometimes as indication of "going crazy."

HIV-Associated Neurocognitive Disorders (HAND) and HIV-Associated Dementia (HAD)/AIDS Dementia Complex (ADC)

The term HAND encompasses a spectrum of progressively severe CNS involvement, ranging from asymptomatic neurocognitive impairment to HAD/ADC. With the introduction of HAART, the incidence of AIDS Dementia Complex (ADC) has dramatically reduced. There is encouraging recent data which looked at a small sample (74) of older (mean age 51) HIV-infected individuals with a mean duration of infection of 17 years, and found successful cognitive aging (defined as an absence of neurocognitive deficits) in 32 %. This, in turn, was associated with better everyday functioning outcomes, including lower rates of decline in activities of everyday living, superior outcomes in dealing with medication management, and a lower rate of major depression and other forms of depression and anxiety (Malaspina et al. 2011). Despite this, HAND and ADC persist and recent estimates of less severe forms of the latter still hover around 20 % (Manji et al. 2013).

Some investigators maintain that HIV-1 proliferation in the brain is needed for development of ADC, while others argue that neurotoxicity can be an indirect result from pro-inflammatory cytokines and chronic, sustained immune activation in the CNS (Tan and McArthur 2012). For patients with ADC on effective antiretroviral regimens, it has been shown that macrophage secretions cause a dysregulation of proteins critical for regular function, but not outright neurotoxicity—thus for patients on antiretroviral therapy ADC is typically milder and a more slowly progressing deterioration in mental functioning.

Some HIV-infected individuals are manifesting a dementia more similar to Alzheimer disease than typical ADC—for example, demonstrating deficits in long-term memory. Some theories include: as patients with AIDS are living longer and aging, they may simply be developing Alzheimer's; some of the newer antiretroviral drugs might be increasing the risk of Alzheimer disease by affecting lipid metabolism and the processing of amyloid; and chronic, low-grade brain inflammation, as occurring in HIV-associated brain disease, might be contributing to a vulnerability to Alzheimer disease. Patients now need to be evaluated for cortical dysfunction as well as the subcortical dysfunction of more "classical" ADC.

Early manifestations of ADC include: (1) cognitive dysfunction, including forgetfulness, slowing, impaired concentration and attention, sequencing problems, (2) behavioral issues, including withdrawal and disinhibition, and (3) motor dysfunction, including slowing, unsteady gait, weakness, and poor coordination. Later manifestations can include: (1) cognitive dysfunction, including memory loss, word-finding problems, poor attention/concentration, impaired judgment, (2) behavioral issues, including withdrawal, apathy, irritability, agitation, disinhibition, (3) psychiatric issues, including mania, depression, psychosis, and (4) motor dysfunction, including slowing, spasticity, paraplegia, and incontinence.

There are neuropsychological tests that can be helpful in the identification of HAND and ADC. The International HIV Dementia Scale (IHDS) is a brief, bedside method that requires no equipment and includes a memory-recall test, a psychomotor-speed test, and a motor-speed test. Using a cutoff of 11 points or lower, researchers report 72 % sensitivity and 44 % specificity for all forms of HAND, even though it was developed for detection of ADC (Spudich et al. 2012). Examination of CSF for HIV RNA can be helpful—"CNS escape" occurs when there is HIV RNA detectable in CSF, but not in plasma. Thus when there is significant HAND or ADC and CNS escape is detected, further cognitive improvement can occur when the antiretroviral

regimen is modified to be more CNS-penetrating (Valcour 2011).

ADC also needs to be differentiated from delirium, which can sometimes be hard in the acute setting. Collateral history can be helpful in this regard, as delirium has an acute or subacute onset, whereas ADC has a more gradual decline. Of course, the two conditions can often be comorbid. Thus, when a patient with ADC develops an acute worsening in mental status, delirium workup should proceed.

Treatment Considerations

HAART can lead to significant improvement in AIDS-related cognitive deficits and AIDS-dementia, provided the particular agent has good CNS penetration. Some are proposing that nanotechnology may one day allow further control in characteristics that allow better penetration of the blood–brain barrier, and are urging research into active drug targeting systems that include nanoparticles. Their hope is that this will one day provide relief for neurological impacts of HIV/AIDS—i.e., HAND and HAD/ADC (Saxena et al. 2012). Case reports have described the use of risperidone (up to 6 mg/day) and clozapine in psychosis associated with HIV-dementia with significant improvement in symptoms and low EPS (Dettling et al. 1998; Zilikis et al. 1998). Behavioral and non-pharmacologic approaches should also be integrated (see Chap. 7).

29.2.5 Drug Interaction Issues in the Psychopharmacological Treatment of Patients with HIV and AIDS

Drug interactions are an important consideration and one needs to have an index of suspicion and investigate potential interactions prior to initiating psychotropic treatment (Ferrando and Wapenyi 2002). An increase in plasma concentration does not always translate into clinical significance—this depends primarily on the therapeutic index of the drug involved (Ferrando and Wapenyi 2002). Most documented interactions involve ritonavir, a potent inhibitor of the CYP 450 3A enzyme (Ferrando and Wapenyi 2002). Ritonavir causes a 145 % increase in AUC (area under the plasma concentration curve) of desipramine, so dose reduction and plasma level monitoring is recommended. Buproprion was listed as contraindicated with ritonavir, but this has been removed since it is metabolized by the 2B6 isoform, not significantly affected by ritonavir. Clozapine, pimozide and several benzodiazepines (clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam), and zolpidem are listed as contraindicated since ritonavir presumptively raises their serum levels. One study did show non-significant effects with zolpidem, so this contraindication is questionable. Methadone levels may be decreased by rifampin (used for TB treatment) and also the antiretrovirals ritonavir, nevirapine, and possibly efravirenz. It is advisable to follow serum methadone levels before and after initiation of HAART (Ferrando and Wapenyi 2002). Sildenafil levels may be raised by concurrent administration of ritonavir, saquinavir, and indinavir resulting in potentially dangerous cardiac side effects. Despite the need to be cautious, there have been few serious drug interactions documented and it is important to provide treatment when needed (Ferrando and Wapenyi 2002).

29.3 Organ Transplantation Patients

29.3.1 Unique Psychosocial Issues and Treatment Considerations

While HIV is an unanticipated "acquired" condition, transplantation-related immunodeficiency is often a long contemplated, desired, and "required" condition for survival. The field of transplantation is based upon the ability to adequately suppress a transplant recipient's immune system to allow tolerance of the graft, ensuring function, while minimizing infectious risk.

Since first attempted in the 1950s, transplantation has become a more common and accepted treatment by the public. Discussion of transplant

candidacy and issues such as adherence to medication are beyond the scope of this chapter, but are well described in the literature (Olbrisch and Levenson 1995; Levenson and Olbrisch 1993; Chisholm 2002). The focus of this section is on general characteristics of transplant recipients of all organ systems. Balanced information is presented to allow practitioners who have not previously treated transplant recipients to approach them with a sense of confidence that they can evaluate and initiate appropriate treatment plans.

A tenuous state of pharmacologically controlled immune function is required for survival among solid organ transplant recipients. This delicate balance requires ongoing vigilance of the recipient and healthcare team for warning signs of rejection and infection, which are primary threats to survival. Strict adherence to medications, diet, and self-surveillance are a way of life among those who adjust well, while depression, anxiety, and other psychiatric issues may result in those who have more difficulty coping (Perez-San-Gregorio et al. 2005).

Improving the side effect and efficacy profile of immunosuppressive agents has been a focus of attention over the last 30 years. The number and type of agents available has grown as a result, but remains limited in scope. All immunosuppressive agents are associated with potentially serious toxicity and side effects that impact short- and long-term functional ability (Hathaway et al. 2003; Umeda et al. 2011; Corbett et al. 2013). Table 29.1 summarizes agents, mode of action, general, and neuropsychiatric side effects that may be observed.

Table 29.1 Immunosuppressive agents commonly used in transplantation with associated medical and psychiatric side effects (Trzepacz et al. 1991; Trzepacz et al. 1993a, 1993b)

Class	Agent	Mode of action	General side effect profile	Psychiatric side effect profile
Corticosteroids (Hathaway et al. 1996; Cerullo 2006; Prasad et al. 2003)	Prednisone methyl prednisolone	Anti-inflammatory	Diminished signs of infection, osteoporosis, impaired glycemic control, hypertension, hyperlipidemia	Depression (especially with late phase weaning) Insomnia cognitive decline Mania Confusion Agitation (prominent in pulse dosing for rejection)
Anti-metabolites (Crawford et al. 1996)	Azathioprine	Blocks DNA synthesis	Neutropenia, increased likelihood of infection, bone marrow suppression	None noted in existing literature
Calcineurin inhibitors (CNI) (De Groen et al. 1987; Ciancio et al. 2004; Chegounchi et al. 2006)	Cyclosporine tacrolimus	Inhibit calcineurin phosphatase and T cell activation	Nephrotoxicity, vulnerability to viral infection, hypertension, diabetes, hyperlipidemia	Depression Confusion Cortical blindness Quadriplegia Seizures Coma
Purine synthesis inhibitors (Prasad et al. 2003)	Mycophenolate mofetil	Prevent B and T cell proliferation	Gastrointestinal cramping diarrhea, neutropenia	Distress from GI side effects
Target of rapamycin inhibitors (TORI) (Kasner et al. 2005)	Sirolimus	Inhibit interleukin 2T cell Proliferation	Hyperlipidemia, thrombocytopenia	None noted in existing literature
Depleting antibodies	ATG (antithymocyte globulin) OKT3 (muromonab-CD3)	Deplete T and/or B cells that have been activated and are acutely injuring graft	Allergic reaction, fever, flushing, hypotension, aseptic meningitis, coma	Confusion Lethargy Coma

Table 29.2 Psychiatric symptoms and medical mimics

Psychiatric symptom	Symptom delineation	Medical mimic
Depression	Fatigue, low energy, difficulty concentrating	Anemia: hemoglobin of 6 Severe B12 deficiency Lymphoproliferative disorder
Anxiety	Apprehension Inability to relax Frequent dyspnea	Sepsis Rejection (pulmonary/cardiac) Pulmonary embolism
Psychosis	Hallucinations Delusions	Stroke CMV infection Cyclosporine toxicity
Mania	Impaired sleep, Motor agitation, racing thoughts, impulsive behavior	Thyrotoxicosis Steroids Central nervous system herpetic infection
Dementia	Forgetfulness, confusion, difficulty concentrating	Hypothyroidism Vascular insufficiency Stroke in evolution

29.3.2 Psychiatric Co-morbidities

29.3.2.1 Diagnostic Issues

Individuals who undergo transplantation are generally very ill and often exhausted by their chronic conditions; the stress and concomitant physiologic dysfunction associated with chronic organ dysfunction may be associated with adjustment, anxiety, cognitive, and mood disorders addressed in other areas of this text. Preexisting symptoms and syndromes may be exacerbated post-transplantation if treatment is not rendered. Willingness to accept mental health care is often challenging post transplantation due to a number of factors, such as limited resources and impaired ability to access treatment due to tenuous health as well as poor motivation on the part of the patient. Preoperative psychosocial assessment can have beneficial effect by educating potential recipients and providers of the likelihood of worsened symptoms post transplantation.

29.3.2.2 Specific Assessment Considerations

Each individual who has undergone solid organ transplantation is unique. Those referred for psychiatric assessment and treatment are manifesting symptoms that are generally significant enough to have raised the attention of their families and/or transplant providers. Attention to detail of pre-transplant, peri-operative, and post-transplant courses will provide the necessary information to accurately diagnose and treat individuals who present for care.

There are general caveats that should guide the approach to all transplant recipients with new onset psychiatric symptoms: (1) symptoms are of an organic etiology unless (and occasionally, even if) medical evaluation is negative; (2) a full review of somatic symptoms will often guide further necessary evaluation; and (3) attention to the timeline of all prescribed medications, supplements, and herbal remedies with respect to psychological symptoms will often provide a clue for iatrogenic symptoms. Table 29.2 presents acute medical mimics of psychiatric symptoms and syndromes.

Unlike more routine evaluations, exposure histories are essential in teasing out potential infectious etiologies for psychiatric symptoms. In addition, inquiry regarding adherence to medications and utilization of herbal remedies should be addressed to the recipient (and support persons if available), as the complexity of treatment regimens leaves little room for error. Moreover, data indicate that adherence can be strongly impacted by the presence of psychiatric disorders and psychosocial problems (Krahn and DiMartini 2005; Carrasco et al. 2009). Up to date medication lists are essential in determining if medications

have been added by outside physicians not associated with the transplant program. Immunosuppressive toxicity or organ rejection related to inadequate immune suppression can result from the addition of a medication(s) that interacts with transplant regimen.

29.3.2.3 Cognitive Disorders/Organic Brain Syndrome (OBS) and Delirium

OBS and delirium are common in early transplant recipients and in the pre-transplant period. The full range of symptoms from quiet withdrawn states to acutely agitated psychotic states may be seen in post-transplant recipients and often serves as an "early warning sign" of an undeclared infection or impending graft dysfunction. The effect of chronic immunosuppressive agents on cognitive decline noted post-transplantation remains unclear though there is evidence of at least short-term neurocognitive effects (Cupples and Stilley 2005; Aridon et al. 2009; Emirolglu et al. 2006; Umeda et al. 2011). Cognitive deficits secondary to prior addictions may be unmasked in the post-transplant period, while pre-transplant decline attributed to organ dysfunction may not remit, suggesting the presence of dementia (Sorrell et al. 2006).

Common underlying medical illnesses associated with organ failure requiring transplantation, including hypertension, diabetes, and hyperlipidemia, place the recipient at an increased risk for central nervous system small vessel ischemic disease, which may manifest as a stepwise progressive cognitive decline. An abrupt, profound change or a progressive decrement in cognitive functioning also requires evaluation for progressive leukoencephalopathy which has been associated with the utilization of calcineurin inhibitors (Munoz et al. 2006; Umeda et al. 2011). Additionally the potential for rare, but debilitating progressive multifocal leukoencephalopathy associated with polyomavirus is a concern in the absence of other definable causes for decline (Shitrit et al. 2005).

29.3.2.4 Mood Disorders

Post-transplantation depressive disorders have been reported in up to 60 % of solid organ recipients (Corbett et al. 2013). Presentation of mood disorders may range from a subtle return to smoking or other unhealthy behaviors, sudden non-adherence to medications or necessary follow up, to pronounced symptoms such as mania and suicidality. Depressive symptoms may be a continuation or exacerbations of those experienced in the pre-transplant period, or occur after transplantation. In the latter case, depression may be part of an adjustment reaction, or be secondary to an incipient medical condition or due to a medication effect. The recognition of depressive symptoms in the post-transplant period is crucial as studies have shown that depression and its related effects predict poorer outcomes such as reduced quality of life, graft failure, and a higher rate of mortality (Favaro et al. 2011; Zelle et al. 2012; Rogal et al. 2013). A recent study of liver transplant recipients found that those with increasing or persistent depression had a two times higher risk of death when compared with patients with more minor symptoms (DiMartini et al. 2011a, b). Research to date indicates that depressive symptoms occurring after transplant may more strongly correlate with adverse outcomes than do pre-existing symptoms (Rosenberger et al. 2012). However, it has yet to be clearly established that treatment of depression results in a reduction in mortality, though some studies have shown that reducing depressive symptoms may promote graft function (Rogal et al. 2013).

Essential evaluation should include a careful review of symptoms, physical evaluation, and if indicated, a diagnostic work-up prior to ascribing a primary psychiatric etiology for the symptoms.

29.3.2.5 Anxiety Disorders

Anxiety symptoms are also prevalent in organ transplant recipients with rates ranging from 14 to 40 % (Dew et al. 2012; Limbos et al. 2000; Tanriverdi et al. 2004). Acute presentation of anxiety symptoms may herald an imminent life threatening illness, and the potential for acute physiologic decompensation needs to be considered. Despite the conviction of many physicians, it is unusual for panic disorder to develop late in life. Thus, new onset anxiety should be viewed as of primary organic etiology until proven otherwise. In addition, substance abuse and

withdrawal may also contribute to anxiety states. More recently, PTSD secondary to medical illness and treatment has been appreciated, particularly in the setting of critical illness, ICU stay and associated delirium (DiMartini et al, 2007). It has been estimated that the prevalence of PTSD in the transplant population is 11–17 % (Favaro et al. 2011) and a recent study found that the prevalence of PTSD in a cohort of lung transplant recipients was two times higher than in the general population (Gries et al. 2013). While the data on PTSD in transplant patients are somewhat limited, evidence to date indicates that post-traumatic symptoms can negatively impact quality of life, and may impair drug adherence and sleep quality. PTSD symptoms have also been correlated with higher rates of re-hospitalization, disease relapse, and increased morbidity and mortality (Favaro et al. 2011; Guimaro et al. 2011; Cavalcanti-Ribeiro et al. 2012; Jin et al. 2012; Gries et al. 2013), and should be considered in the setting of new-onset anxiety.

29.3.2.6 Psychotic Disorders

Transplant centers rarely accept individuals with a known history of schizophrenia or schizoaffective disorder. As such, the number of recipients with these illnesses is small though many have been treated successfully. New onset psychotic disorders post-transplant are usually of organic etiology (Chegounchi et al. 2006; Southworth and Dunlap 2000; Hotson and Enzmann 1988). Central nervous system infection, drug toxicity, systemic infections, and delirium may present with hallucinations, paranoid delusions, disorganized behavior, and thought disorder and must be carefully ruled out.

29.3.2.7 Substance Abuse/ Dependence Disorders

Resumption of prior addictions needs to be considered in evaluating new onset cognitive, mood, anxiety, or psychotic illnesses, especially when substances were utilized in the pre-transplant period, as there is evidence that recipients with a history of substance abuse have a higher incidence of mood and anxiety symptoms and poorer quality of life post-transplant (Stilley et al. 2010). The extent of substance use is also important and should be clarified. Approximately, 70–75 % of liver transplant recipients meet DSM-IV criteria for alcohol dependence, and 20–25 % for alcohol abuse (DiMartini et al. 2008). Return to alcohol consumption has been studied extensively in the liver transplant population (Kelly et al. 2006; Beresford et al. 2004; DiMartini et al. 2002; DiMartini et al. 2006) and it is estimated that 30–50 % of transplant recipients may relapse. However, the incidence of serious use of alcohol is somewhat less, at 10–15 % (Surman et al. 2009). Noted predictors of relapse are a diagnosis of mental illness, lack of insight into substance problem, lack of a stable partner, daily quantity consumed in years prior to transplant assessment, active substance use at time of evaluation, and prior alcohol rehabilitation (DiMartini et al. 2006; Kelly et al. 2006; Bellamy et al. 2001). Resumption of disordered alcohol consumption increases the risk for non-adherence to medications and inattention to self-surveillance, which may lead to increased morbidity, graft failure, and mortality.

Of equal import although less frequently addressed is return to nicotine dependence. Recidivism is common post-transplantation and can negatively affect graft function and place individuals at higher risk for infection (DiMartini et al. 2005; Mehra et al. 2005).

Relapse with other illicit substances is less common, as those who receive transplants are typically carefully selected. Currently, limited numbers of individuals are transplanted while participating in Methadone Maintenance Treatment (MMT) (Koch and Banys 2001, 2002) though a return to opiate abuse appears to be low, with variable reports of survival (Liu et al. 2003; Kanchana et al. 2002). Anecdotal evidence suggests that recipients should remain on methadone unless carefully monitored as the rate of opiate relapse is high when patient is taken off of methadone (DiMartini et al. 2011a, b).

Chronic pain and the neuropathic sequelae of illnesses such as diabetes and *Herpes zoster* require coordinated management to optimize quality of life and assure judicious administration of controlled substances. Overall, it is

recommended that pre-transplant pain regimens should be re-established after surgery (Surman et al. 2009) though dose adjustments in opiates and methadone may be required after transplant when hepatic metabolism normalizes (DiMartini et al. 2011a, b). This may also provide an opportune time to wean the patient from a chronic analgesic opioid dependency (see Chap. 22).

29.3.3 Approaches to Treatment

The adage "start low, go slow, and be aware of side effects" is also appropriately applied in transplant recipients. Symptom identification and treatment are the primary goals of evaluation and an inclusive biopsychosocial approach can facilitate appropriate diagnosis and treatment planning.

Thoughtful consideration of medication side effect profiles may enhance treatment tolerability. For example, the use of an activating agent is imprudent in an agitated depression, while a sedating agent would be ill advised in someone who is unable to get out of bed or attend to activities of daily living. Further, with the addition of many new medications post-transplant, there is a potential for drug–drug interactions, and monitoring for symptoms of toxicity or lack of therapeutic efficacy is important (Vella and Sayegh 1998; Surman et al. 2009). In general, newer psychotropics should be used with special caution in transplant recipients and collaborative planning with a transplant pharmacist can be helpful in establishing a treatment regimen.

The recovery and return to function in family, community, and employment environments simultaneously present the potential for added stressors. The recipient's support system can be severely challenged by the procedure and recuperative period and the role adjustment for patients and those around them can generate significant distress for all.

With an already complex medication regimen to follow, patients may be more open to psychosocial interventions for mood and anxiety symptoms. Psychotherapeutic interventions to treat post-transplant recipients such as cognitive behavioral and mindfulness based approaches have demonstrated promise (Baines et al. 2004; Kreitzer et al. 2005; Gross et al. 2009, 2010) as well as music therapy (Madson and Silverman 2010; Ghetti 2011). Therapies to promote adherence have also been shown to be effective (Lisson et al. 2005), and individual and group psychotherapies can provide an environment for recipients and their support persons to address the challenges inherent to the transplant process.

The solid organ transplantation field strongly requires assessment studies that accurately evaluate the impact of psychosocial factors present prior to transplant on a variety of outcomes as the evidence demonstrates that they are highly correlated with significant morbidity and mortality, primarily through their effect on adherence. The role of the psychiatrist thus is key in aiding the transplant team assesses for pre-transplant psychiatric and psychosocial issues as well evaluating for the presence of new-onset psychiatric disorders after transplantation which may result in poorer medical and psychological outcomes.

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