PSYCHIATRIC CO-MORBIDITY IN PERINATALLY HIV-INFECTED CHILDREN AND ADOLESCENTS

A Multicenter Trial of the Pediatric AIDS Clinical Trials Group

Co-Sponsored by:

The National Institute of Allergy and Infectious Diseases and the National Institute of Mental Health

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PACTG P1055 PROTOCOL TEAM ROSTER

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List of Abbreviations:

- ADD - Attention-Deficit Disorder
- ADHD - Attention-Deficit with Hyperactivity Disorder
- ADHD:C - ADHD, Combined type
- ADHD:H - ADHD, Hyperactive-Impulsive type
- ADHD:I - ADHD, Inattentive type
- ASRI-4 - Adult Inventories-4
- CBCL - Child Behavior Checklist
- CD - Conduct Disorder
- CIS - Columbia Impairment Scale
- CNS - Central Nervous System
- CPRS - Conners' Parent Rating Scale
- DICA - Diagnostic Interview for Children and Adolescents
- DICA-C - Diagnostic Interview for Children and Adolescents-Child Version
- DICA-P - Diagnostic Interview for Children and Adolescents-Parent/Primary Caregiver Version
- DSM-IV - Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition
- FES - Family Environment Scale
- GAD - Generalized Anxiety Disorder
- IEP - Individual Education Plan
- MAGIC - The Missouri Assessment of Genetics Interview for Children (version of DICA)
- MDD - Major Depressive Disorder
- MMPI - Minnesota Multiphasic Personality Inventory
- MPQ - McGill Pain Questionnaire
- ODD - Oppositional-Defiant Disorder
- PDD - Pervasive Developmental Disorders
- PQ - Primary Caregiver Questionnaire
- PR - Primary Caregiver Report
- QOL - Quality of Life Assessment
- SAD - Separation Anxiety Disorder
- SES - Socioeconomic Status
- SF-MPQ - Short-Form McGill Pain Questionnaire
- SI-4 - Symptom Inventory-4 Primary Caregiver Checklist
- SSF - School and Social Functioning
- VAS - Visual Analogue Scales
- WISC-IV - Wechsler Intelligence Scale for Children – Fourth Edition
- YI-4 - Youth's Inventory-4
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APPENDICES

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SCHEMA

PSYCHIATRIC CO-MORBIDITY IN PERINATALLY HIV-INFECTED CHILDREN AND ADOLESCENTS

DESIGN: Multicenter, non-treatment, observational.

SAMPLE SIZE: 800; 400 perinatally HIV-infected subjects and 400 control* subjects.

*HIV-exposed, uninfected children and adolescents or uninfected (or presumed uninfected) children and adolescents living in households with HIV-infected members.

POPULATION: Perinatally HIV-infected and control subjects ages 6 to < 18 years, with an IQ ≥ 70.

STRATIFICATION: By age: 6 to < 12 and ≥ 12 to < 18 years and by gender.

<table>
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<tr>
<th>ACCRUAL</th>
<th>HIV-Infected Subjects</th>
<th>Control Subjects</th>
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<td>BY AGE (M/F)**:</td>
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<td>6 to &lt; 12 years</td>
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<tr>
<td>≥ 12 to &lt; 18 years</td>
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TOTAL ENROLLMENT = 800

**There is an accrual limit of 200 for each age and HIV status cohort, but not for gender cohorts.

REGIMEN: Subjects will not receive treatment in this study; subjects and their parents/primary caregivers will respond to a series of questionnaires/measures which will be used to assess the prevalence and severity of current psychiatric symptoms and disorders and to assess changes over time. The study is divided into two components, the prevalence and severity of current psychiatric disorders and symptoms (Mental Health Component at the first study visit) and changes in symptomatology over time (Follow-Up Component at the second and third study visits). In addition, a subset of perinatally HIV-infected and control subjects (100-120 subjects from each group) and their parents/primary caregivers will receive additional measures, in the form of semi-structured psychiatric interviews, to further identify the differential frequency of psychiatric symptoms in HIV-infected children or adolescents and control subjects and to establish the feasibility of a long-term follow-up study.
The semi-structured interviews will only be conducted at pre-selected sites and will include all subjects from those selected sites.

**STUDY DURATION:** 96 weeks.

**PRIMARY OBJECTIVES:**

1. To examine the rates and severity of psychiatric symptomatology in a cohort of perinatally HIV-infected children and adolescents.

2. To compare the rates and severity of psychiatric symptomatology in HIV-infected children and adolescents to a cohort of demographically matched control subjects.

3. To estimate the prevalence of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition) defined disorders using semi-structured interviews in a subset of children or adolescents and control subjects, and to examine the clinical utility of severity cutoff scores in relation to semi-structured interviews.

**SECONDARY OBJECTIVES:**

1. To examine the changes over time in psychiatric symptom severity in HIV-infected children and adolescents, and compare them with changes over time in control subjects.

2. To examine antiretroviral and psychiatric medication adherence in HIV-infected children and adolescents at baseline, 48, and 96 weeks on study, and to examine the association between medication adherence and co-occurring psychiatric symptoms.

3. To examine the association of lifetime exposure to antiretroviral classes among HIV-infected children and adolescents to severity of psychiatric symptomatology.

4. To examine other factors associated with child or adolescent psychiatric symptomatology, including HIV variables, and family, child, and adolescent behavioral and psychosocial characteristics.

5. To examine the presence and severity of chronic pain in HIV-infected and control populations with and without psychiatric symptomatology.
1.0 INTRODUCTION

1.1 Background and Significance

Effects of HIV on the Central Nervous System

HIV is a neurotropic virus which, in perinatally-infected individuals, is present at the time of birth and is able to cross the blood brain barrier, suggesting that its effects may present differently at different developmental stages. Central Nervous System (CNS) effects of the virus may not just be due to direct cellular damage, but may also be related to treatment neurotoxicities and length of exposure to antiretroviral therapies. As an example of these more diffuse CNS effects, recent data suggest that perinatally HIV-infected children and adolescents have significantly higher rates of psychiatric hospitalizations when compared to both HIV-exposed but uninfected children and adolescents (1), as well as the general pediatric population, underscoring the ongoing cumulative toxicity of the virus, and perhaps its treatments (2).

Currently, we are still faced with the difficulties in evaluating children for the effects of HIV on the CNS. It appears that CNS manifestations may be more common in children than in adults, and that their clinical profiles are different. Progressive encephalopathy used to be recognized as one of the first manifestations of HIV in young children (3). Its presence suggested poor survival and outcomes for those in whom it was found (4, 5). Since the advent of Highly Active Antiretroviral Therapy (HAART), there appear to be fewer events of obvious encephalopathy in children (PACTG 219C database, unpublished results). This may be related to the smaller numbers of infected infants and early diagnoses of their infection, coupled with their prompt treatment with HAART.

At the same time, there is a growing awareness of the effects of HIV on the CNS that are less severe than progressive encephalopathy and are psychosocial in nature. For example, some investigators have found increased rates of Attention-Deficit Disorder (ADD) and Attention-Deficit with Hyperactivity Disorder (ADHD) (6). Other investigators seem to suggest that various stressors (biological, societal, and viral) associated with HIV augment the psychosocial stigmata of HIV, potentiating the effects of the virus on brain processing and disease (7, 8). In these studies, negative life events, such as a family member being hospitalized or dying (which is not uncommon in families with HIV) or loss of wages or housing, play a role in worsening immune suppression, further complicating the effect of virus on the CNS (7, 9, 10, 11). As the model proposed by Antoni et al. shows, life stressors lead to a cascade of neurohormonal responses, culminating in immune suppression and worsening the effects of HIV.
in the sanctuary of the CNS (12, 13). Thus, HIV-infected children and adolescents, who have grown up in disadvantaged households and have been exposed to medications potentially toxic to the CNS, may be at greater risk than other populations for co-morbid symptoms.

For all of these reasons, we believe that children and adolescents with HIV infection are at greater risk for developing psychiatric symptoms when compared with demographically matched control subjects. Higher rates of psychopathology may result in challenges to the treatment of HIV infection and further expose children, adolescents, and families to poorer outcomes.

**Antiretrovirals and Psychiatric Symptoms**

It is likely that the cumulative effects of HIV on brain development, the sanctuary of the brain as it relates to the development of new quasi species, the altered penetration of the different antiretrovirals across the blood brain barrier, and the effects of life stressors all play a role in the increased psychosocial morbidity seen in HIV-infected children and adolescents (14, 15). Conceptually, this proposed study is designed to investigate the long-term psychiatric associations of HIV infection and antiretroviral treatment. It is predicted that children and adolescents who have been exposed to HIV since birth and who may have received HAART for less than 75% of their lifetimes may exhibit different psychiatric symptoms than those who have been treated with HAART for more than 75% of their lifetimes. For example, an 11-year-old who has been treated since age 8 will present with different psychiatric signs and symptoms than an 11-year-old who has been treated since age 3. Of course, one must also look at what is different in the clinical immunologic presentation of a child being treated at 3 years of age, in comparison to a child or adolescent being treated at a later age. As data become available on types of treatments used by the enrolled HIV-infected children and adolescents, this study will also investigate if certain drugs, or classes of drugs, are associated with co-morbid psychiatric symptoms. This study will contrast a younger HIV-infected cohort (6 to < 12 years of age) with an older aged cohort (> 12 to < 18 years of age) as these cohorts may have started therapy at different developmental ages.

Antiretrovirals have been used for the treatment of HIV in children and adolescents since the early 1990s. In the early 1990s, however, the most available therapies included nucleoside analogs such as Zidovudine (AZT, ZDV), Didanosine (ddI), Lamivudine (3TC) and Stavudine (D4T). Non-nucleosides and protease inhibitors were not commonly used until the mid 1990s in adults, and the mid to late 1990s in children. HAART therapy has been defined as three drugs, with two from different classes, such as two nucleosides plus a non-nucleoside or
a protease inhibitor; or a nucleoside, a non-nucleoside and a protease inhibitor. Recent treatment guidelines suggest that triple nucleoside therapy should also be considered HAART. Treatment regimens were designed with the intention to incorporate drugs that inhibit different HIV targets. Early toxicities, such as hematologic and hepatic toxicities, were identified and dosing regimens were modified. After only a few years of use, new and cumulative toxicities were discovered. These new toxicities included lipodystrophies, lactic acidosis and mitochondrial disorders. Based on the findings from the literature, and the toxicities reported to the FDA, suggesting that both HIV infection and antiretroviral agents may produce psychiatric symptoms, it is our hypothesis that these therapies may also pose a risk of CNS toxicity, particularly if used for many years.

Published treatment guidelines and standard of care for HIV-infected children in the late 1990s recommended that all HIV-infected children under the age of one year be placed on a HAART regimen, often at the time of initial HIV diagnosis. This could be as early as several weeks of life to as late as six to nine months of life and was prescribed because of the poor predictive value of immunologic and virologic markers for rapid progression in young infants. Children older than one year who presented with a recent drop in number or percent of CD4 cells, an increase in viral load, or presence of symptoms were to also be treated (16). Recommendations for older children were based on preliminary studies that showed a delay in time to death from HIV, and a decrease in morbidity (development of opportunistic infections, CNS loss of milestones, wasting). These studies all used nucleoside analogs as standard therapy. To date, there is no study that compares and contrasts long-term outcomes using different HAART regimens or delayed treatment strategies in HIV-infected children and adolescents. It is possible that non-nucleosides and protease inhibitors may also pose a risk of CNS toxicity, particularly if used for many years. Therefore, a secondary goal of the proposed study is to examine the relationship between duration of treatment and psychiatric symptoms. It is possible that select classes of antiretrovirals induce, or in some way facilitate, the development of psychiatric symptoms, such that lifetime exposure to different drug classes affects the CNS differently. Alternatively, antiretroviral treatment may have a salutary effect on the emergence of psychiatric symptoms by suppressing a neurotoxic virus. For example, HIV-infected children and adolescents with (a) more than 75% lifetime exposure to HAART regimens (ages 6 to < 12 years) may have similar psychiatric co-morbid symptoms to demographically matched, control subjects, and those with (b) less than 75% lifetime exposure to HAART regimens (ages ≥ 12 to <18 years) may have more psychiatric symptoms than demographically matched, control subjects.
Conceptual Model for Predicting the Psychological Impact of HIV

This study will use a modified vulnerability model as a conceptual guide for understanding the psychological impact of HIV infection (see Figure 1). With regard to children and adolescents, this model draws from research on the psychological effects of chronic illness, risks due to parental psychological impairment, findings from previous research on HIV infection, and our own prior research on psychiatric symptoms and mental health risk factors in children and adolescents with chronic neurological disorders (Personal Communication, Gadow, Vice-Chair, P1055). Therefore, this study will examine the relationship between child and adolescent psychiatric symptoms and HIV variables (e.g., length and type of antiretroviral therapy, severity of HIV symptoms, Center for Disease Control [CDC] clinical and immunological categories), compliance with treatment regimens, and environmental adversities (e.g., exposure to trauma, violence, substance abuse/use, poverty, mental health of primary caregiver, etc.). The influence of these variables on child and adolescent mental health is expected to be nonspecific with regard to measures of multiple symptoms, although the strongest effect, based on prior studies of children and adolescents with chronic illness and our own research on children and adolescents with neurological disorders, is expected to be frequency and severity of anxiety, depression, and ADHD symptoms. The direct and indirect effects of the child or adolescent’s demographic characteristics (age and gender), intellectual functioning, parent/primary caregiver mental health, family stability, and the presence of possible protective factors will also be examined. This study will focus on these characteristics in an attempt to understand the differential vulnerability or resilience to the effects of HIV infection.
Our conceptual model for HIV-related risk variables recognizes the limitations of the extant literature with regard to the specifics of potential viral and treatment toxicities. For example, the adverse effects of antiretrovirals on the CNS may be greater for less mature brains than for more mature brains. Therefore, treatment risk may be greater for early versus later-onset treatment regimens. Conversely, the lack of antiretrovirals and unchecked viral replication on brain development may lead to selective damage by HIV on specific (and, as of yet,-unidentified) areas of the brain. Finally, a specific drug, or drug class, may be associated with a particular psychiatric co-morbidity. Although we do not currently have sufficient scientific information to know which of these possibilities is true, the proposed study is designed to explore these issues.

Collectively, findings from the extant literature and the toxicities reported to the FDA from pharmaceutical companies suggest that both HIV infection and antiretroviral agents may produce psychiatric symptoms. Moreover, there is some evidence indicating that HIV-induced neurological changes, which result in psychiatric impairment, are not symptom specific and may differ by gender (but there may be a differentially increased incidence of ADHD symptoms). Furthermore, there is ample evidence that chronic physical illness in children and adolescents is associated with increased prevalence and severity of anxiety and depression symptoms. Therefore, we hypothesize that HIV-infected children and adolescents versus control subjects, and older versus younger HIV-infected
children and adolescents, are at greater risk for increased rates of psychopathology, due to the cumulative impact of HIV infection and treatment on the CNS, and the emerging role of HIV awareness and cognitive development during adolescence.

**Evidence of Psychiatric Symptoms**

Most reports of neurodevelopmental and neurologic changes in perinatally HIV-infected children and adolescents followed over time indicate that behavioral problems, particularly ADD and hyperactivity, appear to be common in HIV-infected children and adolescents, sometimes reported as high as 50% \(^{17,18}\). However, as previously noted, little is known about the relationship between HIV and psychiatric symptoms in asymptomatic, HIV-infected children and adolescents in the post-HAART era. One recent study sponsored by the Pediatric AIDS Clinical Trials Group (PACTG), Protocol 338, “A Phase II Rolling Arm Master Protocol (PRAM) of Novel Anti-Retroviral Therapy in Stable Experienced HIV-Infected Children,” a multi-center treatment study of clinically stable HIV-infected children over 2 years of age, investigated this issue. In this study, at baseline, prior to receiving HAART, 274 children were evaluated with the Conners' Parent Rating Scale (CPRS). A relatively large percentage of HIV-infected children scored as having symptoms of, or problems with, ADHD (20%), conduct (16%), learning (25%), psychosomatic (28%), impulsivity-hyperactivity (19%), and anxiety (8%) disorders. Fifty-two percent were identified as having at least one behavioral problem. No statistically significant differences were found between children with and without behavioral problems, with respect to race/ethnicity, gender, weight/height adjusted for age and gender, and the median HIV-1 RNA at baseline. Children living with biological parents were significantly less likely to be identified as having conduct problems, learning problems, or ADHD than those not living with biological parents. Children with CD4 counts under 660 cells/mm\(^3\) were significantly more likely to be identified as having conduct problems than those with higher CD4 cell counts (22% versus 11%). The investigators did not find any association, however, between behavior or cognitive functioning and degree of cortical atrophy, white matter abnormalities, focal mass lesions, or basal ganglia calcifications. Interestingly, there was little evidence of the well-documented male predominant gender differences in the distribution of behavior problems, including ADHD \(^{19}\). The significant male predominance in the incidence of ADHD in the general population, especially ADHD primarily hyperactive/impulsive type, is attenuated when the primarily inattentive subtype of ADHD is studied, suggesting possible differences in the pathophysiology of the two ADHD subtypes. Nozyce et. al. speculate that the effects of HIV infection on the brain should not be gender specific and may account for the lack of gender differences found in the HIV-
infected children in this cohort (19). This specific finding is consistent with our prediction that suggests that HIV-infected children and adolescents will exhibit fewer gender differences than demographically matched control subjects, in terms of incidence of psychiatric diagnoses. This lack of gender differences may be due to the direct CNS effect of the virus and not to the familial or environmental stressors that these children and adolescents are exposed to.

A recent study of children with epilepsy, which used the Child and Adolescent Symptom Inventory-4 (SI-4) Parent (Primary Caregiver) Checklist, one of the assessment measures proposed for this study, failed to find the expected male predominant ADHD gender differences in children with epilepsy and ADHD. Dunn et al. reported relatively higher levels of ADHD inattentive type (ADHD:I) when compared with more traditional psychiatric clinic and community-based samples and hypothesized that epilepsy-related variables may cause CNS impairment (resulting in attention deficits) that is different from what is associated with "true" ADHD (20). Similarly, studies of children with autism, using the SI-4 Parent (Primary Caregiver) Checklist, have also found disproportionately higher rates of ADHD:I and much less pronounced gender differences for ADHD (21). These studies suggest that ADHD symptomatology in neurologically-affected children may resemble the inattentive subtype as opposed to the more typical hyperactive/impulsive subtype.

Several studies of children and adolescents with HIV have reported on psychiatric symptoms. For example, Pao et al. reported that 85% of their sample of HIV-infected adolescents, who were infected as a result of risk-taking behavior (n=34), met diagnostic criteria for at least one primary DSM-IV disorder, with 44% meeting criteria for current major depression (22). The behavior patterns of adolescents perinatally-infected with HIV are expected to be similar to those of adolescents infected with HIV as a result of high-risk behavior. It is possible, however, that the etiologies of these behavior patterns may differ. Others have reported higher rates of anxiety disorders in children with HIV (n=17) when compared with other chronic health disorders such as hemophilia or asthma (23). Bose et al. compared HIV-infected children (n=36) and found higher rates of anxiety, social withdrawal, and academic underachievement than in their seronegative peers (24). In a separate study, however, Havens et al. reported no statistical significance when comparing the psychopathology in a sample of children (n=26) with HIV and perinatal drug exposure and a non-HIV sample with perinatal drug exposure (25).

All studies of psychopathology in HIV-infected children and adolescents suffer from one or more of the following limitations: (a) insufficient sample size, (b) non-representative samples, (c) inadequate comparison groups; (d) non-DSM-IV
symptomatology, or (e) pre-HAART exposure. In addition, there are no studies of perinatally-infected children during the adolescent period which investigate psychopathology. This proposed study will address these design limitations.

Studies of children with chronic physical diseases generally indicate higher rates of adjustment problems when compared with controls or normative data, a finding supported by a comprehensive meta-analysis of 87 studies of children with physical disorders (26). The mean effect size for internalizing symptoms of anxiety and depression is much larger than for externalizing symptoms of aggression. Similarly, one of the most robust findings from a recent meta-analysis of 21 studies of children and adolescents with chronic arthritis was a higher rate of anxiety and depression in the arthritic sample than in the control sample (27). These findings suggest that coping with a chronic childhood illness is more likely to be associated with the display of affective symptoms than with patterns of antisocial behavior. The authors also comment on the importance of selecting a rating scale that does not confound physical symptoms with psychiatric symptoms. The primary measure of psychiatric symptoms adopted for our proposed HIV study does not confound these symptom domains. Another meta-analysis of 60 studies of children and adolescents with chronic medical problems revealed that sick children are generally at significantly higher risk for depression symptoms than are controls (28).

Natural History Studies

Although there are a number of published reports (primarily chart reviews or retrospective follow-ups) of developmental changes in the symptomatology of patients with HIV, these data are compromised by numerous well-known methodological problems (29). Data from these studies often have focused on infants and young children with advanced HIV disease or studied populations of HIV-infected children in the pre-HAART era. Correlations were often sought between behavior, findings on brain CT (computerized tomography) or MRI (magnetic resonance imaging), and CD4 count, while studies lacked correlation with viral load, as this measure was not available prior to 1995. Pre-HAART populations no longer exist in the industrialized world, and thus data from these studies may no longer be applicable.

One rare example of a longitudinal study of HIV-infected children that examined emotional and behavioral problems was conducted by Mellins et al. They evaluated a sample of HIV-infected children (n=96) and a sample of HIV uninfected controls (n=211), between 3 and 8 years of age, at 6-month intervals, with the CPRS. None of the children are reported to have been treated with antiretroviral medication. Results failed to show a relationship between HIV
status or prenatal drug exposure and behavior problems (30). Although these investigators make an important contribution with their findings, there are some limitations. By adopting a dimensional rating scale based on multivariate statistical techniques, and not DSM-IV symptomatology, Mellins et al. were unable to study ADHD subtypes, particularly ADHD inattentive subtype. Moreover, as previously discussed, recent research findings indicate disproportionately higher rates of this subtype in children with epilepsy and autism and, unexpectedly, comparable ADHD rates for males and females, including HIV-infected children. Other limitations of this study include a lack of follow-up through adolescence, and a significant loss of children eligible for the study. The Mellins’ study group did not enroll large groups of young HIV-infected children on HAART regimens, so they will be unable to investigate older cohorts who have experienced HAART over many years. Therefore, we believe that Mellins et al.’s assertion that HIV disease is unrelated to psychopathology should be considered tentative, and that much additional research is required before more definitive answers to questions concerning the neurotoxicity of HIV disease are realized.

Psychosocial Risk Factors

Converging evidence, from a number of studies, suggests that behavioral (e.g., conduct problems) and emotional (e.g., depression) disturbances are associated with specific mental health risk factors (31, 32, 33, 34, 35). These risk factors can be grouped into several general domains: maternal psychopathology (e.g., depression, sensation seeking), paternal psychopathology (e.g., antisocial behavior, depression, substance use), child and adolescent cognition and academic performance (e.g., IQ, school performance), home environment (e.g., family disorganization, multiple changes), child rearing practices (e.g., use of harsh punishment), and environmental disadvantage (e.g., low socioeconomic status [SES]/poverty). There are no published prospective outcome studies of children and adolescents with HIV that have examined these risk factors and their relationship to the frequency and severity of psychiatric symptoms and the relationship between HIV severity or treatment and later development of psychiatric symptoms. Mellins et al., however, did examine the relationship between demographic variables and emotional and behavioral symptoms. They report that higher rates of emotional and behavioral problems are associated with gender (higher in males), maternal education (higher in low education mothers), primary caregiver (lower for children living with grandmothers), and ethnicity (higher in Latino children) (30).

Self-knowledge of HIV
The effects of children and adolescents knowing their HIV status have been evaluated by several investigators (7, 36, 37). Some authors suggest that knowing one’s status is not associated with increased mental health problems (38, 39), while others suggest that knowledge of one’s status contributes to depression, anxiety, and behavioral problems (1, 26, 37, 40). In PACTG 219C, a study of late outcomes in HIV-infected and exposed children and adolescents, available data from over 1,800 HIV-infected children and adolescents under 15 years of age suggest that knowledge of HIV status is associated with an increased risk of psychiatric hospitalizations (HR=6.13). Therefore, it is reasonable to examine the relationship between HIV self-knowledge and development of psychiatric symptomatology over time (Personal Communication, Van Dyke, Chair, PACTG 219C).

Adherence

Recent studies of adherence to medications in HIV-infected adults suggest that poor adherence is related to the presence of psychiatric morbidity (41, 42). Other studies, evaluating the association between the presence of psychiatric diagnosis and response to HAART, suggest that better attention paid to treatment of psychiatric disorders may lead to better adherence, and thus better outcomes from HAART (43). It is not known if psychiatric drug therapy, given to children and adolescents with identified psychological morbidity, leads to improved adherence to antiretroviral medication.

Studies of children or adolescents and adults with chronic physical conditions, who are required to follow prescribed treatment regimens, indicate that the presence of psychiatric symptoms is a negative predictor of compliance and, therefore, predicts less compliance in more impaired children and adolescents. Therefore, this study will utilize a recall adherence tool named the Adherence Questionnaire. This tool was utilized in PACTG 377, and has been validated and published (44). This tool demonstrated that a 3-day recall tool was an excellent surrogate marker for monthly adherence and predicted virologic response to HAART. This tool is currently used as part of standard practice in primary therapy PACTG studies. It is proposed that the Adherence Questionnaire be used in this study to evaluate both HAART adherence and adherence to neuropsychiatric medications. We predict that children and adolescents with depression symptomatology, and possibly those with impulse control problems, will display lapses in HAART adherence.

Methods for Assessing DSM-IV Symptoms
The study acknowledges the strengths and weaknesses of both categorical (in this study, DSM-IV-defined disorders) and dimensional (in this study, severity of DSM-IV symptoms as assessed with the SI-4 Primary Caregiver Checklist and abbreviated Child Behavior Checklist - CBCL) approaches to evaluating child and adolescent psychopathology by adopting representative measures for both strategies. Structured clinical interviews were initially designed to determine caseness in epidemiological studies, and therefore typically include the full complement of diagnostic criteria (e.g., age of onset, impairment). Nevertheless, they are generally costly (i.e., time consuming to administer) and require training, which will be impractical for some of our sites; they are not standardized (e.g., lack T scores based on normative data); and because they are categorical, they lack the statistical advantages of dimensional scales. In the proposed study, findings from the semi-structured interviews (MAGIC DICA, which is defined in section 5.14) will be used to estimate the prevalence of DSM-IV-defined disorders in study samples, as well as to establish the clinical utility of SI-4 Primary Caregiver Checklist (defined in section 5.11) symptom severity cutoff scores.

All of the children and adolescents will be evaluated with the SI-4 Primary Caregiver Checklist, and a parallel version will also be used to assess psychopathology in the parent/primary caregiver (psychosocial risk factor). A sub-sample of children and adolescents will also be evaluated with an abbreviated semi-structured psychiatric interview (MAGIC Diagnostic Interview for Children and Adolescents - DICA) (45, 46, 47, 48, 49).

DSM-IV-referenced rating scales are playing an ever-increasing role in research owing to their simplicity, flexibility, and practicality. Perhaps their greatest advantage over traditional behavior ratings scales generated from multivariate statistical techniques is their one-to-one correspondence with the diagnostic system used in clinical practice (high content validity). Although there are currently a number of scales that purportedly measure DSM-IV syndromes, most are not based specifically on DSM-IV criteria; rather, they are re-analyses of items from non-DSM-based scales. The SI-4 Primary Caregiver Checklist (50, 51, 52, 53) is unique in that it (a) assesses a broad array of disorders, including the behavioral symptoms of anxiety, mood, and pervasive developmental disorders (PDD), (b) has parallel formats for preschool through adulthood and self-report formats for adolescents and adults, (c) uses frequency of occurrence ratings that are identical to DSM-IV, (d) has validated scoring formats for DSM-IV criteria, Symptom Severity, and T scores from normative samples, (e) can be used to structure a clinical interview, (f) has computer scoring and computer-presented formats, (g) is internet accessible for on-line testing and scoring, and (h) has been translated into over 14 languages, including Spanish. The psychometrics of the SI-4 Primary Caregiver Checklist are described in the Subject Management
section (section 5.0). Major advantages of using the SI-4 Primary Caregiver Checklist in a study such as the one being proposed are that it is both cost-effective and easy to use. Moreover, as the findings of several studies have demonstrated, SI-4 Primary Caregiver Checklist scores are minimally correlated with age, IQ, or SES (53, 54, 55, 56, 57).

Investigations using the SI-4 Primary Caregiver Checklist in studies of chronically ill (neurologically impaired) children with spina bifida (58), epilepsy (59), tic disorder (60), and mental retardation (61) show high rates of psychopathology, particularly ADHD, Oppositional-Defiant Disorder (ODD), anxiety disorder, and depressive disorder symptoms. When compared with screening prevalence rates and symptom severity in SI-4 Primary Caregiver Checklist normative data samples (62), it is clear that chronic illness or disability results in higher than expected rates of DSM-IV-defined psychopathology in the general population. For example, in the normative sample, 7.2% received SI-4 Parent (Primary Caregiver) Checklist screening cutoff scores for at least one subtype of ADHD according to parent ratings, whereas rates for children with epilepsy (38%) or spina bifida (33%) were much higher. Similarly, screening rates of aggression were also higher. Rates of ODD were higher in the epilepsy (20%) and spina bifida (13%) samples than the normative sample (5.3%). It is important to emphasize that the "true" rate of these disorders, which is arbitrary, owing to differential informant-specific validity and variable diagnostic criteria for symptoms and impairment, is not the issue. The real issue is that these symptoms are exhibited with variable severity in HIV-infected samples, which is the primary focus of many of the proposed study's hypotheses.

Pain

Sources of pain in HIV-infected children include neural inflammation; systemic manifestations of AIDS, such as cardiomyopathy and myositis; toxicities and adverse drug reactions; invasive secondary infections; discomfort related to invasive procedures; or pain associated with non-AIDS-related conditions, such as a tension headache. Pancreatitis, erosive esophagitis, recurrent abdominal pain of unclear etiology, and neuropathic pain are some of the chronic pain problems affecting HIV-infected children and adolescents that are among the most difficult to manage.

The relationship between chronic pain, anxiety, depression and catastrophizing coping strategies in children and adolescents with other painful chronic conditions, including fibromyalgia (63, 64, 65), arthritis (66, 27), cancer (67), sickle cell disease (68), and other conditions (69) has been described, although the literature is limited. To date, no studies have been conducted examining this
relationship in HIV-infected children and adolescents, although there is adult literature documenting the high incidence of poorly treated pain with resultant impaired quality of life, and adverse emotional sequelae (70, 71).

Almost 60% of HIV-infected pediatric outpatients followed at the National Cancer Institute reported pain that affected their daily lives, but the study did not include structured data concerning functional status or disability related to pain (72). It is interesting to note that only 55% of caregivers described their child as having pain, a finding similar to one describing inadequate pediatric pain recognition and treatment by health care providers (73). The authors found no correlation between pain, CD4 counts, or disease progression.

Approximately 20% of the 985 HIV-infected children participating in Pediatric AIDS Clinical Trials Group study 219C (PACTG 219C) reported having pain (1). In contrast to Hirschfeld's findings (72), data from PACTG 219C identified a significant association between the report of pain and the increased likelihood of death, as subjects with pain were five times more likely to die than those who did not report pain. Pain was also associated with lower CD4 percentages and more severe immunosuppression. While there have been publications from PACTG 219C regarding the impact of negative life events upon immune status (36) and the incidence of psychiatric hospitalizations and diagnoses among HIV-infected participants (74), the relationship between pain, life stressors and psychiatric distress in this cohort has not been explored.

Preliminary Research

This study will examine differential rates of psychiatric symptoms in HIV-infected children and adolescents and control subjects to better understand the relationship of the prevalence and severity of psychiatric symptomatology with HIV infection. The investigators have conducted preliminary studies of psychiatric symptoms in HIV-infected children and a number of studies of DSM-IV symptoms in a variety of neurological disorders. The findings from these studies have shaped the specific aims, design, and planned analyses of the proposed study. As previously noted, preliminary findings from PACTG studies indicate relatively high rates of psychiatric symptoms in HIV-infected children and relatively high rates of psychiatric drug prescribing. Specifically, Nachman, Gaughan, et al. reviewed hospitalizations and diagnoses of the participants of PACTG 219C from September 2000 to October 2002 (74). In this data set, 21 out of 1807 HIV-infected children were hospitalized for psychiatric manifestations. The diagnoses listed included depression, behavior disorders, and, rarely, psychosis. The overall incidence rate was 6.84 per 1000 patient years, significantly higher than the general pediatric reported rate of 1.7 per 1000 patient
years (75). It is of great concern that the median age at hospitalization was 12 years (range: 5-14 years). These are children just entering puberty, when their adherence to medication drops (and pharmacokinetics of antiretrovirals are poorly studied) and they begin to engage in antisocial behaviors, putting themselves at increased risk for HIV disease progression. Neither gender nor ethnicity was associated with hospital admission. No psychiatric hospitalizations were noted among the 976 HIV-exposed, uninfected members of the cohort (all also born to HIV-infected women).

From among 2188 HIV-infected children in the 219C database, 459 (21%) children were prescribed psychostimulant, antidepressant, or antipsychotic medications: Ritalin (n=140), Adderall (n=55), Zoloft (n=39), Risperdal (n=37), Dexedrine (n=30), Paxil (n=21), and Prozac (n=16). Other medications prescribed included Trazodone, Elavil, Celexa, Remeron and Zyprexa, among others. Of the 1,129 HIV uninfected children, only 12 were receiving psychiatric medication.

In summary, children and adolescents with psychiatric disorders complicated by HIV infection may display more severe psychopathology and, possibly, different responses to medications used to treat these disorders.

1.2 Rationale

The significance of this study rests in its focus on a potentially high-risk sample exposed to a neurotropic virus and therapeutic regimens with altered penetration into the brain. By using an epidemiological design, the study will generate data that will potentially contribute to existing research on the effects of HIV infection on the mental health of children and adolescents.

The study seeks to apply findings from uninfected children and adolescents and extend this research to HIV-infected children and adolescents to better understand the ontogeny of psychopathology in this important, global clinical population. Studies conducted examining risk factors for disruptive behavior disorders (i.e., ADHD, ODD, Conduct Disorder [CD]) and anxiety/depressive disorders have identified risk factors common to both groups of disorders, as well as factors that show some specificity. In addition to standard risks for childhood psychopathology, studies evaluating the many risk factors associated with HIV infection in children and adolescents must also account for life-long presence of a neurotropic virus, medications that have significant toxicities (many of which are being learned about for the first time), familial psychiatric issues, and disordered living conditions. It is anticipated that these variables, in combination, may act synergistically rather than simply additively, and may explain the severity of
DSM-IV defined psychopathology found in these patients. With regard to specific hypotheses, it is predicted that initial risk factors will vary for different types of symptoms (e.g., maternal depression will predict child and adolescent depression and aggression).

The study of co-occurring psychiatric symptoms in children and adolescents is still an emerging discipline and it is, therefore, difficult to make predictions about chronic illness and illness-related variables on the prevalence of, or risk and protective factors for, symptom co-occurrence. A primary goal of the proposed study is to better understand the co-occurrence of psychiatric symptoms in children and adolescents with HIV infection. Three models of co-morbidity will be evaluated, each of which posits a causal relationship between the disorders. The first two models state that having one disorder may lower the threshold for the expression of, or serve as a risk factor for, the other disorder: (a) disorder A is a risk factor for disorder B and (b) disorder B is a risk factor for disorder A. The third causal model suggests that (c) the disorders arise from common etiological or risk factors. The most rigorous way to evaluate these hypotheses is by testing them simultaneously, through prospective or longitudinal research, where development and persistence of disorders and risk factors can be evaluated over time.

Several issues should be explored with regard to co-occurring psychiatric symptoms in children and adolescents with HIV. First, are HIV-infected children and adolescents more likely to develop co-morbid psychiatric conditions than children and adolescents who are uninfected? In other words, does the presence of HIV confer a specific risk for co-occurring psychiatric conditions? We hypothesize that the HIV-infected group is at greater risk for co-morbid psychiatric symptoms because of more commonly shared risk factors than for control subjects (e.g., HIV and treatment are common or nonspecific risk factors for emotional and behavioral symptoms). Second, are patterns of co-morbid psychiatric conditions similar or different between these groups? We predict that HIV neurotoxicity and antiretroviral behavioral toxicity will be a shared risk factor for several disorders (i.e., nonspecific), resulting in increased rates of symptom co-occurrence. Therefore, although the HIV-infected group is expected to exhibit higher rates of psychopathology, the developmental pattern of co-occurring symptoms is predicted to be similar across groups. Third, do co-morbid psychiatric conditions develop by the same means (e.g., one disorder causes another versus shared risk factors) in children and adolescents with and without HIV? We predict that emerging psychiatric symptoms in both groups of children and adolescents will share similar etiology, with the obvious exception of HIV and its treatment. Understanding the means by which co-occurring symptoms develop in the HIV-infected population, as compared to the control population,
could inform prevention and early intervention efforts to decrease the likelihood that these children and adolescents would have to deal with additional psychosocial stressors.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To examine the rates and severity of psychiatric symptomatology in a cohort of perinatally HIV-infected children and adolescents.

2.12 To compare the rates and severity of psychiatric symptomatology in HIV-infected children and adolescents to a cohort of demographically matched control subjects.

2.13 To estimate the prevalence of DSM-IV defined disorders using semi-structured interviews in a subset of children or adolescents and control subjects, and to examine the clinical utility of severity cutoff scores in relation to semi-structured interviews.

2.2 Secondary Objectives

2.21 To examine the changes over time in psychiatric symptom severity in HIV-infected children and adolescents, and compare them with changes over time in control subjects.

2.22 To examine antiretroviral and psychiatric medication adherence in HIV-infected children and adolescents at baseline, 48, and 96 weeks on study, and to examine the association between medication adherence and co-occurring psychiatric symptoms.

2.23 To examine the association of lifetime exposure to antiretroviral classes among HIV-infected children and adolescents to severity of psychiatric symptomatology.

2.24 To examine other factors associated with child or adolescent psychiatric symptomatology, including HIV variables, and family, child, and adolescent behavioral and psychosocial characteristics.
2.25 To examine the presence and severity of chronic pain in HIV-infected and control populations with and without psychiatric symptomatology.

3.0 STUDY DESIGN

P1055 is a multicenter, non-treatment, observational study designed to better understand the impact of HIV on the development of psychiatric symptomatology in a cohort of perinatally HIV-infected children and adolescents, when compared to a cohort of demographically matched control subjects. This study will be open to all domestic PACTG sites. For the purposes of this study, subjects in the control group will be frequency matched (i.e., will be matched with the same percentage of 6 to < 12 year-old females, 6 to < 12 year-old males, ≥ 12 to < 18 year-old females, and ≥ 12 to < 18 year-old males) to those in the HIV-infected group by gender and age strata.

The study is divided into two components, the prevalence and severity of current psychiatric disorders and symptoms (Mental Health Component at the first visit) and changes in symptomatology over time (Follow-Up Component at the second and third visits).

The Mental Health Component will compare 400 perinatally HIV-infected children and adolescents ages 6 to <18 years with 400 demographically-matched control subjects for a total of 800 subjects. The 400 HIV-infected children and adolescents and 400 control subjects will be further stratified into two age groups (ages 6 to < 12 and ages ≥ 12 to <18 years) and by gender for a combined total of four cohorts. Subjects and their parents/primary caregivers will be asked to respond to a number of mental health, pain, and adherence measures or questionnaires, in order to assess the prevalence and severity of current psychiatric symptoms and disorders.

The Follow-Up Component of the study will assess any changes in symptomatology at 48 and 96 weeks, by using a subset of the original measures, to be completed by subjects and their parents/primary caregivers. This component of the study will be used to note any changes in the prevalence and severity of psychiatric symptoms and disorders over 96 weeks.

In addition, a subset of HIV-infected subjects and control subjects (100–120 in each group) and their parents/primary caregivers will receive additional measures, in the form of semi-structured psychiatric interviews, to further identify the frequency of psychiatric

* HIV-exposed, uninfected children and adolescents or uninfected (or presumed uninfected) children and adolescents living in households with HIV-infected members.
symptoms in HIV-infected children/adolescents and control subjects. For this part of the study, approximately six to eight selected sites in the PACTG, with projected collective enrollments of at least 100-120 HIV-infected children and adolescents and the same number of control subjects, and demographics similar to those of the PACTG and the HIV epidemic in the United States, will be asked to administer additional psychiatric measures to all of their enrolled subjects who both speak and understand English fluently (the team may consider administering the MAGIC DICA to Spanish-speaking subjects at a later date). These sites will be selected by the team, based on information provided in their Site Implementation Plans (SIPs). Site selection for completing the semi-structured interviews will be based on a number of criteria, including site willingness to participate, enrollment potential, time constraints, and previous participation in neuropsychiatric studies. At selected sites, all subjects (HIV-infected and control) will receive abbreviated versions of the Diagnostic Interviews for Children and Adolescents (MAGIC versions of DICA-P – parent/primary caregiver or DICA-C - children and adolescents), which are semi-structured psychiatric interviews that will be given by personnel who have been trained in the administration of the MAGIC DICA. Approximately 20% of these interviews will be audio-taped, in order to verify scoring procedures. Sites which are asked to audio-tape selected MAGIC DICA interviews may be required to add in additional IRB-approved language regarding the use of audio-tapes into any applicable consent and/or assent forms. Tapes will be forwarded to designated members of the team and then erased and returned to the site to be destroyed. If enrollment is low from the first group of sites that have been selected, the protocol team will invite other PACTG sites, with documented MAGIC DICA trained personnel, to also complete the MAGIC DICA on all subjects enrolled at their sites. Selected sites will be provided with MAGIC DICA training. MAGIC DICA training was previously administered by Dr. Wendy Reich, co-originator of the MAGIC DICA; future training will be administered by her or one of her colleagues. If necessary, training will also be provided in Spanish at a later date (and a Spanish version of the MAGIC DICA will be obtained). Alternate site selection will be based on earlier responses to site SIPs. Findings from the semi-structured interviews will be used to estimate the prevalence of DSM-IV defined disorders in the study samples and to establish the tentative clinical utility of SI-4 Primary Caregiver Checklist cutoff scores for this particular group of children and adolescents. Based on findings for children in other chronically-ill samples, and our own hospital admissions survey, we conservatively estimate that at least 40% of the study sample will meet tentative diagnostic criteria for at least one primary psychiatric disorder.

Historically, children with an IQ ≤ 69 have had trouble responding to certain screening tool questionnaires. Therefore, an IQ of ≥ 70 is proposed for this study.

The schedule of evaluations is described in Appendix I, Schedule of Evaluations and Time Estimates for Measures and Other Evaluations for HIV-Infected and Control
Subjects. An Operations Manual will also be provided to participating sites as a reference tool for administering study measures.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 HIV-Infected Subjects

4.111 Age 6 years to < 18 years at entry.

4.112 Perinatally acquired HIV infection, as defined by:

- two separate peripheral blood specimens drawn on different days and positive by direct detection of HIV or one of its components or
- a confirmed\(^1\) positive antibody test at ≥ 18 months of age

NOTE: Because of the child’s/adolescent’s HIV status, it is also assumed that the biological mother will have been HIV-infected (prior to the child’s/adolescent’s birth).

4.113 Child or adolescent must have at least one CD4 count, CD4%, total lymphocyte count, and viral load documented within 90 days of study entry as part of routine clinical care; the team will accept documentation from PACTG and non-PACTG competitive Luminex Immunoassay (CLIA)-compliant or licensed clinical laboratories.

4.114 Child or adolescent must be living with the same parent/primary caregiver for at least 12 months prior to screening.

4.115 Parent/primary caregiver must be able and willing to provide signed informed consent. Assent of the minor subject should be obtained where required.

4.12 Control Subjects

4.121 Age 6 years to < 18 years at entry.

\(^1\) DNA or RNA PCR testing plus one antibody test after 18 months of age are acceptable.
4.122 Either (or both) of the following two sets of conditions must be satisfied:

4.1221 Biological mother is known or suspected to be HIV-infected (with infection prior to child’s/adolescent’s birth) and child/adolescent has one of the following:
   a) a negative HIV ELISA test at ≥ 18 months of age.
   b) two negative DNA PCR tests for HIV, both of which have to have been performed after the child is two weeks of age.
   c) a negative HIV DNA PCR test (after two weeks of age) and one negative HIV ELISA test at ≥ 12 months of age.

Note: If child/adolescent meets these criteria, he or she may be living in a household with or without an HIV-infected household member; or

4.1222 Child/adolescent is HIV-negative or HIV status is unknown and child/adolescent is not suspected of being HIV-infected AND child/adolescent lives in a household with an HIV-infected household member.

Note: Child/adolescent may or may not have been perinatally-exposed. Biological mother may be HIV-infected, HIV-uninfected, or HIV status may be unknown.

4.123 Child or adolescent must be living with the same parent/primary caregiver for at least 12 months prior to screening.

4.124 Parent/primary caregiver must be able and willing to provide signed informed consent. Assent of the minor subject should be obtained where required.

4.2 Exclusion Criteria

4.21 HIV-Infected Subjects

4.211 Child or adolescent IQ known to be ≤ 69, Individual Education Plan (IEP) with the diagnosis/classification of mental retardation,
or known mental retardation.

4.212 Child or adolescent with HIV acquired through adult high-risk behavior (i.e. sexual behavior, IV drug use, etc.), blood transfusion, or abuse.

4.22 Control Subjects

4.221 Child or adolescent IQ known to be \( \leq 69 \), IEP with the diagnosis/classification of mental retardation, or known mental retardation.

4.3 Allowed/Disallowed Medications

There are no medication restrictions for participation in this protocol.

4.4 Co-enrollment Guidelines

Subjects may co-enroll in other PACTG protocols.

4.5 Enrollment Procedures

Subjects for the HIV-infected samples will be recruited from the patients who are routinely evaluated at each PACTG site. Subjects for the control samples will be recruited from members of households with a parent, sibling, or other family member who has been infected with HIV; household members of subjects who have been chosen for the HIV-infected sample, and are in the desired age ranges, may be recruited.

The control sample will be matched to the HIV-infected sample by gender and age group (6 to < 12 years or \( \geq 12 \) to < 18 years). Screening forms for these two groups should be submitted in two stages (as per section 7.3 of the protocol) and within three months (for the first stage) and approximately four months (for the second stage) from when the protocol has been sent out to the sites. The effectiveness of the screening procedure will be assessed annually to ensure an adequate representation of gender and minority group members.

PACTG sites interested in participating in P1055 must first submit an SIP to the protocol team. An approved SIP is required prior to initiating the protocol registration process. Protocol Registration for P1055 must occur with the DAIDS Protocol Registration Office at the Regulatory Compliance Center before subjects
can be enrolled. Subjects will be screened for eligibility prior to enrollment, and will be registered to the study at either screening or entry.

Each site will be required to submit an SIP, which will include descriptions of the following: 1) how sites plan to contact families and compose lists of potentially eligible subjects, along with a detailed and well-developed plan for subject retention; 2) how sites plan to respond to subjects and their parents/primary caregivers who find the measures too burdensome to fill out completely in one visit (i.e. offering a break or other incentive, etc.); 3) how children will be supervised or kept occupied, while their parents/primary caregivers complete their measures, which are expected to take longer than the subject-completed measures; 4) how sites plan to deal with any unintended disclosure of HIV status (although risk of disclosure is minimal, as the measures do not discuss HIV); 5) how sites will deal with referrals of subjects and/or their parents/primary caregivers who are tentatively diagnosed with mental health issues and need further follow-up with a Mental Health Specialist; and finally, 6) sites will be asked questions to determine whether they would be interested, available, and able to participate in the semi-structured interview portion of the study. Other questions may be added by the team as necessary.

In order to obtain the most complete and accurate data, subjects and their parents/primary caregivers will not be allowed to complete the measures at home or location other than the hospital or clinic at which they are participating in the study. Subjects and their parents/primary caregivers will be given the option of returning to complete the measures within 90 days from their screening or entry visit if they find the measures too burdensome to complete in one sitting. Site staff should be available to answer any questions that subjects and their parents/primary caregivers may have and be available to review the measures for missing data. Designated team members will be available to answer any questions that site staff may have.

5.0 SUBJECT MANAGEMENT

In this study the child or adolescent and parent/primary caregiver will receive initial and follow-up screening assessments of psychiatric symptoms. Children, adolescents, and parents/primary caregivers who are tentatively diagnosed with emotional disturbances, at any point throughout this study, will be referred to experts in child and adolescent or adult emotional and behavioral disorders (with their permission) for further evaluation; they will be referred by their primary care physicians. NOTE: Subjects must be asked for permission to notify parents/primary caregivers of any tentative diagnoses, unless in the case of potential harm to self or others. Any indications of harm to self or others, or feelings of severe pain (based on the VAS, described in section 5.3) must be reported to
the primary care physician (and other appropriate site staff) immediately so that the necessary referrals can be made. The primary care physician (and other appropriate site staff) can share results with subjects and/or parents/primary caregivers, as necessary, when they receive them (i.e. immediately for severe pain and/or harm to self and others; or within approximately 90 days for any other mental health concerns).

5.1 Psychiatric and Other Mental Health Measures

The measures to be administered in this study include instruments completed by the parent/primary caregiver and subject to assess mental health and family environment. Study staff should be available to read/administer the questions to subjects and their parent/primary caregivers as needed (even for typically “self-administered” questionnaires), to ensure complete data. Parents/primary caregivers and subjects should write their own answers, if possible, with the exception of the semi-structured interview (MAGIC DICA). The current research strategy is to make all measures (with the possible exception of the MAGIC DICA) available in Spanish.

5.11 Parent/Primary Caregiver Assessment of Child or Adolescent's Mental Health

a. Primary Caregiver Questionnaire (PQ) – Child’s medical, mental health, academic history, and quality of life

Parents/primary caregivers provide information about their child's past and current treatment, medical history, temperament, developmental milestones, school history, social functioning, and family psychiatric history.

The PQ also contains questions from the School and Social Functioning (SSF) and the Quality of Life Assessment (QOL).

The SSF questionnaire is self-administered and obtains information about the child's/adolescent’s level of academic functioning, as provided by primary caregivers, based on their child’s/adolescent’s report cards. Performance is rated using a 5-point scale: 1=far below grade level to 5=far above grade level. Academic functioning is considered to be the child's/adolescent’s mean performance in all academic subjects. The SSF also obtains information about the child's/adolescent’s school attendance, suspensions (and other disciplinary actions), grade retentions, failed courses, and special and remedial education services.
The QOL measurement provides an important tool to learn about the impact of illness and its treatment on children/adolescents. It provides a standardized way to measure aspects of health that cannot be evaluated by a physical exam or laboratory tests. QOL measurement is also important because it helps to capture the “patient’s perspective”. Basically, it provides an “objective method” to examine the “subjective experience” of illness and its treatment by examining functioning in different areas. The QOL measurement to be used in this study includes 2 items from the QOL Assessment. One version will be used for children between the ages of 6 and < 12 years and one version will be used for children and adolescents between the ages of ≥ 12 and < 18 years. It will be completed by the parent/primary caregiver to assess the subject.

b. Symptom Inventories-4 (SI-4) Primary Caregiver Checklist

The SI-4 Primary Caregiver Checklist is a series of parent/primary caregiver and self-completed pencil and paper rating scales (50, 51, 53); individual items bear one-to-one correspondence with DSM-IV symptoms (i.e., high content validity). The SI-4 Primary Caregiver Checklist is designed to be used by parents/primary caregivers who have children/adolescents between the ages of 5 and 18 years. The present study includes SI-4 Primary Caregiver Checklist symptom categories for the following DSM-IV disorders: ADHD: I; ADHD, Hyperactive-Impulsive type (ADHD:H); ADHD, Combined type (ADHD:C); ODD; CD; Generalized Anxiety Disorder (GAD); Social Phobia; Separation Anxiety Disorder (SAD); Major Depressive Disorder (MDD); Dysthymic Disorder; Schizophrenia; Sleep Disorders; Eating Disorders; Substance Use; and PDD. There are two scoring procedures, which include the Symptom Count (number of symptoms necessary to meet DSM-IV threshold criteria) and Symptom Severity (total number of symptoms to give a dimensional rating that may not be at the level of a specific diagnosis). When the Symptom Count score is equal to, or greater than, the number of symptoms specified by DSM-IV as being necessary for a diagnosis, the child receives a Screening Cutoff score of "yes" for the disorder. Although the SI-4 Primary Caregiver Checklist contains the behavioral symptoms of specific disorders, it does not include additional diagnostic criteria, such as age of onset of symptoms or level of impairment of functioning, in addition to other criteria. Therefore, Screening Cutoff scores do not signify a tentative clinical diagnosis.
Existing research indicates that, for the parent/primary caregiver version of the SI-4 Primary Caregiver Checklist, individual symptom categories have satisfactory internal consistency, test-retest reliability, and convergent and discriminant validity with corresponding scales of the CBCL (76). In addition, the parent/primary caregiver version of the SI-4 Primary Caregiver Checklist is able to differentiate clinical versus non-clinical samples, and demonstrate moderate to high sensitivity for screening disruptive behavior disorders, and relatively high specificity for most disorders, when compared with chart diagnoses. Finally, this version of the SI-4 Primary Caregiver Checklist provides clinical utility for evaluating response to stimulant medication (ADHD and ODD categories) in children with ADHD (50, 51, 55, 57, 60, 62, 77, 78).

c. **Child Behavior Checklist (CBCL)**

The CBCL (76) contains 118 behavioral items and is one of the most commonly used measures in published studies of child psychopathology (79). Items are rated: 0=not true; 1=somewhat or sometimes true; or 2=very true or often true. The CBCL has broadband Internalizing and Externalizing scales and eight narrowband scales. The scales have satisfactory test-retest reliability, internal consistency, and construct validity (76).

d. **Columbia Impairment Scale (CIS)**

The CIS is a 13-item scale that provides a global measure of impairment. Four major areas of functioning are assessed: interpersonal relations, broad psychopathological domains, functioning in job or schoolwork, and use of leisure time. The CIS has been shown to have good reliability and validity (80). Level of impairment may change over time given the effects of psychotherapy, psychopharmacology, and/or involvement in the HIV prevention intervention.

e. **Child Cognitive Impulsivity Scale**

The Child Cognitive Impulsivity Scale is an 11-item scale that assesses adolescent impulsivity by distinguishing cognitive cues used in rational decision-making from affective and physiological cues used in impulsive decision-making (81). This scale has been shown to have good internal consistency (.7 -.8) and one-year test-retest reliability.
around .5 (81). Parents/primary caregivers will complete this assessment for subjects aged 6 to < 13 years. It will be administered directly to subjects ≥13 years.

5.12 Parent/Primary Caregiver Assessment of Self and Family Environment

a. Primary Caregiver Questionnaire (PQ) - Demographic characteristics and Communication Style

Parents/primary caregivers are asked to indicate their level of education and occupation for calculating Hollingshead's (82) SES index, ethnicity, family composition, marital status, and possible psychosocial stressors.

The PQ also contains questions from the parent/primary caregiver version of the Caregiver-Child Interaction. The subject version of the Caregiver-Child Interaction will be administered separately.

The Caregiver-Child Interaction is a 10-item, self-administered, communication scale, which will be completed by the parent/primary caregiver. It was adapted from the Child's Report of Parental Behavior Inventory (83), and assesses maternal communication style, nurturing, and emotional reaction to misbehavior. Parents/primary caregivers are also asked questions about how they utilize punishment using an 8-item scale that pertains to physical punishment, removal of privileges, verbal reprimands/insults, and nagging.

b. Adult Inventories-4 (ASRI-4) – Parent/Primary Caregiver Mental Health

The Adult Inventories are self-administered DSM-IV-referenced rating scales (84) that are designed to obtain information from patients (Adult Self-Report Inventory-4 or ASRI-4) and significant others (Adult Inventory-4 or AI-4). Both versions contain similar items, allowing direct comparisons to be made between respondents for specific symptoms. Symptom categories include GAD, Social Phobia, Schizoid Personality Disorder, Somatization Disorder, Posttraumatic Stress Disorder, Eating Problems (Anorexia, Bulimia), MDD, Dysthymic Disorder, Bipolar Disorder, Sleep Disorder, ADHD, Antisocial Personality Disorder, Schizophrenia, Substance Use, Dissociative Disorder, and Borderline Personality Disorder. There are also individual screening items for a number of other disorders,
including specific phobias, panic attacks, compulsions, obsessions, motor tics, and vocal tics. Research has been conducted to examine the internal consistency, test-retest reliability, and convergent and discriminant validity with corresponding scales of other adult measures of psychopathology and structured psychiatric interviews. The parent/primary caregiver will complete the ASRI-4 with regard to his/her own behavior.

c. **Family Environment Scale (FES) - Family Functioning**

The FES, Form R assesses family social environments, as perceived by family members (85). The FES contains 90 items (10 subscales), and respondents are asked to indicate (true, false) if the statements characterize their family. Research shows that the FES demonstrates adequate internal consistency, test-retest reliability, and validity (85).

d. **Abbreviated Sensation Seeking Scale (Zuckerman)**

The Abbreviated Sensation Seeking Scale is a 16-item scale, adapted from Zuckerman’s work, which taps into risk taking and thrill seeking behavior (86). Alpha for the scale has been reported at .79, and previous studies have shown it to be associated with adolescent sexual and substance use behaviors (81).

e. **Primary Caregiver’s Report (PR)**

The PR (87, 88) contains 25 operationally-defined behavioral items that pertain to how parents/primary caregivers interact with their children. Items are rated using a 7-point scale (0=never, 6=always). There are five factors, with four items each. The PR is divided into two sections: how parents/primary caregivers actually interact (real section) and how the ideal parent/primary caregiver would interact (ideal section). The Real factor score can be subtracted from the Ideal factor score (real-ideal disparity measure), thus offering “one approach to determining individual conceptions of social desirability and permits assessment of areas of parental dissatisfaction” (87; p. 446). The PR is reported to have satisfactory reliability and validity.

### 5.13 Child or Adolescent’s Self-Report of Mental Health and Family Environment

a. **Youth’s Inventory-4 (YI-4)**
The YI-4 (52) is a self-report rating scale for children and adolescents, ages 8 to 18 years, with items parallel to those in the SI-4 Primary Caregiver Checklist. Research indicates (52, 89) that the YI-4 demonstrates satisfactory internal consistency (alphas=.66 to .87), test-retest reliability (r values = .54 to .92), and convergent and discriminant validity with corresponding scales of other child self-report measures, including the Youth Self Report (90), and the Multidimensional Anxiety Scale for Children (91). YI-4 scores differentiate children and adolescents with and without diagnosed ADHD, conduct disorder, substance use, GAD, or MDD. In this study, children under 8 years old will not complete this instrument. Children between the ages of 8 and < 12 years old will complete an abbreviated version of the YI-4 (i.e., excludes adolescent onset disorders). Children ages ≥ 12 years will complete the original version.

b. Caregiver-Child Interaction

To assess care-giving communication style, children ≥ 12 years of age are asked questions about general punishment using an 8-item scale that pertains to physical punishment, removal of privileges, verbal reprimands or insults, and nagging.

c. Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) IQ (Letter-Number and Coding Subscales)

The WISC-IV Fourth Edition Integrated (92) is a standard cognitive measure with satisfactory reliability and validity. Two subscales (Letter –Number Sequencing and Coding Recall) will be administered in this study to provide an indication of the subject’s attention span, memory, and processing speed since these are the most likely cognitive factors to be impaired in this population. These subscales are designed to minimize cultural or educational influences and will be used as a screen for intellectual impairment.

d. Child Cognitive Impulsivity Scale (for subjects ≥ 13 yrs)

The Child Cognitive Impulsivity Scale, which is described above (in section 5.11e), will be completed by the subject for those ≥ 13 years to < 18 years old. Parents/primary caregivers will assess children <13 years on this scale.
5.14 Semi-Structured Psychiatric Interviews

a. **Diagnostic Interview for Children and Adolescents-Parent/Primary Caregiver Version (DICA-P)**

Parents/primary caregivers of a subset of subjects will be interviewed using a subset of questions from the DSM-IV (MAGIC) version of the DICA-P (49). The DICA-P is a semi-structured interview, designed to assign psychiatric diagnoses and measure symptoms of child and adolescent psychopathology, and is one of the most widely used semi-structured interviews in clinical practice and research. Numerous studies of the DSM-IV version of the DICA-P indicate satisfactory test-retest reliability and high levels of interrater agreement (45, 46, 47, 48), including comparisons between trained lay interviewers and child psychiatrists (93). In the present study, the following disorders will be included: ADHD, ODD, CD, major depressive episode, dysthymic disorder, mania/hypomania, GAD, social phobia, specific phobia, panic disorder, SAD, obsessive-compulsive disorder, somatization, tics, and psychosocial stressors. The DICA-P is administered by a trained interviewer. The MAGIC version of the DICA is described below.

b. **Diagnostic Interview for Children and Adolescents-Child Version (DICA-C)**

Children and adolescents ≥ 12 years of age, from a subset of the original study sample, will be interviewed using a subset of questions from the DSM-IV (MAGIC) version of the DICA-C (94). The DICA-C is a semi-structured interview designed to assign psychiatric diagnoses and measure symptoms of child and adolescent psychopathology in children and adolescents between the ages of 6 and 18 years; it is one of the most widely used semi-structured interviews in clinical practice and research. Numerous studies of the DSM-IV version of the DICA-C indicate good reliability and validity for children and adolescents (48), including acceptable agreement with clinical diagnoses and high agreement with the CBCL. Although test-retest reliability for adolescents is good (and consistent with other structured interviews), it varies for children; for example, test-retest reliability was found to be low for disruptive behavior disorders (.32 to .46) and good for anxiety and depressive disorders (.55 to .65). The following disorders will be included in the present study: CD, major depressive episode, dysthymic disorder, mania/hypomania, GAD,
social phobia, specific phobia, panic disorder, SAD, obsessive-compulsive disorder, and somatization. Based on the scoring algorithms, children will be assigned all tentative diagnoses for which they meet criteria. The DICA-C is administered by a trained interviewer.

The Missouri Assessment of Genetics Interview for Children (MAGIC) is a version of the DICA (48). The MAGIC was originally designed to be used in studies of the genetics of ADHD in a sample of twins assessed through birth records in the state of Missouri. Since then, it has been used in a number of genetic and family studies throughout the country although it is used in epidemiological and clinical studies as well. Because the interview was originally designed for an ADHD study it has an expanded ADHD section. The interview makes DSM-IV tentative diagnoses.

The MAGIC has no skips and thus can be used to develop scales for the analyses of psychopathology. It shows good psychometric properties (95). Like the DICA, the MAGIC has separate interviews for children 7 to 12, and adolescents 13 to 17 as well as a parent/primary caregiver version that assesses children/adolescents of all ages. There is also a version of the MAGIC for young adults 18-25 and another for their parents/primary caregivers. An adult version of the interview, ≥ 26 has just been completed.

Like the DICA, the MAGIC contains a perinatal section as well as a section on birth to 5 years.

5.2 Adherence Questionnaire

The Adherence Questionnaire is a form to be completed by a member of the site staff in a face-to-face interview with study subjects (if they are responsible for administering their own medications) or with their parents/primary caregivers (if they are responsible for administering medications). It asks about medications missed over the past three days. Adherence will be assessed at each visit. The subject (or parent/primary caregiver) will be asked to identify medications taken, frequency of administration, and number of doses missed within the three days prior to the clinic visit. A list of commonly prescribed psychiatric medications is included as a reference in Appendix II.
5.3 Pain Measurement Tools

Strategies to assess and measure pain in children and adolescents include self-report measures, which may be modified to include: parent/primary caregiver report, behavioral, and biological measures (96). In this study, we propose to measure pain through self and parent/primary caregiver report.

Self-report measures include direct questioning, lists of words to describe pain, and qualitative or numerical rating scales of pain intensity. The most widely used rating scales are visual analogue scales (VAS), which consist of a horizontal or vertical line with pictures or verbal anchors at regular intervals, with a zero starting point for no pain, to a 10 cm line indicating maximum, or extremely severe, pain. Multiple studies have shown the VAS to be a reliable and valid measure of pain in children as young as 5 years of age, and to correlate well with ratings by parents and other caregivers (97, 98).

The VAS includes faces scales that measure categories of distress by assigning each facial representation of distress a numerical value. Multiple versions have been developed and validated for use in children above the ages of 5 to 6 years (99, 100, 101). Patients, parents and health care providers have acquired considerable experience with this tool, as it is widely used in pediatric hospitals, clinics and offices.

The experience of pain can be more comprehensively evaluated in older children and adolescents using the Short-Form McGill Pain Questionnaire (SF-MPQ) (102) combined with a series of direct questions. The SF-MPQ is a widely used, valid, and reproducible tool to measure acute and/or chronic pain and contains 11 questions referring to the sensory dimension of the pain experience and four questions related to the affective dimension of the pain experience. Each descriptor is ranked on a four-point intensity scale (0=none, 1=mild, 2=moderate, 3=severe). A VAS is incorporated. The SF-MPQ is highly correlated with the McGill Pain Questionnaire (MPQ). Elevations of the affective score of the MPQ have been related to increased scores on depression instruments used with cancer patients (103, 104). Affective scores were found to contribute to the prediction of Minnesota Multiphasic Personality Inventory (MMPI) profiles (105). The SF-MPQ was developed to provide a brief assessment of both acute and chronic pain.

6.0 SERIOUS ADVERSE EXPERIENCE REPORTING

The Division of AIDS has determined that Serious Adverse Experiences (SAEs) do not need to be reported to the Regulatory Compliance Center (RCC) SAE Office for this
study. However, local IRB policies regarding reporting of adverse events will be followed.

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design Issues

P1055 is a multicenter, non-treatment, observational study of the effect of HIV on the prevalence and severity of psychiatric symptoms in 400 perinatally HIV-infected children and adolescents ages 6 to <18 as compared to a demographically matched control group of 400 children and adolescents who are uninfected but HIV-exposed, or are living with a household member who is HIV-infected. Enrollment of HIV-infected subjects will be stratified by gender and age group (6 to < 12 or ≥ 12 to < 18), and then control subjects will be selected to be frequency matched within the four strata created by gender and age group. All 800 subjects will be assessed for the prevalence and severity of psychiatric symptoms at entry and at approximately 1 year (48 weeks) and 2 years (96 weeks) after entry. In addition, a subset of 200-240 HIV-infected subjects and control subjects (100 – 120 in each group) and their parents/primary caregivers will participate in semi-structured psychiatric interviews to clinically evaluate tentative psychiatric diagnoses based on DSM-IV defined disorders. This subset will be limited to certain pre-selected sites, and may be limited to English-speaking subjects.

The designation of the control group may pose challenges as it requires subjects who are not ill to participate in this clinical research study and the cooperation of sites in identifying all potentially eligible control subjects. Care must be taken to not exclude potentially eligible subjects from the control group due to characteristics which may be related to the study outcomes (i.e., psychiatric issues). Limiting the control group to uninfected siblings of HIV-infected children and adolescents may form a more natural comparison group, but could pose more difficulty in accruing sufficient numbers of control subjects. This option was considered in designing the study, but rejected in favor of a more broadly-defined and inclusive control group.

7.2 Outcome Measures

7.21 Outcomes related to Primary Objectives

7.211 To examine the rates and severity of psychiatric symptomatology in a cohort of perinatally HIV-infected children and adolescents. Endpoints include:
(1) Rates (proportion of subjects with positive symptom cut-off score based on symptom counts, which result in a yes/no variable indicative of the disorder) for selected psychiatric disorders as defined by symptom checklists: At baseline, 48 weeks, and 96 weeks.

(2) Severity (mean severity ratings) of selected psychiatric disorders, as defined by symptom checklists: At baseline, 48 weeks, and 96 weeks.

Note: Children and adolescents ≥ 8 years of age will complete the YI-4. Parents/primary caregivers will assess children of all ages (SI-4 Primary Caregiver Checklist, CBCL, PQ).

Children between the ages of 8 and < 12 years of age will complete an abbreviated version of the YI-4 (i.e., excludes adolescent onset disorders). Children ages ≥ 12 years will complete the original version.
<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Symptom inventories</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Children &lt; 8 years of age</td>
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<tr>
<td></td>
<td>Parent/primary caregiver-endorsed</td>
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<tr>
<td>ADHD (H, I, Combined)</td>
<td>x (SI-4 Primary Caregiver Checklist)</td>
</tr>
<tr>
<td>Aggression and conduct problems (ODD; CD)</td>
<td>x (SI-4 Primary Caregiver Checklist)</td>
</tr>
<tr>
<td>Depression (MDD)</td>
<td>x (SI-4 Primary Caregiver Checklist)</td>
</tr>
<tr>
<td>Anxiety (GAD)</td>
<td>x (SI-4 Primary Caregiver Checklist)</td>
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<tr>
<td>Academic performance</td>
<td>x (PQ)</td>
</tr>
<tr>
<td>Social adjustment</td>
<td>x (PQ)</td>
</tr>
<tr>
<td>CBCL-Internalizing scale (e.g., includes Depression, anxiety)</td>
<td>x (CBCL)</td>
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<tr>
<td>CBCL-Externalizing scale (e.g., includes Impulsivity)</td>
<td>x (CBCL)</td>
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</table>

7.212 To compare the rates and severity of psychiatric symptomatology in HIV-infected children and adolescents to a cohort of demographically matched control subjects. For Endpoints, refer to section 7.211 (primary objective 1).

Note: Potential confounders will be examined and adjusted for, if necessary: These will include Cognitive ability, SES, family
adversity, parent/primary caregiver mental health, and home environment variables. Note: See 7.224, secondary objective 4, for complete list of potential explanatory variables/confounders.

7.213 To estimate the prevalence of DSM-IV defined disorders using semi-structured interviews in a subset of children or adolescents and control subjects, and to examine the clinical utility of severity cutoff scores in relation to semi-structured interviews. Endpoints include:

(1) Baseline rates (proportion of subjects with positive symptom cut-off score based on symptom counts, which result in a yes/no variable indicative of the disorder) for selected psychiatric disorders, as defined by symptom checklists. See 7.211 for details. Parents/primary caregivers will complete symptom inventories for children and adolescents of all ages. Only children and adolescents ≥ 8 years of age will complete self-reports.

(2) Proportions of psychiatric disorders, as defined by MAGIC DICA, at baseline. Parents/primary caregivers will be interviewed regarding children of all ages. Only children and adolescents ≥ 12 years of age will be interviewed.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>MAGIC DICA</th>
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<tr>
<td></td>
<td>Children &lt;12 years of age</td>
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<td>ADHD (H,I, Combined)</td>
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<td>x</td>
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<tr>
<td>Anxiety (GAD)</td>
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7.22 Outcomes related to secondary objectives

7.221 To examine the changes over time in psychiatric symptom severity in HIV-infected children and adolescents, and compare them with changes over time in control subjects. Endpoints include:

1. Mean severity scores, psychiatric symptoms (See 7.211, primary objective 1), at baseline, 48 weeks, and 96 weeks for six main domains.

2. Incident tentative diagnoses: the number of subjects of who exceed the screening cutoff or receive a tentative diagnosis during the course of the study, but who had no tentative diagnosis and did not exceed the SI-4 Primary Caregiver Checklist screening cutoff at baseline (this analysis assumes that those subjects without a tentative diagnosis or without exceeding the SI-4 Primary Caregiver Checklist screening cutoff at entry never did so in the past).

Potential confounders will also be considered: age, gender, HIV variables, family characteristics, and child and adolescent characteristics. Note: See 7.224, secondary objective 4 for complete list of potential explanatory variables/confounders.

7.222 To examine antiretroviral and psychiatric medication adherence in HIV-infected children and adolescents at baseline, 48 weeks, and 96 weeks on study, and to examine the association between medication adherence and co-occurring psychiatric symptoms. Endpoints include, for HIV-infected children and adolescents only:

1. Antiretroviral medication adherence at baseline, 48 weeks, and 96 weeks.
   1. Overall percentage of expected doses taken based on 3-day recall (Adherence Questionnaire).
   2. Percentage of expected doses taken by class:
      i. NRTIs
      ii. NNRTIs
      iii. PIs
      iv. Other (T20, gp120, hydroxyurea, etc.)
(2) Psychiatric medication adherence at baseline, 48 weeks, and 96 weeks.

1. The number and percentage of subjects prescribed each psychiatric medication individually, and by class, as defined preliminarily in Appendix II, will be summarized.
   i. antipsychotic medications
   ii. antidepressant
   iii. ADHD
   iv. insomnia
   v. antianxiety
   vi. anticonvulsant/mood stabilizer/antiepileptic

2. Adherence to psychiatric medications over all classes, as percentage of expected doses taken based on 3-day recall (Adherence Questionnaire), will be summarized.

3. If there are many subjects taking specific medications or classes of medications, adherence by these specific categories or classes (as preliminarily defined in Appendix II), as percentage of expected doses taken, will be summarized. This will be done at baseline, 48 weeks, and 96 weeks.

(3) Psychiatric symptoms, rates, and severity, at baseline, 48 weeks, and 96 weeks for each of the six main domains (See 7.211, primary objective 1).
   i. ADHD
   ii. ODD/CD
   iii. MDD
   iv. GAD
   v. Academic performance
   vi. Social adjustment

Note: Percentage of adherence will be divided into the following categories: <50%, 50-70%, 70-99%, and 100% adherence, unless the data suggest other appropriate categories.

In this analysis, potential confounders will also be considered: Other demographic and environmental factors (e.g., age, gender, home environment measures) will also be adjusted for in evaluating adherence. Note: See 7.224, secondary objective 4 for a complete list of potential explanatory variables/confounders.
Note: For the association of psychiatric medication adherence to severity of symptoms and antiretroviral medication adherence, the relevant medication and/or class of psychiatric medications according to the symptom/disorder domain under analysis will be observed.

Note: The relationship between psychiatric medication adherence and psychiatric symptoms, across both HIV-infection status groups, may also be explored.

7.223 To examine the association of lifetime exposure to antiretroviral classes among HIV-infected children and adolescents to severity of psychiatric symptomatology. Endpoints include:

(1) Number of months/number of years of exposure to:
   i. Antiretrovirals, overall
   ii. NRTIs
   iii. NNRTIs
   iv. PIs
   v. Other (T20, gp120, hydroxyurea, etc.)

(2) Mean severity scores, psychiatric symptoms (See 7.211, primary objective 1), at baseline, 48 weeks, and 96 weeks for six main domains.

In this analysis, the potential confounders will also be considered:

(1) Exposure to psychiatric medications.

(2) Severity of HIV/AIDS illness (i.e., using various measures, such as CDC category, CD4 counts and percents (nadir, at study entry, and annually), the Pediatric AIDS Severity Score (PASS), total lymphocyte count, and HIV viral load (at study entry and annually).

Note: See 7.224, secondary objective 4, for a complete list of potential explanatory variables/confounders.

7.224 To examine other factors associated with child or adolescent psychiatric symptomatology, including HIV variables, and family, child, and adolescent behavioral and psychosocial characteristics. Endpoints include:
(1) Mean severity scores, psychiatric symptoms (See 7.211, primary objective 1), at baseline, 48 weeks, and 96 weeks, for six main domains.

Related factors – predictors and confounders:

(1) **HIV variables**: Infection status; For HIV-infected: HIV symptom severity, CDC category, CD4 count and percent at entry and nadir (versus PASS Score), total lymphocyte count, and lifetime exposure to antiretrovirals.

(2) **Family behavioral and psychosocial characteristics**: parent/primary caregiver mental health diagnoses, trauma history, substance abuse history, SES/poverty, life stressors, parent/primary caregiver ethnicity, family members with HIV, family stability, parent/primary caregiver relation to child/adolescent, child-rearing practices, parent/primary caregiver-child/adolescent communication, and family environment scale measures.

(3) **Child and adolescent behavioral and psychosocial characteristics**: age, gender, ethnicity, physical measure, HIV status self-knowledge, neuropsychological diagnosis history, intellectual functioning, global functioning, impulsivity, QOL self-report, psychiatric medication history.

Note: Models will be developed separately for HIV-infected and HIV-uninfected subjects.

**7.225** To examine the presence and severity of chronic pain in HIV-infected and control populations with and without psychiatric symptomatology. Endpoints include:

(1) Pain assessments at baseline, week 48, and week 96.

a. Overall mean pain severity (SF-MPQ, ≥ 12 years of age)

b. Sensory pain severity (SF-MPQ, ≥ 12 years of age)

c. Affective pain severity (SF-MPQ, ≥ 12 years of age)

d. Present pain level assessment
   i. SF-MPQ, Present Pain Intensity Index (≥ 12 years of age)
   ii. Pain Level Assessment, VAS (all ages).
(2) Psychiatric symptoms (See 7.211, primary objective 1) at baseline, 48 weeks, and 96 weeks for six main domains, using symptom cutoff scores.

(3) Models will relate pain measures to explanatory factors noted in 7.224, secondary objective 4, above.

7.23 Outcomes for other supporting and descriptive analyses:

7.231 Psychiatric Symptom Clustering: co-occurrences and patterns of psychiatric co-morbidities.

(1) Psychiatric symptoms, mean severity, and endorsement of disorder according to symptom cutoff score (see 7.211, primary objective 1).

7.232 Gender differences: gender differences in psychiatric symptoms, particularly ADHD-related symptoms, for HIV-infected, compared to HIV-uninfected children and adolescents.

(1) Psychiatric symptoms, mean severity, and endorsement of disorder according to symptom cutoff score (see 7.211, primary objective 1).

7.233 Genetic versus Home Environment: differences in rates of psychiatric symptoms between HIV-uninfected and HIV-infected biological siblings (who share both genetic and home environments) versus non-biological siblings (who share only home environment). A similar comparison will be made between HIV-uninfected and HIV-infected household-members who are not

---

<table>
<thead>
<tr>
<th>Measure</th>
<th>Child/adolescent- endorsed</th>
<th>Parent/primary caregiver-endorsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-MPQ</td>
<td>x *</td>
<td></td>
</tr>
<tr>
<td>Pain Level Assessment</td>
<td>x**</td>
<td>x</td>
</tr>
</tbody>
</table>

* Completed only by children and adolescents ≥ 12 years of age.
** If needed, parent/primary caregiver can help child/adolescent complete.
siblings (again, separating biological versus non-biologically-related household members).

(1) Psychiatric symptoms, mean severity and endorsement of disorder according to symptom cutoff score (see 7.211, primary objective 1).

7.3 Randomization/Registration and Stratification

Subjects for the HIV-infected group will be recruited from the patients who are routinely evaluated at each PACTG site, and have been seen at the site within the past 12 months. Subjects for the control group will be recruited from members of households with a parent, sibling, or other household member who has been infected with HIV; household members of subjects who have been chosen for the HIV-infected group, and are in the desired age ranges, may be recruited.

The registration of subjects will proceed as follows:

1. Sites will obtain a screening number for each potential subject using the Data Management Center (DMC) Randomization System and Screening Log PS2001.
2. A screening form will be entered via the DMC data entry system, eData, using the screening number. The form will collect HIV status (infected or control group), gender, race, age in years, and current or previous PACTG 219C participation (yes/no). No unique identifying information will be collected for each screening ID, since subjects will not yet have signed a consent form.
3. Selection of subjects will take place in two stages, with the first stage for HIV-infected subjects and the second stage for control subjects. For the first stage, at a cutoff date, communicated in advance to the participating sites (approximately three months after version 1.0 is sent to the sites), SDAC will retrieve the lists of HIV-infected subjects entered on the screening form, and randomly order all of the HIV-infected subjects within each site. Each site list will be ordered within blocks of four subjects. The DMC randomization department will load this list into a randomization database; the P1055 team will then notify sites that this process has been completed and that they can begin enrollment of the HIV-infected subjects.
4. For the second stage, control subjects will be selected from among all those for whom a screening form has been entered by a second cutoff date (approximately one month after the cutoff date for infected subjects). Control subjects will be selected by randomly ordering all screened subjects within each of the four strata defined by age group and gender, and then by frequency matching subjects across all sites by block. For example, if the first block of
infected subjects across all sites includes 20% female 6 to < 12 years of age, 30% male 6 to < 12 years of age, 40% female 12 to < 18 years of age, and 10% male ≥ 12 to < 18 years of age, then the first block of control subjects pooled over all sites would have the same percentage in each strata.

5. If a patient is approached for P1055 but does not enroll into the study, the site will submit a Failure Result Form via eData using the screening number. This form will collect the reason(s) for not enrolling (i.e., ineligibility, refusal, and associated reasons for ineligibility or refusal).

6. When a subject is enrolled into P1055, the screening number, in addition to the normal eligibility criteria, will be entered into the data base. The DMC randomization system will verify that the screening number is on the list and in the correct sequence. Screening numbers will be randomly ordered in blocks of four, and sites will be able to enroll anyone from the current block, but not from the following block(s) until all from the previous block are enrolled and/or have a failure result form entered.

Although there will be no cap on the number of subjects enrolled at any single site, total enrollment will be capped at 400 HIV-infected and 400 control subjects. In addition, there will be a cap of 200 subjects within each of the two age groups within the HIV-infected and control groups. There will be no caps on enrollment within strata defined by gender.

7.4 Sample Size and Accrual

This study is designed to enroll 400 HIV-infected children and adolescents and 400 control subjects frequency matched by gender and age group (6 to < 12 years and ≥ 12 to < 18 years), for a total sample size of 800 children and adolescents. The accrual of these 800 subjects is expected to be completed within 1 ½ years of when accrual opens (approximately three months after version 1.0 of the protocol is available). As noted in section 7.3, the total number of subjects enrolled within each age group will be capped at 200 HIV-infected and 200 control subjects. The impact of this sample size on the ability to address the primary objectives of this study was evaluated as follows. For objective 7.211, exact 95% confidence intervals (CI’s) were constructed for various possible observed outcome rates of psychiatric symptoms, both within strata and overall. For objective 7.212, detectable differences in mean severity scores between HIV-infected and control subjects were calculated to provide 80% power, both within strata, and overall. In these calculations, it was assumed that an equal proportion of males and females would be enrolled, which is supported based on data from PACTG 219C. For objective 7.213, exact 95% CI’s were again calculated for various possible observed proportions of subjects with DSM-IV defined disorders, based on the subset of subjects with MAGIC DICA evaluations.
Table 1, below, presents a summary of the exact 95% CI’s that would result from various observed outcome rates of psychiatric symptoms (ranging from 0.01 to 0.30), based on sample sizes of 100 subjects (within age and gender), 200 subjects (within age or gender), or 400 subjects (overall within HIV-infected or within control group). Clearly, as the sample size (or subgroup considered) becomes larger, the CI’s become narrower or more precise. To aid in interpreting Table 1, with respect to specific domains, some estimates of disorders in other chronic illnesses are provided by data on epilepsy: 15% for ADHD-H, 34% for ADHD-I, 21% for ODD, 18% for CD, 3% for depressive disorder, and 2% for anxiety. Among normative controls, rates for these domains typically range from 1-5%. Among clinic-based referrals, published rates are 33% for ADHD-I, 5-8% for ADHD-H, 35-40% for ODD, approximately 20% for CD, approximately 8% for generalized anxiety, and 1-5% for MDD.

Objective 7.212 is the primary comparison which drives the power of the study. For this comparison, the minimum detectable difference in mean SI-4 Primary Caregiver Checklist severity scores at 80% power was calculated and is shown in Table 2. Note that both the adjusted and unadjusted detectable differences are shown. The unadjusted differences assume a significance level of 0.05 for each comparison (e.g., within each domain or subdomain). The adjusted differences account for the fact that multiple comparisons are conducted within each hypothesis using a Bonferroni adjustment (a significance level of 0.05/6 for each of the six domains). These differences are all less than 0.5 standard deviations, indicating that the study is well powered to detect differences of interest. In addition, a simulation study was conducted to evaluate the power of detecting a 0.2 difference in standard deviations comparing HIV-infected to control among all 800 subjects, while controlling for age, gender, and age by gender interaction in a linear regression model; this simulation study also showed a power of 80.4% for detecting such a difference between the two groups. The table below applies to any continuous measurement which can be assumed to follow a normal distribution. Since many other outcomes will be evaluated in this study in addition to the SI-4 Primary
Caregiver Checklist severity score, the table below can be used to provide guidance on the detectable differences for other such outcomes.

Table 2: Minimum detectable differences in mean SI-4 Primary Caregiver Checklist severity scores at entry, at 80% power

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Sample Sizes</th>
<th>Detectable difference in SDs, unadjusted</th>
<th>Detectable difference in SDs, adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (HIV-infected)</td>
<td>N (control)</td>
<td></td>
</tr>
<tr>
<td>(1) within age and gender</td>
<td>100</td>
<td>100</td>
<td>0.398</td>
</tr>
<tr>
<td>(2) within age strata</td>
<td>200</td>
<td>200</td>
<td>0.280</td>
</tr>
<tr>
<td>(3) overall</td>
<td>400</td>
<td>400</td>
<td>0.198</td>
</tr>
</tbody>
</table>

Table 3 presents a summary of the exact 95% CI’s that would result from various observed proportions of subjects with psychiatric disorders, based on the subset of 200-240 subjects with MAGIC DICA evaluations. Note that some entries could not be completed because there was no possible number of subjects with disorders that would yield this proportion, given the relatively small sample size.

Table 3: Exact 95% confidence intervals for various observed proportions of subjects with DSM-IV defined psychiatric disorders, by strata and overall

<table>
<thead>
<tr>
<th>Proportion with Symptom</th>
<th>Enrollment per group, N=100</th>
<th>Enrollment per group, N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Within Age Group (N=50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.01</td>
<td>(0 - 0.054)</td>
<td>---</td>
</tr>
<tr>
<td>0.05</td>
<td>(0.016 – 0.113)</td>
<td>---</td>
</tr>
<tr>
<td>0.10</td>
<td>(0.049 – 0.176)</td>
<td>(0.033-0.218)</td>
</tr>
<tr>
<td>0.20</td>
<td>(0.127 – 0.292)</td>
<td>(0.100-0.337)</td>
</tr>
<tr>
<td>0.30</td>
<td>(0.212 – 0.400)</td>
<td>(0.179,0.446)</td>
</tr>
</tbody>
</table>

The power for the secondary objectives which involve follow-up data may be diminished as a result of loss to follow-up. The extent to which the power is diminished will depend on the proportion of subjects that are lost after one and two years.

7.5 Monitoring
During the finalization of the protocol, a monitoring plan will be developed for this study to ensure that the data collected are clean, complete, and of high quality, and to make the team aware of the study’s progress in an ongoing manner. The monitoring plan will identify which data items will be reviewed by the team and what the timing of such routine reviews will be. Monthly conference calls will be held by the study team to assess accrual of both HIV-infected and control subjects, timely and appropriate urgent mental health referrals, and rate of inadvertent disclosures of HIV status or other sensitive health issues. More extensive monitoring reports are more likely to be produced on a quarterly or semi-annual basis. The focus of such reports would be to evaluate study conduct, in terms of registration of eligible subjects at each site (including reasons for lack of enrollment); to assess baseline characteristics in order to ensure comparability of the two groups; and to evaluate data completeness for the primary data measures (mean severity scores, presence of pain, adherence measures, antiretroviral therapy, CD4, total lymphocyte count, and viral load, etc.). Evaluation of the percent of subjects who are maintained on study through the week 48 and week 96 evaluations will help to establish the feasibility of a longer-term study for further research funding applications. After approximately one year of accrual, the study team may consider conducting an interim monitoring review of the data, in which preliminary data on rates and severity of psychiatric symptoms could be evaluated. Although this is not a treatment study, and there are no safety issues of concern, an interim monitoring review may be very helpful in establishing the feasibility of the study and checking that the quality of the data is high. Consideration will be given to including one or more experts outside the study team to an interim monitoring review panel in order to improve the critical and productive nature of such a review.

A DSMB will be organized by NIMH which will monitor the study progress over time, and make recommendations to the study team. In particular, the DSMB may consider the option of extending the study past the current plan of 96 weeks and will evaluate feasibility and futility, as well. Recommendations made by the DSMB may result in an amendment to the protocol to extend the study or make other appropriate changes.

7.6 Analysis

7.6.1 Analyses for primary objectives:

The primary objectives of the proposed study are to assess the rates and severity of specific emotional and behavioral symptoms in HIV-infected children and adolescents, and to compare these rates and symptom severities with control subjects within each of two age groups. In
addressing these objectives, a primary emphasis will be placed on six domains of interest. Four of the six domains are derived from symptom categories measured on the SI-4 Primary Caregiver Checklist (see section 5.11 (a), and include ADHD, aggression and conduct problems (ODD and CD), MDD, and GAD. The remaining two domains of interest are derived from the PQ (formerly from the SSF) and include academic performance and social adjustment. In addition, supporting analyses for the primary objectives will consider the internalizing (e.g., depression, anxiety) and externalizing (e.g., impulsivity) outcomes measured on the CBCL. Within each domain, 95% CI’s will first be constructed for observed psychiatric symptom rates (i.e., the proportion of children exceeding screening cutoffs based on the SI-4 Primary Caregiver Checklist score, or for the semi-structured interview subgroup, the proportion with specific tentative psychiatric diagnoses based on MAGIC DICA). The two groups (HIV-infected versus control) will then be compared with respect to psychiatric symptom rates and mean severity scores from the SI-4 Primary Caregiver Checklist within each domain. The domains and their measures are as follows: (1) ADHD categories (ADHD category of the SI-4 Primary Caregiver Checklist); (2) aggression and conduct problems (ODD and CD categories of the SI-4 Primary Caregiver Checklist); (3) depressive symptoms (Depressive Disorder categories of the SI-4 Primary Caregiver Checklist and YI-4); (4) anxiety symptoms (Anxiety Disorder categories of the SI-4 Primary Caregiver Checklist and YI-4); (5) academic performance (PQ); and (6) social adjustment (PQ).

The two groups will first be compared for potential differences in characteristics such as IQ, SES, family adversity, parent/primary caregiver mental health, and home environment variables. The primary analysis of symptom severity (SI-4 Primary Caregiver Checklist) will be conducted by comparing mean severity scores between groups within each separate domain using a general linear regression model, controlling for the potential confounders identified above. The primary analysis of differences in rates of symptoms (MAGIC DICA) will be conducted separately within each domain using a logistic regression model, again controlling for potential confounders. A supporting analysis will be conducted, including all six domains simultaneously, to evaluate differences in symptom severity and rates of symptoms, while accounting for the intercorrelations among the domains. This analysis will be likely to have greater power to detect differences between HIV-infected and demographically matched control subjects.
For each of the above analyses, the goodness-of-fit and assumptions of the model will be evaluated to ensure that it is an appropriate model. For example, for the linear regression model, the outcome of mean severity scores will be evaluated for normality. If the mean severity scores exhibit large departures from normality, then transformations of the outcomes (square root, logarithmic, etc.) will be considered, as well as alternative models, such as a generalized estimating equation (GEE) model which does not require the assumption of normality and, thus, tends to be more robust for highly skewed data. In addition, the data will be checked for outliers, and residuals will be evaluated for model fit, both for the linear regression model (comparing mean severity scores) and the logistic regression model (comparing rates of psychiatric symptoms).

For primary objective 7.213, the validity and tentative clinical utility of the SI-4 Primary Caregiver Checklist instrument will be assessed, relative to the tentative MAGIC DICA diagnoses, on the subset of subjects who complete the semi-structured interviews. In this analysis, the tentative semi-structured interview diagnosis will be treated as the gold standard, and the sensitivity and specificity of the SI-4 Primary Caregiver Checklist instrument, with screening cutoffs within each of the domains of interest, will be assessed.

7.62 Analyses for secondary objectives:

Changes over time in psychiatric symptoms (objective 7.221) will be modeled using GEE repeated measures models or mixed effect models, in order to account for the correlation among multiple measurements made on the same subject over time (at entry, 48 weeks, and 96 weeks). The primary goal of this analysis will be to compare the two groups (HIV-infected versus control) with respect to changes in severity scores within each of the domains. For ease of clinical interpretation, a simpler model may also be considered by constructing the difference in mean severity scores for week 96 versus entry for each subject, and then comparing the distribution of mean changes between the HIV-infected and control groups. Collection of psychiatric symptom data at these three time points will also allow evaluation of incident tentative diagnoses (with the assumption that those subjects without a tentative diagnosis or exceeding an SI-4 Primary Caregiver Checklist screening cutoff at entry never had one or did so in the past). As with all of the secondary objectives, the above models will consider all potential confounders, such as age, gender, HIV variables, family characteristics, and child and adolescent characteristics.
The adherence objective 7.222 can be viewed in two ways – either 1) that greater psychiatric symptomatology will lead to increased non-adherence to medication regimens, or 2) that increased non-adherence (especially with respect to psychiatric medication) will lead to increased symptomatology. To evaluate this objective, non-adherence will be categorized into groups (e.g., <50%, 50-70%, 70-99%, and 100% adherence) based on the 3-day recall Adherence Questionnaire, which measures the percentage of expected doses taken by the subject over the past three days. The actual categories will be based on the observed distribution of adherence; if a high percentage (>75%) of subjects report complete adherence, then there may only be two adherence groups - adherent versus non-adherent. Adherence to antiretrovirals will be assessed overall, and within each major antiretroviral drug class (NRTIs, NNRTIs, PIs); adherence will also be assessed overall for psychiatric medications, when applicable. The rates of psychiatric symptoms will be compared among the adherence categories for HIV-infected subjects using a general chi-square test in order to test for differences in rates among groups; a chi-square test will also be used for trend - to test for increasing or decreasing rates over the adherence levels. The mean (or median) severity scores will also be compared across adherence groups. These analyses will be conducted for the overall antiretroviral regimen, within each antiretroviral drug class, and for psychiatric medications at each of three time points - entry, 48 weeks, and 96 weeks - within each of the six domains. Since there are five different adherence measures, this will result in a total of 90 comparisons. Due to the large number of comparisons, the results will be considered mostly descriptive in nature, with emphasis on consistency across measures, domains, or time points. In addition, a multivariate model for non-adherence, using all six domains, will be evaluated at each time point, and overall. Because of the potential for high within-subject correlation among the symptom domain scores, the between-domain correlation structure will first be evaluated; reduced models may be considered, if required, for model stability. Other demographic and environmental factors (e.g., age, gender, home environment measures) will also be adjusted for in evaluating adherence. This objective will be addressed solely within the subset of HIV-infected subjects, since they are those who will be receiving antiretroviral medications.

The association of antiretroviral therapy with severity of psychiatric symptomatology (objective 7.223) will be evaluated by modeling the mean severity scores as a function of receipt and/or duration of antiretroviral
therapy overall, and within major drug classes. However, there is a great potential for confounding by indication – that is, the subjects who are most severely ill are also most likely to start potent antiretroviral therapy. As a result, attempts will be made in such models to adjust for such potential confounders by controlling for severity of illness (i.e., using CD4 counts, CD4 percents, total lymphocyte count, HIV-1 RNA viral load when available, PASS score [Personal Communication, Seage, December 2003], etc).

The evaluation of specific risk factors and their association with psychiatric symptomatology is a secondary objective of this study (objective 7.224), which will be evaluated via multivariate models using robust model selection, verification of goodness of fit, and other appropriate model diagnostics. For each of the six symptom domains, a separate multivariate model will be developed for the mean SI-4 Primary Caregiver Checklist severity score. These models will be developed separately for the subgroups of HIV-infected and control subjects. Thus, a set of 12 multivariate models will be developed, and the risk factors included in each model will then be compared across the six symptom domains and between the two groups defined by infection status. These analyses will help address the hypothesis that risk factors will vary for different types of psychiatric symptoms, and that risk factors for psychiatric symptomatology will be different for HIV-infected subjects than for the control subjects. Similar analyses will evaluate the risk factors which are important predictors of social and academic functioning, and compare these risk factors between HIV-infected and control groups.

The assessment of the presence and severity of chronic pain (objective 7.225) will be based on the SF-MPQ, along with the present pain level assessment and VAS. This questionnaire includes 15 items (11 sensory, 4 affective) which are each rated on a scale of 0 (none), 1 (mild), 2 (moderate), or 3 (severe). Three pain scores are derived as totals for the sensory, affective, and overall descriptors. The mean scores for the three totals will be summarized by age and gender, and models relating these pain scores to various other subject, family, and home environment variables will be constructed.

Other supporting and descriptive analyses:

Psychiatric Symptom Clustering: To gain an understanding of the co-occurrence and pattern of psychiatric comorbidities, the correlation of SI-4 Primary Caregiver Checklist average severity scores across the six
domains will be evaluated. In addition, using the screening cutoff scores for the SI-4 Primary Caregiver Checklist to indicate presence or absence of psychiatric symptoms, the clustering of specific psychiatric symptoms (e.g., ADHD and ODD) will be assessed.

**Gender differences:** It has been hypothesized that HIV-infected children will exhibit fewer gender differences in psychiatric symptoms, particularly ADHD-related symptoms, than uninfected children. This hypothesis will be evaluated by estimating the average gender difference both in mean severity scores, and rates of symptoms, for each SI-4 Primary Caregiver Checklist domain, and then comparing these gender differences (in average scores or rates) between the HIV-infected and control groups.

**Genetic versus Home Environment:** It is expected that many of the control subjects will be siblings of HIV-infected subjects in the study. Some control subjects may be biological siblings of HIV-infected subjects, while others may be non-biological siblings. If there are sufficient numbers of each, there may be adequate power for conducting a subset analysis of differences in rates of psychiatric symptoms between biological siblings (who share both genetic and home environments) versus non-biological siblings (who share only home environment). Other control subjects may have a different household member who is HIV-infected, and we will evaluate the effect that the relationship of control subject to HIV-infected household member has on their psychiatric symptomatology. Similarly, we will evaluate differences in rates of psychiatric symptoms between control subjects eligible through perinatal exposure to HIV, control subjects eligible as a result of living in a household with an HIV-infected member, and control subjects who share both risk factors.

8.0 **HUMAN SUBJECTS**

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs for the recruitment of prisoners.

8.1 **Institutional Review Board (IRB) Review and Informed Consent**

Once it has been determined that a subject may qualify for the protocol and the study details are discussed, questions will be answered, and written informed consent and/or assent will be obtained from the parent/primary caregiver and the subject (if required by the local IRB) before any study related procedures are performed.
This protocol, the informed consent document (Appendix V), the assent document and any subsequent modifications must be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. Written informed consent must be obtained from parents/primary caregivers; assent must also be obtained from subjects who are able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the parent/primary caregiver.

8.2 Subject Confidentiality

All evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the NIAID, NICHD, and NIMH.

8.3 Study Discontinuation

The study may be discontinued at any time by the IRB, NIAID, NICHD, or the NIMH.

9.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by PACTG policies.
10.0 REFERENCES


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## APPENDIX I

**SCHEDULE OF EVALUATIONS AND TIME ESTIMATES FOR MEASURES AND OTHER EVALUATIONS FOR HIV--AND CONTROL SUBJECTS**

<table>
<thead>
<tr>
<th>Event</th>
<th>Screening</th>
<th>Entry</th>
<th>Study Week</th>
<th><strong>Time Estimates (5-10 questions per minute)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>*</td>
<td>48 weeks</td>
<td>96 weeks</td>
</tr>
<tr>
<td>History&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim History&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical exam&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assessment of HIV-related symptoms</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adherence Questionnaire&lt;sup&gt;5&lt;/sup&gt; (Parent/primary caregiver or subject completed; assesses the subject)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>MENTAL HEALTH MEASURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Caregiver Questionnaire (PQ)*** (Assesses the subject and parent/primary caregiver/family demographics)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Symptom Inventories-4 (SI-4) Primary Caregiver Checklist (Assesses the subject)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Adult Inventories-4 (ASRI-4, AI-4) (Assesses the parent/primary caregiver)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Family Environment Scale (FES) (Assesses the parent/primary caregiver and family environment)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Abbreviated Sensation Seeking Scale (Zuckerman) (Assesses the parent/primary caregiver)</td>
<td>X</td>
<td></td>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td>Primary Caregiver’s Report (PR) (caregiver-child interactions) (Assesses the parent/primary caregiver/family environment)</td>
<td>X</td>
<td></td>
<td></td>
<td>10 minutes</td>
</tr>
<tr>
<td>Child Behavior Checklist (CBCL) (Assesses the subject)</td>
<td>X</td>
<td></td>
<td></td>
<td>20 minutes</td>
</tr>
<tr>
<td>Columbia Impairment Scale (CIS) (Assesses the subject)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Child Cognitive Impulsivity Scale**** (Assesses the subject)</td>
<td>X</td>
<td></td>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td><strong>SUBJECT COMPLETED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth’s Inventory-4 (YI-4)***** (Assesses the subject)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Caregiver-Child Interaction (Assesses parent/primary caregiver communication style/family environment - subject ≥ 12 years of age-completed)</td>
<td>X</td>
<td></td>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td>Wechsler Intelligence Scale for Children - WISC-IV IQ (Letter-Number and Coding Subscales) (Assesses the subject)</td>
<td>X</td>
<td></td>
<td></td>
<td>15 minutes</td>
</tr>
<tr>
<td>Child Cognitive Impulsivity Scale**** (Assesses the subject)</td>
<td>X</td>
<td></td>
<td></td>
<td>5 minutes</td>
</tr>
<tr>
<td><strong>PAIN MEASURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Level Assessment (Assesses the subject and parent/primary caregiver completed)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 minutes</td>
</tr>
<tr>
<td>McGill Pain Questionnaire – Short Form (SF-MPO) (Assesses the subject - subject ≥ 12 years of age-completed)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 minutes</td>
</tr>
<tr>
<td><strong>SEMI-STRUCTURED PSYCHIATRIC INTERVIEWS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAGIC Version of the Diagnostic Interview for Children and Adolescents – Parent/Primary Caregiver Version (DICA-P) (Assesses the subject)</td>
<td>X</td>
<td></td>
<td></td>
<td>60 minutes</td>
</tr>
<tr>
<td>MAGIC Version of the Diagnostic Interview for Children and Adolescents – Child Version (DICA-C) (Assesses the subject - subject ≥ 12 years of age-completed)</td>
<td>X</td>
<td></td>
<td></td>
<td>30 minutes</td>
</tr>
</tbody>
</table>
APPENDIX I (Cont.)

1. The Informed Consent will be signed at the screening visit. Screening and entry can occur at the same visit or up to six weeks apart.

2. History – includes source documentation for lifetime exposure to antiretroviral medications; CDC diagnoses; CD4 count and CD4%, including nadir CD4 count and CD4%; neuropsychiatric diagnoses; and lifetime exposure to neurotropic medications. Note: Within 90 days of entry, sites must provide the most recent CD4 count, CD4%, viral load, and total lymphocyte count for HIV-infected subjects only.

3. Interim History – includes changes in history from previous visit. Note: Within 90 days of the study visit, sites must provide the most recent CD4 count, CD4%, viral load, and total lymphocyte count for HIV-infected subjects only.

4. Physical Exam - height, weight, and symptoms.

5. Adherence Questionnaire – includes measurement of adherence to antiretroviral regimens and adherence to neuropsychiatric drug regimens.

6. Semi-Structured Psychiatric Interviews (MAGIC DICA) will only be conducted at approximately six to eight selected sites on a subset of the original study population. All of the subjects and their parents/primary caregivers at the selected sites must participate in this part of the study. The semi-structured interviews must be administered by site personnel who are trained in the administration of the MAGIC version of the DICA and will be completed by subjects and parents/primary caregivers within 90 days following study entry and completion of the original study measures (for the subset of subjects and parents/primary caregivers at sites that have been selected for these additional measures). The protocol team strongly recommends that selected sites administer the parent/primary caregiver version of the MAGIC DICA prior to administering the subject version. Approximately 20% of these interviews will be audio-taped, in order to verify scoring procedures. Sites which are asked to audio-tape selected MAGIC DICA interviews may be required to add in additional IRB-approved language regarding the use of audio-tapes into any applicable consent and/or assent forms. Tapes will be forwarded to designated members of the team and then erased and returned to the site to be destroyed. Sites will be selected by the team, based on information provided in their Site Implementation Plans (SIPs). Site selection will be based on a number of criteria, including site willingness to participate, enrollment potential, time constraints, previous MAGIC DICA training or availability for future MAGIC DICA training, and previous participation in neuropsychiatric studies.

*Subjects and their parents/primary caregivers will be given the option of returning to complete the measures within 90 days from their screening or entry visit if they find the measures too burdensome to complete in one sitting.

**The total maximum times for filling out the Mental Health Measures (at entry) are expected to be:
1) For parent/primary caregiver: 125 minutes; 185 minutes with the MAGIC DICA.
2) For subject: 55 minutes; 85 minutes with the MAGIC DICA.
NOTE: This does not include time estimates for completing history, assessment of HIV-related symptoms, physical exam, and adherence questionnaire.

***Parts of the Primary Caregiver Questionnaire will be administered at each study visit. The complete Primary Caregiver Questionnaire will only be administered at entry.

****The Child Cognitive Impulsivity Scale will be completed by the parents/primary caregivers for subjects 6 to < 13 years of age and will be completed by the subject for those ≥ 13 < 18 years of age.

*****One version of the YI-4 will be administered to subjects ≥ 8 to < 12 years of age and a second version of the YI-4 will be administered to subjects ≥ 12 years of age. Children under 8 years of age will not complete the YI-4.
APPENDIX II

LIST OF COMMONLY PRESCRIBED PSYCHIATRIC MEDICATIONS

<table>
<thead>
<tr>
<th>Drug Code</th>
<th>Drug Name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>99999998</td>
<td>Abilify (aripiprazole)</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>28160408</td>
<td>Adapin (doxepin)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28200023</td>
<td>Adderall (amphetamine salts)</td>
<td>ADHD</td>
</tr>
<tr>
<td>28249218</td>
<td>Ambien (zolpidem)</td>
<td>insomnia</td>
</tr>
<tr>
<td>28249210</td>
<td>Atarax (hydroxyzine)</td>
<td>antianxiety</td>
</tr>
<tr>
<td>28240812</td>
<td>Ativan (lorazepam)</td>
<td>antianxiety</td>
</tr>
<tr>
<td>28249203</td>
<td>Buspar (buspirone)</td>
<td>antianxiety</td>
</tr>
<tr>
<td>28080001</td>
<td>Catapres - TTS (clonidine)</td>
<td>ADHD</td>
</tr>
<tr>
<td>28080002</td>
<td>Catapres (clonidine hcl)</td>
<td>ADHD</td>
</tr>
<tr>
<td>28160430</td>
<td>Celexa (citalopram)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28160803</td>
<td>Chlorpromazine (thorazine)</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>28160822</td>
<td>Compazine</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>28200017</td>
<td>Cylert (pemoline)</td>
<td>ADHD</td>
</tr>
<tr>
<td>28129204</td>
<td>Depakene (valproic acid)</td>
<td>anticonvulsant/mood stabilizer</td>
</tr>
<tr>
<td>28129202</td>
<td>Depakote (divalproex, valproate)</td>
<td>anticonvulsant/mood stabilizer</td>
</tr>
<tr>
<td>28160418</td>
<td>Desyrel (trazodone)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28200009</td>
<td>Dexedrine (dextroamphetamine)</td>
<td>ADHD</td>
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<tr>
<td>28121204</td>
<td>Dilantin</td>
<td>antiepileptic</td>
</tr>
<tr>
<td>28160426</td>
<td>Effexor (venlafaxine)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28160401</td>
<td>Elavil (amitriptyline)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28280001</td>
<td>Eskalith, Lithobid (lithium carbonate)</td>
<td>antipsychotic/mood stabilizer</td>
</tr>
<tr>
<td>28280002</td>
<td>Eskalith, Lithobid (lithium citrate)</td>
<td>antipsychotic/mood stabilizer</td>
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<tr>
<td>28160837</td>
<td>Geodon (ziprasidone)</td>
<td>antipsychotic</td>
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<tr>
<td>28160812</td>
<td>Haldol (haloperidol)</td>
<td>antipsychotic</td>
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<tr>
<td>28160813</td>
<td>Haldol Decanoate</td>
<td>antipsychotic</td>
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<tr>
<td>28160814</td>
<td>Haldol Injection</td>
<td>antipsychotic</td>
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<tr>
<td>28120801</td>
<td>Klonopin (clonazepam)</td>
<td>anticonvulsant (antianxiety/mood stabilizer)</td>
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<tr>
<td>28160431</td>
<td>Lexapro (escitalopram)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28160423</td>
<td>Luvox (fluvoxamine)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28160825</td>
<td>Mellaril (thioridazine)</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>Drug Code</td>
<td>Drug Name</td>
<td>Indication</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>28129206</td>
<td>Neurontin (gabapentin)</td>
<td>anticonvulsant/mood stabilizer</td>
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<td>28160414</td>
<td>Pamelor (nortriptyline)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28120402</td>
<td>Phenobarbital, Mysoline</td>
<td>anticonvulsant</td>
</tr>
<tr>
<td>28160409</td>
<td>Prozac (fluoxetine)</td>
<td>antidepressant</td>
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<tr>
<td>28160429</td>
<td>Remeron (mirtazepine)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28160834</td>
<td>Risperdal (risperidone)</td>
<td>antipsychotic</td>
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<tr>
<td>28200016</td>
<td>Ritalin, Concerta, (methylphenidate)</td>
<td>ADHD</td>
</tr>
<tr>
<td>28160836</td>
<td>Seroquel (quetiapine)</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>99999998</td>
<td>Strattera (atomoxetine)</td>
<td>ADHD</td>
</tr>
<tr>
<td>28129201</td>
<td>Tegretol (carbamazepine)</td>
<td>anticonvulsant/mood stabilizer</td>
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<tr>
<td>28129208</td>
<td>Topamax (topiramate)</td>
<td>antiepileptic/anticonvulsant/mood stabilizer</td>
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<tr>
<td>24080013</td>
<td>Tenex (guanfacine)</td>
<td>ADHD</td>
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<tr>
<td>28160802</td>
<td>Thorazine Suppository</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>28160803</td>
<td>Thorazine (chlorpromazine)</td>
<td>antipsychotic</td>
</tr>
<tr>
<td>28160410</td>
<td>Tofranil (imipramine)</td>
<td>antidepressant</td>
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<tr>
<td>28160422</td>
<td>Trileptal (oxcarbazepine)</td>
<td>anticonvulsant</td>
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<tr>
<td>28240808</td>
<td>Valium (diazepam)</td>
<td>antianxiety</td>
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<tr>
<td>28240813</td>
<td>Versed</td>
<td>antianxiety</td>
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<tr>
<td>28160405</td>
<td>Wellbutrin, Zyban (bupropion)</td>
<td>antidepressant</td>
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<tr>
<td>28240801</td>
<td>Xanax (alprazolam)</td>
<td>antianxiety</td>
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<tr>
<td>28160420</td>
<td>Zoloft (sertraline)</td>
<td>antidepressant</td>
</tr>
<tr>
<td>28160835</td>
<td>Zyprexa (olanzapine)</td>
<td>antipsychotic</td>
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</tbody>
</table>
APPENDIX III
Table of variable definitions

For each proposed outcome and explanatory variable, this table identifies the source research instrument, notes who will complete the instrument, and details relevant measurement scales and subscales.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parent/PrimaryCaregiver</td>
</tr>
<tr>
<td>A. Outcomes (Child/Adolescent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Psychological symptom clusters</td>
<td>Depression, Anxiety, ADHD (I;H;Combined), Conduct disorders; Scores based on: 1. symptom counts, and 2. mean severity of symptom cluster</td>
<td>Child and Adolescent Symptom inventory – Parent/Primary Caregiver endorsed (SI-4 Primary Caregiver Checklist; 140 of 144 items)</td>
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<td></td>
<td>Externalization, Internalization</td>
<td>Child Behavior Checklist, CBCL (112-items)</td>
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<tr>
<td></td>
<td>Presence/absence of Depression, Anxiety, ADHD (I;H;Combined), Conduct disorders</td>
<td>Diagnostic interview for children and adolescents, (Missouri assessment of genetics interview for children version, MAGIC DICA).</td>
</tr>
<tr>
<td>Variable</td>
<td>Measures</td>
<td>Instrument completed by or administered to:</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parent/PrimaryCaregiver</td>
</tr>
<tr>
<td>2. Academic performance *</td>
<td>Global grade performance and others</td>
<td>School and Social Functioning, SSF (PQ)</td>
</tr>
<tr>
<td>3. Social functioning*</td>
<td>Indicators of peer conflict and others</td>
<td>School and Social Functioning, SSF (PQ)</td>
</tr>
<tr>
<td>4. Pain*</td>
<td>Over all Pain rating (sensory, affective); Present pain intensity measures</td>
<td>SF-MPQ (15 items)</td>
</tr>
<tr>
<td></td>
<td>Location of pain and interference with daily activities;</td>
<td>Pain level assessment (with parent/primary caregiver assistance, if needed)</td>
</tr>
<tr>
<td></td>
<td>Over all pain severity</td>
<td></td>
</tr>
<tr>
<td>5. Adherence*</td>
<td>See section B3</td>
<td>If parent/primary caregiver responsible for administration:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PACTG Adherence Module I, QL5003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If child/adolescent is responsible for administration:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PACTG Adherence Module I, QL5003</td>
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APPENDIX III (Cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
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<tbody>
<tr>
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<td>Parent/Primary Caregiver</td>
</tr>
<tr>
<td>B. Risk factors:</td>
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</tr>
<tr>
<td>1. Child/Adolescent characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>ACTG registration tables</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>ACTG registration tables</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>ACTG registration tables</td>
<td></td>
</tr>
<tr>
<td>Physical measures</td>
<td>Height, weight</td>
<td>PACTG forms (PE0031)</td>
</tr>
<tr>
<td>HIV status self knowledge</td>
<td></td>
<td>PACTG Adherence CRF</td>
</tr>
<tr>
<td>Neuropsychological diagnosis history</td>
<td>Presence/absence of selected conditions</td>
<td>PACTG CRFs (PE0054)</td>
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<tr>
<td>Intellectual functioning (cognition)</td>
<td>Attention span, memory and processing speed</td>
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<td>Functioning</td>
<td>Global impairment</td>
<td>Columbia Impairment Scale, CIS (13 items)</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>Rational (cognitive) versus impulsive (affective, physiological)</td>
<td>Child cognitive impulsivity scale (11 items); If child &lt; 13 years</td>
</tr>
<tr>
<td>QOL*</td>
<td>General health ratings</td>
<td>PQ (PACTG QOL 4004/QOL 4005)</td>
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</table>
## APPENDIX III (Cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotropic medications, lifetime history</td>
<td># years, months exposed</td>
<td>Parent/Primary Caregiver: PACTG medication history form, Other concomitant medications, PE0450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child/Adolescent: PACTG Screen CRF</td>
</tr>
<tr>
<td>Biological relationship or household member among study participants</td>
<td>Classify by biological relationship and household membership.</td>
<td>PACTG Screen CRF</td>
</tr>
</tbody>
</table>

### 2. HIV variables (Child/Adolescent)

<table>
<thead>
<tr>
<th>Infection status</th>
<th>Infected, uninfected, unknown</th>
<th>PACTG registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV demographic risk factors (of child/adolescent and biological mom)</td>
<td>Perinatal exposure risk, etc.</td>
<td>PACTG forms (DMW)</td>
</tr>
<tr>
<td>Severity of HIV-related symptoms</td>
<td>HIV-health-related symptoms (20 items)</td>
<td>PACTG HIV-Related Symptoms Checklist</td>
</tr>
<tr>
<td>CDC clinical and immunological categories</td>
<td></td>
<td>PACTG forms: PE0009 (&lt;13 years), PE5809 (≥13 years)</td>
</tr>
<tr>
<td>CD4 count and %</td>
<td>Current (at entry); lowest ever, annual</td>
<td>PACTG CRFs</td>
</tr>
<tr>
<td>HIV Viral load</td>
<td>Current (at entry); highest ever, annual</td>
<td>PACTG CRFs</td>
</tr>
<tr>
<td>PASS score</td>
<td>CD4%, CDC category, Total lymphocytes, weight/BMI</td>
<td>PACTG forms</td>
</tr>
</tbody>
</table>
### APPENDIX III (Cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parent/Primary Caregiver</td>
</tr>
<tr>
<td>Antiretroviral therapy – Lifetime exposure</td>
<td># months/years of exposure, by class (NRTIs, NNRTIs, PIs; other – T20, gp120, etc.)</td>
<td>PACTG forms antiretroviral medications (PE0420)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child/Adolescent</td>
</tr>
<tr>
<td>3. Compliance with Treatment regimens – Adherence (Child/Adolescent)</td>
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<td></td>
</tr>
<tr>
<td>Anti-retroviral</td>
<td>% expected doses (3-day recall) over all drug classes and by class (NRTIs, NNRTIs, PIs,Other)</td>
<td>If parent/primary caregiver responsible for administration: PACTG Adherence Questionnaire, QL5003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARV concomitant medications, PE0420</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If child/adolescent responsible for administration: PACTG Adherence Questionnaire, QL5003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antiretroviral concomitant medications, PE0420</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>% expected doses (3-day recall) for specific drugs and over all drug classes</td>
<td>If parent/primary caregiver responsible for administration: PACTG Adherence Questionnaire, QL5003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other Concomitant medications (PE0450)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If child/adolescent responsible for administration: PACTG Adherence Questionnaire, QL5003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other Concomitant medications (PE0450)</td>
</tr>
</tbody>
</table>
### APPENDIX III (Cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parent/Primary Caregiver</td>
</tr>
<tr>
<td>4. Caregiver psychopathology</td>
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<td></td>
</tr>
<tr>
<td>Psychiatric symptom clusters for:</td>
<td>Depression, Antisocial personality, Substance Abuse, etc.; Score based on: 1. symptom counts, and 2. mean severity of symptom cluster</td>
<td>The Adult Self-Report Inventory (ASRI-4; 136 items)</td>
</tr>
<tr>
<td>Sensation seeking</td>
<td>Risk-taking and thrill seeking behavior, over all</td>
<td>Abbreviated Sensation Seeking Scale – 16 items</td>
</tr>
<tr>
<td>5. Environmental disadvantage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma/violence</td>
<td>Specific life stressors and/or total # experienced</td>
<td>PQ (PACTG QOL 4004/4005), MAGIC DICA; Also see life stressors</td>
</tr>
<tr>
<td>Substance abuse/use</td>
<td>Symptom cluster (yes/no), mean severity</td>
<td>Adult Self-Report Inventory (ASRI-4)</td>
</tr>
<tr>
<td>SES/Poverty</td>
<td>Hollingshead index (marital status, education, occupation)</td>
<td>PQ</td>
</tr>
<tr>
<td>Life stressors</td>
<td>18 item ACTG list plus others-selected indicators plus total count</td>
<td>PQ (PACTG QOL 4004/4005); Also collected on MAGIC DICA</td>
</tr>
</tbody>
</table>
### APPENDIX III (Cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parent/Primary Caregiver</td>
</tr>
<tr>
<td>6. Home environment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent/primary caregiver ethnicity</td>
<td>PACTG registration database</td>
<td></td>
</tr>
<tr>
<td>Parent/primary caregiver relation to child</td>
<td>PQ</td>
<td></td>
</tr>
<tr>
<td>Household composition</td>
<td>PQ</td>
<td></td>
</tr>
<tr>
<td>Marital status of parent/primary caregiver</td>
<td>PQ</td>
<td></td>
</tr>
<tr>
<td>Siblings or household members with HIV**</td>
<td>PACTG screening CRF and eligibility checklist</td>
<td></td>
</tr>
<tr>
<td>Family stability/disorganization/change</td>
<td>Multiple measures</td>
<td>See life stressors and specific questions on PQ</td>
</tr>
<tr>
<td>Child rearing practices (use of harsh punishment)</td>
<td>Overall score – 8 items</td>
<td>PQ (Caregiver-Child interaction, punishment scale, 8-items)</td>
</tr>
<tr>
<td>Caregiver-child interaction/communication</td>
<td>Overall score – 10 items</td>
<td>PQ (Caregiver-Child interaction, communication scale)</td>
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</tbody>
</table>
### APPENDIX III (Cont.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measures</th>
<th>Instrument completed by or administered to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiver-child interaction/communication (continued)</td>
<td>Overall score; Real, Ideal, and disparity: 5 factors</td>
<td>Primary Caregiver’s report, 20 items</td>
</tr>
<tr>
<td></td>
<td>Factors include: 1) Respect for autonomy (parent/primary caregiver gives child/adolescent independence); 2. control through guilt and anxiety; 3. consistency (of parent’s/primary caregiver’s commitment to established rules), 4. child-centeredness (warmth, concern for child/adolescent), 5. parental/primary caregiver temper and detachment (distance/withdrawal from child/adolescent).</td>
<td>Parent/Primary Caregiver</td>
</tr>
<tr>
<td>Family environment</td>
<td>10 subscales reflect relationship; personal growth; system maintenance:</td>
<td>Family environment scale, FES (90 items)</td>
</tr>
</tbody>
</table>

Relationship dimension includes: 1. cohesion (commitment, help and support), 2. expressiveness (expression of feelings), 3. conflict (openly expressed anger/conflict).
Personal growth: 1. independence, 2. achievement orientation, 3. intellectual-cultural orientation, 4. active-recreational orientation, 5. moral-religious emphasis.
System maintenance: 1. Organization (importance of clear organization and structure for family), 2. control (use of rules and procedures).

* These variables can also be considered as risk factors, or explanatory variables in understanding psychiatric symptoms/disorders.

** During screening, we will collect data for control subjects who qualify because they live with an HIV-infected household member, identifying the HIV-infected household member and his/her relationship (biological or not) to the study subject.

Note: Antiretroviral medication measures and HIV-severity laboratory measures (CD4 count, CD4%, total lymphocyte count, HIV-RNA viral load, PASS score measures) will only be collected for HIV-infected subjects.
APPENDIX IV

Protocol Conceptual model

Psychiatric Co-morbidity in Perinatally HIV-infected Children/Adolescents

<table>
<thead>
<tr>
<th>A. Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Psychiatric symptoms (Generalized anxiety, Major depression, ADHD, Conduct disorders)</td>
</tr>
<tr>
<td>2. Academic performance *</td>
</tr>
<tr>
<td>3. Social functioning*</td>
</tr>
<tr>
<td>4. Pain*</td>
</tr>
<tr>
<td>5. Adherence*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Risk factors/ Explanatory factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Child/Adolescent characteristics</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Physical measures: Height, Weight</td>
</tr>
<tr>
<td>HIV status self-knowledge</td>
</tr>
<tr>
<td>Neuropsychological diagnosis history</td>
</tr>
<tr>
<td>Intellectual functioning (cognition)</td>
</tr>
<tr>
<td>Global functioning</td>
</tr>
<tr>
<td>Impulsivity</td>
</tr>
<tr>
<td>Psychiatric medications- Lifetime exposure</td>
</tr>
<tr>
<td>Biological relationship/household membership with other study subjects (Screen form)</td>
</tr>
<tr>
<td>Quality of Life (QOL)</td>
</tr>
</tbody>
</table>
APPENDIX IV (Cont.)

2. HIV-related variables (Child and Adolescent)
   
   **HIV Infection status**
   **HIV demographic risk factors (of child/adolescent and biological mom)**
   **HIV severity:**
   - Severity of HIV-related symptoms
   - CDC clinical and immunological categories
   - CD4 count and percent (HIV-infected only; at entry; nadir; annually**)
   - HIV Viral load (HIV-infected only; at entry; annually**)
   - Total lymphocyte count (HIV-infected only; at entry; annually**)
   - Pediatric AIDS Severity Score (PASS)**
   **Antiretroviral therapy – Lifetime exposure**

3. Compliance with Treatment regimens – Adherence (Child/Adolescent)
   
   - Anti-retroviral
   - Psychiatric

4. Parent/primary caregiver psychopathology
   
   - Depression
   - Sensation seeking
   - Antisocial behavior
   - Substance use
   - Other disorders

5. Environmental disadvantage
   
   - Trauma/violence
   - Substance abuse/use
   - SES/Poverty
   - Life stressors
APPENDIX IV (Cont.)

6. Home environment

   Household characteristics:
       Ethnicity of parent/primary caregiver
       Household composition
       Marital status of parent/primary caregiver
       Parent/primary caregiver relation to child
       Siblings/household members with HIV*** (from screen form)
       Family stability/disorganization/change
       Child rearing practices (use of harsh punishment)
       Parent/primary caregiver-child interaction/communication
       Family environment scale.

NOTES:
* These variables can also be considered as risk factors, or explanatory variables in understanding psychiatric symptoms/disorders.
** CD4 count and CD4%, HIV RNA, total lymphocyte count, and PASS score will only be collected for HIV-infected children/adolescents.
*** During screening, we will collect data for control subjects who qualify because they live with an HIV-infected household member, identifying the HIV-infected household member and his/her relationship (biological or not) to the study subject.
DIVISION OF AIDS
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)
SAMPLE INFORMED CONSENT
For protocol:
P1055, Version 1.0

PSYCHIATRIC CO-MORBIDITY IN PERINATALLY HIV-INFECTED CHILDREN AND ADOLESCENTS

SHORT TITLE FOR THE STUDY: Psychiatric Co-morbidity in HIV-Infected Children.

INTRODUCTION

You and your child are being asked to take part in this research study because:

- you are and/or your child is infected with the human immunodeficiency virus (HIV), the virus that causes AIDS, or
- you are and/or your child is not infected with HIV, but we would like to compare your child’s study results with the study results of children who are infected with HIV.

This study is sponsored by the following Institutes at the National Institutes of Health (NIH): the National Institute of Mental Health (NIMH), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Child Health and Human Development (NICHD). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you and your child decide if you want to be a part of this study, we want you and your child to know about the study.

This is a consent form which will give you and your child information about this study. The study staff will talk with you and your child about this information. You and your child are free to ask questions about this study at any time. If you and your child agree to take part in this study, you will be asked to sign this consent form. You will be given a copy to keep.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if HIV and/or HIV medicine cause mental health problems or make mental health problems worse in children and adolescents who were infected
APPENDIX V (Cont.)

with HIV during birth. The study will compare these children and adolescents to children and adolescents without HIV who are the same age, sex, and race. The study will see if their mental health problems are the same, better, or worse. The study will look to see if mental health problems change over 2 years. The study will also look to see whether these children and adolescents take their medicine (antiretroviral and/or psychiatric) when they should, if they are supposed to take any. Finally, the study will look to see if these children and adolescents are in pain a lot.

The study will also ask parents/primary caregivers to be in the study and answer questions about themselves and their children/adolescents. Parents/primary caregivers will be asked questions about different things. These include questions about how they see their and their children’s/adolescent’s behavior, feelings, and how family members get along with one another.

Using semi-structured interviews, this study will look more closely in a smaller group of children and adolescents. The interviews will be used to see if there are differences in mental health problems between children and adolescents with and without HIV. The interviews will also be used to see if there are differences in mental health problems between children and adolescents using HIV medicine or not. A semi-structured interview is an interview in which a staff member who is trained to ask questions about different behaviors and emotions in you or your child will interview you and your child. The “semi-structured” part means that the interviewer will have a bunch of questions to ask but they will be asked in a way that it is like a conversation about you or your child. There are no right or wrong answers to these questions.

This is an “observational” study, meaning that information about you and your child will be collected but there is no treatment as part of this study.

WHAT DO I HAVE/DOES MY CHILD HAVE TO DO IF I AM/MY CHILD IS IN THIS STUDY?

Screening:

You and your child will be told about the study and you will be asked to sign a consent form. You and your child can choose to enter the study on the same day. You can also choose to come back for your and your child’s entry visit on another day. The entry visit should take place between now and 6 weeks from now.

Entry – Parent/Primary Caregiver:

You will be asked about your child’s health and medicine history. You will be asked to fill out about 11 questionnaires. These can be filled out with help from the study staff, if you would like. They can read the questions to you. These questionnaires will take about 125 minutes
APPENDIX V (Cont.)

(about 2 hours) to complete. These questionnaires will ask about different things. These include questions about your and/or your child’s behavior, feelings, school performance, ability to take medicine, feelings of pain, how family members get along with one another, how parents/primary caregivers and children get along with one another, and other such information. If you find these questionnaires too hard to complete in one study visit, you will be allowed to return for another visit to fill them out. Questionnaires must be completed within 90 days from study screening or entry.

Semi-Structured Interviews – Subset of Parents/Primary Caregivers: (*this information should not be included in the site informed consent unless your site has been selected to participate in the semi-structured interviews*)

You may be asked to come back for an additional visit. If so, you will be asked more questions about your child’s behavior and feelings. You will be asked these questions by site staff who are trained to ask them. These questions will be given in the form of a semi-structured interview (questions asked in a way that is like a conversation about you or your child).

If you and your child are taking part in this study at a site that has been chosen for the interview, you will be asked to come back for the extra visit within 90 days after completing your and your child’s original questionnaires. These questions will take about 60 minutes (about 1 hour) for you. Your interview may be tape recorded, in order to check on scoring methods at the sites. These tapes will be kept in a locked cabinet. They will not be used to identify you in any presentations or publications that result from the study. Once selected team members have reviewed the tape for scoring methods, the tape will be erased and returned to the site.

Entry – Child/Adolescent:

Your child will be asked about his/her health and medicine history. Your child will have a physical exam. Your child will be asked to fill out about 6 questionnaires. These will be filled out with help from the study staff. They will read the questions to your child. These questionnaires will take about 55 minutes (about 1 hour) to complete. These questionnaires will ask about different things. These include questions about your child’s behavior, feelings, ability to take medicine, feelings of pain, how parents/primary caregivers and children get along with one another, and other such information. If your child finds these questionnaires too hard to complete in one study visit, he/she will be allowed to return for another visit to fill them out. Questionnaires must be completed within 90 days from study screening or entry.

Semi-Structured Interviews – Subset of Children/Adolescents: (*this information should not be included in the site informed consent unless your site has been selected to participate in the semi-structured interviews*)
APPENDIX V (Cont.)

Your child (if 12 years or older) may be asked to come back for an additional visit. If so, he/she will be asked more questions about his/her behavior and feelings. He/she will be asked these questions by site staff who are trained to ask them. These questions will be given in the form of a semi-structured interview (questions asked in a way that is like a conversation about you or your child). If you and your child are taking part in this study at a site that has been chosen for the interview, your child may be asked to come back for the extra visit within 90 days after completing your and your child’s original questionnaires. These questions will take about 30 minutes (about ½ hour) for your child. Your child’s interview may be tape recorded, in order to check on scoring methods at the sites. These tapes will be kept in a locked cabinet. They will not be used to identify your child in any presentations or publications that result from the study. Once selected team members have reviewed the tape for scoring methods, the tape will be erased and returned to the site.

Study Visits - Parent/Primary Caregiver:

You will return to the clinic at weeks 48 (about 1 year) and 96 (about 2 years). You will be asked about any changes in your child’s health or medicine history since your and your child’s last visit. You will be asked to fill out about 6 questionnaires with the help of study staff, if you would like. They can read the questions to you. These questionnaires will take about 75 minutes (about 1 ¼ hours) to complete.

Study Visits – Child/Adolescent:

Your child will return to the clinic at weeks 48 (about 1 year) and 96 (about 2 years). Your child will have a physical exam. Your child will be asked to fill out about 3 questionnaires. These will be filled out with help from the study staff. They will read the questions to your child. These questionnaires will take about 30 minutes (about ½ hour) to complete.

WHEN WILL I AND/OR MY CHILD BE TOLD THE RESULTS

Your and/or your child’s study doctor (and other necessary study staff) will be told immediately if your and/or your child’s answers to the questionnaires show that you or your child may cause harm to you, your child, or others. Your child’s study doctor (and other necessary study staff) will also be told of any severe pain that your child is feeling, based on answers to the questionnaires. They will share this information with you. Your and/or your child’s study doctor (and other necessary study staff) will be told of all other mental health concerns within about 90 days (3 months) of each study visit. They will share this information with you and/or your child if appropriate.

OTHER INFORMATION:

Some of the information collected in this study may be used for other PACTG-approved HIV-related research. Your and your child’s information will be kept in a locked cabinet. Only
approved researchers will be able to see your and your child’s information if they need to. The information will not have your or your child’s name on it. It will also not have any other way to directly identify you or your child on it. Any possible future research studies using your and your child’s information will be reviewed by at least one of the following Institutes at the National Institutes of Health (NIH): the National Institute of Mental Health (NIMH), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Child Health and Human Development (NICHD). There is no limit on how long your and your child’s information will be kept. If you decide that you do not want your and your child’s information kept for future research studies, please tell your or your child’s doctor. You may decide this at any time. In this case, your and your child’s information collected from this study will not be used for any future studies. If some of your or your child’s information has already been used for another study, that information will be destroyed unless the work has already been done (in which case there will be no way to identify you or your child directly). You and your child can still participate in this study even if you and your child make this decision.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 800 children and adolescents and their parents/primary caregivers will take part in this study.

About 200-240 children and adolescents and their parents/primary caregivers will take part in the semi-structured interview (questions asked in a way that is like a conversation about you or your child) part of the study.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

You and your child will be in this study for about 96 weeks.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you and your child off the study early without your or your child’s permission if:

- the study is cancelled by any of the three Institutes at the National Institutes of Health (NIH): the National Institute of Mental Health (NIMH), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Child Health and Human Development (NICHD), or the site’s Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research subjects.
- you and your child are not able to attend the study visits as required by the study.

WHAT ARE THE RISKS OF THE STUDY?
APPENDIX V (Cont.)

You and/or your child may become tired during the testing. Some of the questions are personal. You and your child may not have discussed them with anyone before. Because of this, you and your child may feel uncomfortable answering some of the questions. Even though the study staff will do their best to make you and your child feel comfortable, you and your child may still feel uncomfortable.

As a part of the study you and your child may learn that you have and/or your child has mental health problems that you and your child did not know about. These may include depression or attention difficulties. This could cause stress to you and/or your child. If this happens, you and/or your child will be given names of doctors who can help you and/or your child with these conditions if you and/or your child agree(s). Before we speak to another doctor, you and your child will be asked to sign a form to allow us to share information about your/his/her mental health.

Your child will complete his/her own private forms and/or interviews as a part of the study. If we learn about mental health problems he/she may be having we will need to have his/her permission to share that information with you. Any problems that involve danger and/or abuse to himself/herself or others will be shared with you even without his/her permission. The study staff will help you and your child make plans to help with emotional or behavioral problems that have to do with the safety of you, your child, or others. This will include immediately telling your and/or your child’s study doctor (and other necessary study staff) about any answers to questionnaires that show the possibility of harm to you, your child, or others.

To keep your and your child’s information confidential, your and your child’s name will not be recorded as part of this study. You and your child will be identified only by a coded number. All records will be kept in a locked cabinet. Only study staff will be able to look at your and your child’s information. Even though the study staff will do their best to protect your and your child’s privacy and/or HIV status, this cannot be absolutely guaranteed.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you and your child take part in this study, there may be no direct benefit to you or your child. It is possible that you and your child may benefit from learning about a mental health problem for which treatment may be available, but no guarantee can be made.

Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study, you and your child have the choice of:
APPENDIX V (Cont.)

- not being in this study.
- having mental health testing/evaluations done somewhere else.
- having no testing/evaluations done.

Please talk to your and/or your child’s doctor about these and other available choices. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your and your child’s privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to release information that may identify you and your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you and your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

People who may review your and your child’s records include: the (insert Name of Site) IRB, representatives of the National Institute of Mental Health (NIMH), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Child Health and Human Development (NICHD), study staff, study monitors, and their designees.

You should understand that a Certificate of Confidentiality does not prevent you, your child, or a member of your or your child’s family from voluntarily releasing information about you or your child or your or your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or risk of harm to you, your child, or others, we will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME?

The questionnaires will be provided to you and your child for free as part of this study. Any medicine or follow-up treatment (for example, if you or your child decide to be referred or you allow your child to be referred to a mental health specialist) that you receive as part of this study will be charged to you or your or your child’s insurance company. In some cases, it is possible that your or your child’s insurance company will not pay for these costs because you and your child are taking part in a research study.
WILL I RECEIVE ANY PAYMENT?

You and your child will not receive money for being in this study.

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?

If you are and/or your child is injured as a result of being in this study, you and/or your child will be given immediate treatment for your and/or your child’s injuries. The cost for this treatment will be charged to you or your or your child’s insurance company. There is no program for compensation either through this institution, or the Institutes of the National Institutes of Health (NIH): the National Institute of Mental Health (NIMH), the National Institute of Allergy and Infectious Diseases (NIAID), or the National Institute of Child Health and Human Development (NICHD). You and your child will not be giving up any of your or your child’s legal rights by signing this consent form.

WHAT HAPPENS IF I WANT/MY CHILD WANTS TO PREMATURELY DISCONTINUE PARTICIPATING IN THIS STUDY?

If you and/or your child decide(s) at any time that you and/or your child would no longer like to participate in this study, you and your child can let the study staff know. You and your child will not be asked to complete any more questionnaires or procedures.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You and your child may choose not to take part in this study. You may also choose to leave this study at any time. You and your child will be treated the same no matter what you and your child decide.

We will tell you and your child about new information from this or other studies that may affect your or your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your and your child’s rights as a research subject, contact:
APPENDIX V (Cont.)

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____________________                              __________________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________                __________________________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

________________________                        _________________________________________
Study Staff Conducting    Study Staff Signature and Date
Consent Discussion (print)

________________________                          _________________________________________
Witness’ Name (print)     Witness’s Signature and Date
(As appropriate)