COGNITIVE, BEHAVIORAL, AND PSYCHOSOCIAL CORRELATES OF MEDICATION ADHERENCE IN CHILDREN AND ADOLESCENTS WITH HIV-1 INFECTION

A Multicenter Trial of the Pediatric AIDS Clinical Trials Group

Sponsored by:

The National Institute of Allergy and Infectious Diseases

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PACTG P1042s PROTOCOL TEAM ROSTER

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SCHEMA

COGNITIVE, BEHAVIORAL, AND PSYCHOSOCIAL CORRELATES OF MEDICATION ADHERENCE IN CHILDREN AND ADOLESCENTS WITH HIV-1 INFECTION

DESIGN: PACTG 1042s is a cross-sectional study that will correlate cognitive, behavioral, and psychosocial functioning with the degree of responsibility for and adherence to antiretroviral medication regimens in children and adolescents with perinatally acquired HIV infection. It will also correlate cognitive, behavioral and psychosocial functioning with measures of virologic suppression and immunological status, and compare self-report and pill count measures of adherence.

SAMPLE SIZE: 200 evaluable participants

POPULATION: Children and adolescents with perinatally acquired HIV-1 infection 8 to <19 years of age, who are enrolled and in active follow-up in PACTG 219C.

STRATIFICATION: Group A: <12 years of age
Group B: =12 years of age

DURATION OF STUDY: Forty-eight weeks.

OBJECTIVES:

Primary

1. To assess the relationship of age, cognitive, behavioral, and psychosocial functioning (including language, memory, attention, and academic skills) with adherence to medication regimens, as measured by self-report and pill count.

2. To assess the relationship of age, cognitive, behavioral, and psychosocial functioning with the degree of responsibility placed on participants for taking medications, as measured by caregiver and self-report questionnaires.
Secondary

1. To characterize cognitive, behavioral, and psychosocial functioning in children and adolescents with perinatally acquired HIV infection.

2. To correlate cognitive, behavioral, and psychosocial functioning with virologic and disease variables.

3. To assess interactions between participants’ cognitive status and the complexity of their medication regimens in predicting adherence, as measured by self-report and pill count.

4. To assess the ability of baseline cognitive, behavioral, and psychosocial variables to predict adherence at a later time point (24 and 48 weeks following enrollment).

5. To assess the correlation of self-report and pill count measures of adherence.

6. To assess the stability of adherence over time as measured by self-report and pill counts.

7. To correlate measures of adherence with disease severity as measured by viral load, CDC disease category and CD4 counts and to assess whether the association between adherence and disease severity is stable over time.

8. To develop a predictive model that could be used by clinicians to identify children and adolescents who are more likely to have problems adhering to their antiretroviral medication regimens.
1.0 INTRODUCTION

1.1 Background

“The act of remembering to take a medication at the appointed time represents only the final point in a complex chain of cognitive and psychosocial behaviors that begins when an individual is prescribed a medication.” (1)

In recent years, medication adherence has become a critical issue for HIV-infected children and adolescents because of drug resistance and the increased complexity of treatment regimens. In antiretroviral clinical trials, non-adherence to medication complicates our ability to measure the effectiveness of new drugs, and the lower response rate observed in children compared to adults is partially explained by problems with adherence (2).

Medication adherence becomes increasingly problematic during adolescence. The growing population of preteens and adolescents with perinatally acquired HIV infection demands an understanding of factors that influence medication adherence. Effective interventions that promote adherence and can be integrated into both clinical care and research need to be developed. Clinicians should understand what factors influence an adolescent's ability to follow a complex treatment regimen before therapy is initiated (3).

Some recent PACTG protocols include modules that measure self-reported adherence (Adherence Modules 1 and 2), as well as some variables that could be related to poor adherence (1). Identification of key caregiver characteristics, the impact of disclosure to family, school and friends, and demographic variables that might predict adherence is possible from existing PACTG 219C data. However, little information that might be most predictive of readiness to assume responsibility for medication adherence is currently collected about behavioral and cognitive characteristics of children and adolescents.

Responsibility for Treatment Adherence:

Responsibility for taking medication is usually expected in early to middle adolescence as children become more independent. For example, studies of children with diabetes show they are often given complete responsibility for their medications by age 15 (4), even if they lack the cognitive maturity to carry out their regimen appropriately. Increasing age is associated with increased responsibility for medications, but also with poorer adherence and worse metabolic control in participants with diabetes (5). These investigators also found that disagreement between parent and child on how medication responsibility was shared predicted metabolic control. Providers at Ryan White sites rated psychosocial and developmental issues as more difficult to manage than educational,
cultural/community, or provider-client issues, and that the developmental issues included, “child with responsibility for medication beyond years” (6).

Inappropriate responsibility for medications may be partly related to parent-child issues, lack of supervision, or frequent changes in caregiver. It might also be related to the failure of caregivers and clinicians to recognize specific cognitive problems in the child/adolescent, such as memory impairment. It is important to identify factors that can help determine which children and adolescents are able to manage their medications without caregiver assistance (7).

**Cognitive Functioning and Adherence:**

Research has shown that cognitive factors are related to medication adherence in adults with HIV infection. Forgetting to take medication was the most common reason given for non-adherence in a sample of HIV-infected adults studied by Eldred et al. (8). A review of adherence factors for adults with HIV found that some participants have difficulty recalling simple information about medication (9). In a sample of HIV-infected adults of low socioeconomic status, Benedict and colleagues found that those with cognitive impairment were more likely to fail in a medication management task. He concluded, “neuropsychological testing could be used to assist clinicians in determining which subjects require assistance with medication management” (9). Unfortunately, immune-compromised participants who need complex combination therapies are also more likely to manifest memory problems, and may require greater assistance from family members or others (10).

The literature on adherence and cognition in children is not extensive. In a study of children with attention deficit disorder, however, lower IQ was related to poorer medication adherence (11). Cognitive factors may be even more important for children and adolescents with HIV, who can have problems in language and academic functioning in the absence of obvious encephalopathy. Children with HIV infection can show specific deficits in the areas of language, memory, and attention, as well as global intellectual deficits in some cases (12-16). Even children and adolescents with HIV-infection with normal intellectual abilities tend to fall behind academically (14). Such deficits may make it more challenging to understand medication schedules, remember to take the medication, recall whether one has already taken it, understand and follow instructions, read medication bottles, and communicate effectively with health professionals. Failure to recognize specific cognitive or academic problems in adolescents who appear to be functioning at age level may cause caregivers to place an inappropriate degree of responsibility on them. Health professionals may not recognize the need to provide mnemonic or other adherence aids.
Behavioral and Emotional Issues and Adherence:

Children and adolescents with HIV face depression, anxiety, denial, and rebellion that may interfere with their motivation to take medication. These factors have not been fully explored as contributors to poor adherence. Children and adolescents with HIV may also face loss or abandonment by a caregiver, and fear that taking medication may label them as “different” or reveal their HIV status and cause further isolation. A survey of PACTG personnel conducted in 2001 revealed that learning, behavior, and emotional problems are frequently observed among children and adolescents with HIV at 70-95% of PACTG sites (17). Personnel at 75% of sites reported that they do not have adequate resources to meet the mental health needs of their patient population.

Assessing emotional and behavioral functioning in children and adolescents with HIV may help in predicting adherence and explaining adherence failure. In adults with HIV, depression and self-perceived social support have been found to predict medication adherence (10, 18, and 19). Children with other chronic diseases are less likely to adhere to their medication regimens if they also have behavioral or emotional problems (20, 21). Conversely, adjustment and coping, higher self-esteem and social functioning, and more highly developed problem-solving skills predict better adherence to treatment for diabetes, juvenile rheumatoid arthritis, and seizure disorders (22). Therefore, both caregiver and self-report measures of emotional and behavioral functioning will be included as potential predictors of adherence.

Measurement of Adherence:

Choosing the most efficient and accurate method for measuring adherence is a critical challenge. PACTG 1042s will compare two methods of measuring adherence: self-report and pill count (See Appendix III for a description of the pill count methodology to be used in PACTG 1042s). Although self-report measures have some shortcomings, such as the potential to overestimate adherence, they predict virologic response in adults (8) and in PACTG studies (22). Self-report produced higher estimates of adherence than pill count or electronic monitoring in an indigent adult population (23), but the three measures were closely related.

1.2 Rationale

PACTG 1042s will examine how cognitive, behavioral and psychosocial factors relate to medication adherence in children and adolescents with perinatally acquired HIV-infection enrolled in PACTG 219C. PACTG 1042s will evaluate the responsibility assigned to older children and adolescents for their medication adherence. It will also evaluate the relationship between responsibility for medications, and cognitive, behavioral, and caregiver characteristics. The proposed study provides an important opportunity to identify unrecognized problems that may
affect adherence to medication regimens in adolescents with perinatal HIV infection, and to define current responsibilities for medication management in the families of these adolescents. It will also provide information about cognitive, behavioral, and academic functioning in these children and adolescents. PACTG 1042s includes measures of memory, attention, language, academic skills, and behavior.

Because of the potential problems associated with self-report measures of adherence, a pill count will be used. Although labor intensive, pill counts may be the most efficient non self-report adherence assessment tool. The inclusion of two measures of adherence will increase reliability. Virologic suppression measures collected in PACTG 219C also will be used as an indirect measure of adherence. PACTG 1042s will assess the relationships among self-report, pill count and virologic suppression, along with their differential relationships to participant and family variables.

The accuracy of self-reporting in adolescents is unknown and the presence of memory problems may be an obstacle to accurate self-report (10). Therefore we will ask both caregivers and adolescents to complete a questionnaire regarding problems with adherence, and then we will examine the relationship between caregiver and adolescent reports and participants’ memory functioning.

PACTG 1042s will utilize data already being collected for PACTG 219C. These include data from the neuropsychological evaluation, Adherence Module 1 (administered every 6 months), selected items from the Quality of Life Questionnaire (administered every 12 months), Baseline Supplemental Demographic Data, viral load, lymphocyte subsets, and medical and psychiatric diagnoses and concomitant medications.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To assess the relationship of age, cognitive, behavioral, and psychosocial, functioning (including language, memory, attention, and academic skills) with adherence to medication regimens, as measured by self-report and pill count.

2.12 To assess the relationship of age, cognitive, behavioral, and psychosocial functioning with the degree of responsibility for taking medications placed on participants, as measured by caregiver and self-report questionnaires.

2.2 Secondary Objectives
2.21 To characterize cognitive, behavioral, and psychosocial functioning in children and adolescents with perinatally acquired HIV infection.

2.22 To correlate cognitive, behavioral, and psychosocial functioning with virologic and disease variables.

2.23 To assess interactions between participants’ cognitive status and the complexity of their medication regimens in predicting adherence, as measured by self-report and pill count.

2.24 To assess the ability of baseline cognitive, behavioral, and psychosocial variables to predict adherence at a later time point (24 and 48 weeks following enrollment).

2.25 To assess the correlation of self-report and pill count measures of adherence.

2.26 To assess the stability of adherence over time as measured by self-report and pill counts.

2.27 To correlate measures of adherence with disease severity as measured by viral load, CDC disease category and CD4 counts, and to assess whether the association between adherence and disease severity is stable over time.

2.28 To develop a predictive model that could be used by clinicians to identify children and adolescents who are more likely to have problems adhering to their antiretroviral medication regimens.

3.0 STUDY DESIGN

PACTG 1042s is a cross-sectional study that will correlate cognitive, behavioral, and psychosocial functioning with the degree of responsibility for and adherence to antiretroviral medication regimens in children and adolescents with perinatally acquired HIV infection. It will also correlate cognitive, behavioral and psychosocial functioning with measures of virologic suppression and immunological status, and compare self-report and pill count measures of adherence.

This study will randomly select a subset of perinatally infected participants (age 8 to <19 years) already enrolled and in active follow-up in PACTG 219C (see section 8.1). From this subset, this study will enroll 200 evaluable participants. Participants will be stratified by age (<12 years and >=12 years) to insure adequate representation of both groups in the analysis. Participants will be enrolled in PACTG 1042s for 48 weeks. Participants who were randomly selected, but refused P1042S will be asked to consider providing written permission for the substudy team to access their PACTG 219C data.
The P1042s Neuropsychological Assessment consists of standardized measures of academic achievement, attention, memory, language comprehension and behavior. All neuropsychological measures will be administered by the site psychologist, and may be performed on the same day, or within 3 months of a PACTG 219C visit where the PACTG 219C neuropsychological measures are administered. The PACTG 1042s Questionnaires will include: the Adolescent Questionnaire, the Parent/Caregiver Questionnaire, and the Health Beliefs Questionnaire. The Health Beliefs Questionnaire will be administered ONLY to adolescents who are aware of their HIV Status as well as to all available caregivers. Participation of a caregiver in the questionnaires is not required in order for the child/adolescent to participate in the study, even when a caregiver must give consent for the child to enroll in PACTG 1042s. When participants are enrolled in the study, the Data Manager will record whether or not a caregiver is available and willing to complete the study questionnaires. PACTG 1042s will include two pill counts (See Appendix III for a description of the pill count methodology).

The schedule of evaluations for P1042s is described in Appendix I.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria:

4.11 Randomly selected children and adolescents (age 8 to <19 years) already enrolled and in active follow-up in PACTG 219C.

4.12 HIV-1 infection, defined as two positive test results obtained on two different days from two different samples. These two tests can be a combination of the following:
- HIV antibody (ELISA +WB) obtained at any age >18 months.
- HIV culture, any age
- HIV DNA PCR, any age
- HIV RNA PCR (copy number >10,000 copies/ml), at any age
- Neutralizable HIV p24 antigen obtained >28 days of age

4.13 Child’s first language is English or Spanish.

4.14 Currently prescribed antiretroviral medications regimen at the time of enrollment, regardless of compliance with regimen, with no planned treatment interruptions.

4.2 Exclusion Criteria
Any participant who acquired HIV via routes other than perinatal transmission, participants with HIV-2 infection, or participants whose source of infection is unknown.

4.3 Enrollment Procedures

A site implementation plan (SIP) for the study is required prior to site participation in this study. The SIP must describe site availability of psychologists and Spanish-English interpreters. The SIP will be reviewed and approved by members of the PACTG 1042s team prior to registration.

Sites must be registered with and approved by the DAIDS Regulatory Compliance Center (RCC) Protocol Registration Office before protocol registration can occur. Registration must occur before participants can be enrolled in the study.

The site will receive a participant identifier (PID) list of participants to be approached for participation in P1042s (see Section 8.1). Participants will either:

1.) consent to participate in P1042s,
2.) refuse to participate in P1042s, but allow use of their PACTG 219C data, or
3.) refuse to participate in P1042s, and refuse use of their PACTG 219C data.

Participants who select option 1 or 2 will be enrolled to DM1042 using the ACTG Subject Enrollment System. The DM1042 enrollment will ask if the participant has consented to allow the use of his/her PACTG 219C data by the substudy team. After enrolling to DM1042, participants who select option 1 will then continue on and complete enrollment to P1042S.

4.4 Co-Enrollment Guidelines

Participants may co-enroll in opportunistic infection, vaccine, or immunomodulator protocols with the consent of the Chairs of PACTG P1042s, and the co-enrollment protocols. Co-enrollment in PACTG 219C is required.

5.0 STUDY EVALUATION

In addition to using existing PACTG 219C data, this study will add three evaluations for PACTG 219C participants who enroll in P1042s. An interpreter or bilingual examiner will be used for testing of participants whose primary language is Spanish.

1. A psychologist will administer a brief battery of standardized tests of academic achievement, attention, memory, language comprehension, and behavior to the
participant (Appendix I and II). This battery will take approximately 60-90 minutes. Both the participant and the caregiver, if available, will also be asked to complete a behavior questionnaire that takes approximately 20 minutes. These evaluations will be performed on the same schedule as the existing PACTG 219C neuropsychological (NP) testing, either on the same day as the NP evaluation or within 3 months following the NP evaluation. The tests will be administered in a standard order and sites will be provided with information on prioritizing testing in the event that not all measures can be completed. Sites may complete the evaluation in two sessions, if necessary. All measures are standardized tests.

2. Measurement of adherence will be expanded by using a 4 week pill count (Appendix III). The pill count will be conducted at two time points: 4-12 weeks (depending on the participant's refill schedule) and 16-32 weeks following enrollment. The instructions for the pill count will be given to participants at the time of study enrollment and again, by telephone, when the 24 week pill count begins.

3. The P1042s Adolescent and Parent/Caregiver Questionnaires will be used to assess responsibility for medications, problems relating to adherence, and self-reports of physical and emotional health status (see Appendix II). The caregiver and participant will complete separate versions of this questionnaire. A separate Health Beliefs Questionnaire will assess the caregiver’s and child/adolescent’s view of HIV and the impact of treatment. All caregivers can complete this questionnaire; however, because it contains references to HIV, it should NOT be administered to children or adolescents who are not aware of their HIV status. The P1042s Questionnaires will be administered within 12 weeks of study entry, at 16-32 and at 40-56 weeks following enrollment into 1042s (See Appendix I).

6.0 PARTICIPANT MANAGEMENT

6.1 Study Management Plan

Upon request, participants and caregivers (for minors) may receive evaluation results for the purpose of planning education and care. Site psychologists will provide appropriate feedback to adolescents and families concerning the results of the P1042s evaluation and assist families in sharing the results with medical or school personnel if the information would be useful in decisions regarding medical treatment or educational planning. The site psychologist will obtain appropriate parental and/or participant consents before releasing the results. The site psychologists will be asked to document on a case report form (CRF) how the data from P1042s are used (e.g., obtaining educational services or providing referrals for further psychological evaluation).
6.2 Criteria for Evaluation Discontinuation

- The participant or legal guardian refuses evaluations.
- The site principal investigator determines that further participation would be detrimental to the participant's health or well-being.

7.0 SERIOUS ADVERSE EXPERIENCE REPORTING

The Division of AIDS has determined that Serious Adverse Experiences (SAE) 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.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a cross-sectional study designed to explore the relationships between adherence to antiretroviral medication and cognitive, behavioral, psychosocial factors. Adherence data will also be collected over time. These relationships will be complex. For example, good adherence to antiretroviral medication could predict improved cognitive status, but behavioral problems might also predict poor adherence. Other factors such as degree of responsibility for the medication regimen and complexity of the regimen are likely to be related to adherence as well as cognitive functioning. The results of PACTG 1042s will therefore be hypothesis-generating.

In order to get as representative a sample as possible of the HIV-infected children and adolescents 8 to <19 years of age participating in PACTG 219C, the Statistical and Data Management Center (SDMC) will generate a participant identifier (PID) list of participants to be approached for participation in P1042s. Sites will need to commit to participating in P1042s and agree to approach all selected participants. All HIV-infected participants in the eligible age range enrolled and on study PACTG 219C as of a given calendar date, and approaching a visit where neuropsychological testing is required, will be selected as the sampling frame. Using sampling fractions based on the number of sites agreeing to participate in P1042s, the age strata, and the timing of the participants’ next neuropsychological test batteries, a list of approximately 280 selected participants will be sent to the sites. Sites will approach these participants for participation in P1042s. Participants will either:

1.) consent to participate in P1042s,
2.) refuse to participate in P1042s, but allow use of their PACTG 219C data, or
3.) refuse to participate in P1042s, and refuse use of their PACTG 219C data.

Anticipating a 30% ineligibility and refusal rate, approaching 280 participants
should yield 200 evaluable participants.

Participants agreeing to participate in P1042s will register through the SDMC
system. Sites will keep a separate log, provided every 3 months by the protocol data
manager, of all participants to be approached for PACTG 1042s and record reasons
for refusal to participate or reason for ineligibility for all participants.

Data from PACTG 219C:

The study will also utilize data already being collected for PACTG 219C.

8.2 Outcome Measures

a. Cognitive Functioning:
   • Language Comprehension
   • Verbal Memory
   • Nonverbal Memory
   • Attention
   • Academic Achievement

b. Emotional and Psychosocial Functioning:
   • Behavioral Questionnaire
   • Quality of Life

c. Adherence:
   • Self-report (Data from PACTG 219C Adherence Module I)
   • Pill Count
   • Problems with Adherence
   • Medication Responsibility
   • Health Beliefs

d. Medication Regimen:
   • Medications Used
   • Complexity of Regimen

e. Clinical Indicators:
   • Viral Load
   • Lymphocyte Subsets
   • Diagnoses (Medical and Psychiatric)
Concomitant Medication

8.3 Sample Size and Accrual

The randomly selected participants will be approached for participation in P1042s at their regularly scheduled PACTG 219C visits which occur every 3 months. It should be possible to approach all participants within 12 months of the study opening to accrual.

Primary objective 1 compares cognitive functioning between participants who can adhere to medication schedules (taking >95% of their antiretroviral medication in the previous 3 days) versus those who cannot. Using the Wechsler Individual Achievement Test-II or Wechsler Memory Scale-III (please see Appendix II for descriptions of these tests), which have a mean of 100 and a standard deviation of 15, with 200 participants, assuming, for example, that 100 were adherent and 100 were not, the study would have 80% power to detect a difference of at least 6 points between the two groups. It will also investigate the relationship between those who can and cannot adhere and the degree of responsibility placed on them. Responsibility can be classified along a continuum: those who are solely or primarily responsible for their medication regimen, sharing responsibility, or not responsible. Assuming roughly one-third of participants fall into each category (N=67), and assuming a rate of perfect adherence of 60% in the worst group, there would be an 80% power to detect a 10% improvement in third group defined by degree of responsibility.

A similar approach can be taken for assessing primary objective 2, which is related to whether cognitive status is related to the degree of responsibility for taking medication. Assuming roughly one-third of participants fall into each category, with 200 participants overall, there would be 80% power to detect differences between categories of 7.5 points.

8.4 Monitoring

Monthly accrual reports will be generated by the SDMC. Every three months, a more detailed report, including demographic characteristics, will be sent to the study team.

An administrative review will be held when 50 participants have been enrolled, or after nine months, whichever occurs first. The review team will consist of the Study Chair, Vice Chairs, Medical Officers, Statisticians, Clinical Trials Specialist, Data Manager, and one member of the Complications of HIV RAC not participating on the study team. The review team will address any problems with accrual or rates of refusal to participate in PACTG 1042s.
An interim analysis will be held when 100 participants have been enrolled and all PACTG 1042s entry and week 4 adherence measures have been submitted to the SDMC database. The report will be reviewed by a formal study monitoring committee consisting of the Medical Officers, Statisticians, and members appointed by the Complications of HIV Research Agenda Committee (RAC). The review committee will address any problems with accrual or rates of refusal to participate in PACTG 1042s. If key characteristics differ between participants who agree to participate and those who do not, or between the participants enrolled so far and the eligible but not selected PACTG 219C participants, the team will need to consider whether the sample is sufficiently representative of the PACTG 219C population. If refusal rates are high, but the sample is deemed representative, a second list of participants to approach for participation in P1042s will be generated in order to achieve the target sample size of 200 evaluable participants.

The report will also include preliminary analyses of the primary objectives of the study. Variability of the outcomes in the primary objectives will be assessed and sample size calculations updated. Power calculations will be done for selected secondary objectives. The review committee will assess the results and recommend whether the protocol should continue accrual to the target sample size of 200 evaluable participants or be closed to accrual. This recommendation will be brought to the Pediatric Executive Committee (PEC) for approval.

8.5 Analysis

This study will provide preliminary data to investigate the issues outlined in the study objectives, and search for other important predictors of the two outcomes such as age, gender, race/ethnicity, socioeconomic status, social variables such as housing stability, family and caregiver functioning, and person responsible for monitoring medications (caregiver, participant, or both). Using data at the primary collection point, univariate comparisons of the cognitive and behavioral measures (including the WISC-III/WAIS-III and the additional measures described below) will be compared, first, between participants classified as being completely, partially, or not responsible for their medication regimens, and then between those assessed as adherent or not adherent to their regimen. The relationship between adherence and degree of responsibility will be cross tabulated. Since these categorizations are somewhat subjective, measures may also be treated as continuous outcomes and/or other cut points defined. Multivariate regression analyses, controlling for important confounders, will be performed. Secondary analyses will evaluate the ability of the measures collected at the primary data collection point to predict absolute adherence or changes in adherence over the subsequent year of follow-up.

The primary analysis will focus on the entry data collection point (with data collection obtained over two visits within 12 weeks of enrollment). Self-reported adherence data at the 24 and 48 week visits and adherence rates assessed by pill
count at the 24 week visit following this time point will be used for secondary analyses examining the value of the cognitive and behavioral measures in predicting future adherence. Other data routinely collected in PACTG 219C (e.g., viral load, CD4 counts, diagnoses etc.) will be included in the analyses when relevant, but will not involve any additional visits or testing for the participants in PACTG 1042s.

8.5.1 Primary Objectives:

To assess the relationship of age, cognitive, behavioral, and psychosocial functioning with:

a. adherence to medication regimens, as measured by self-report and pill count and

b. the degree of responsibility placed on participants as measured by both caregiver and self-report questionnaires, and to assess the relationship between adherence and the degree of responsibility.

Since PACTG 1042s is cross-sectional, there is no clear response variable. PACTG 1042s will use the adherence measures as a response variable and use the behavior factors as independent predictors, recognizing that causation can not be determined using this study design. Primary outcome variables will include the:

1. percent of pills taken over 3 days from Adherence Module 1 (either continuous or binary depending on distribution of data)

2. person responsible for medication (binary variable: participant/caregiver)

3. percent of pills taken in past 30 days from Pill Count Form (continuous outcome)

Since adherence will be affected by the drug regimen and frequency of administration, all analyses will be adjusted for these factors, as well as disease severity.

Using data from the primary collection point, summaries of the cognitive and behavioral measures will be compared by each outcome measure, adjusting for complexity of regimen and disease severity. Other variables such as age, gender, race/ethnicity, socio-economic status, social variables such as housing stability, family and caregiver functioning will also be summarized. Factors which predict adherence in these models (including degree of responsibility for medication which will be used as an outcome variable and a predictor) will be included in multivariate models to see which significant predictors remain. These models should provide insight into what factors are related to full adherence.
8.52 Secondary Objectives

1. To characterize cognitive, behavioral, and psychosocial functioning in children and adolescents with perinatally acquired HIV infection.
   • Each cognitive, behavioral, and psychosocial outcome (age adjusted scores) will be summarized, including percentages of children with invalid/incomplete tests.

2. To correlate cognitive, behavioral, and psychosocial functioning with virologic and disease variables.
   • Each cognitive, behavioral, and psychosocial outcome (age adjusted scores) will be summarized by whether viral load is controlled (<400 copies/mL) and by Center for Disease Control disease category based on CD4% and CD4 count.

3. To assess the interactions between participants’ cognitive status and the complexity of their medication regimens in predicting adherence, as measured by self-report and pill count.
   • Each cognitive, behavioral, and psychosocial outcome (age adjusted scores) will be used in models predicting adherence, adjusted for complexity of the study regimen (types of drugs, number of drugs, pill burden, and frequency of administration). Significance of interaction terms between the cognitive outcomes and medication complexity will be included in these models to explore whether the factors affect medication adherence differently.

4. To assess the ability of baseline cognitive, behavioral, and psychosocial variables to predict adherence at a later time point (24 and 48 weeks following enrollment).
   • Adherence at the 24 (self-report and pill count) and 48 week (self-report only) visits after the primary data collection will be used as the outcome variable in these models to see if adherence changes over time, and whether the correlation of the behavioral, psychological and cognitive factors with adherence changes over time.

5. To assess the correlation of self-report and pill count measures of adherence.
   • Correlations will be measured using non-parametric methods at each time point where both measures are available. Regression methods may be used to adjust for other prognostic variables as necessary.

6. To assess the stability of adherence over time as measured by self report and pill counts.
Adherence will be summarized at each time point for each measure separately. In addition, numbers of participants showing clinically significant changes in levels of adherence from entry to each time point will be reported.

7. To correlate measures of adherence (self-report and pill count) with disease severity as measured by viral load, CDC disease category and CD4 counts and to assess whether the association between adherence and disease severity is stable over time.
   - Each measure of adherence will be correlated with each measure of disease severity separately at each measurement time point. Regression methods may be used to develop multivariate models to see if certain measures of disease severity are more strongly correlated with adherence.

8. To develop a predictive model that could be used by clinicians to identify children and adolescents who are more likely to have problems adhering to their antiretroviral medication regimens.
   - The primary and secondary analyses should identify a set of factors which correlate with adherence, as measured by self-report and pill count. If clinicians had a simple scoring system to identify which participants are likely to have difficulty adhering to a regimen with different complexity, it might help their decision about which regimen to prescribe. Using the factors identified as predictive of adherence, and subdividing the factors into 2 or 3 categories, it may be possible to develop a simple score using exploratory data analysis techniques. This score would require validation in an independent data set before being recommended as a useful tool to clinicians.

9.0 HUMAN PARTICIPANT

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.

9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent document (Appendix IV), 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 the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The participant's assent must also be obtained if he or she is 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 participant (or parent or legal guardian).

9.2 Participant Confidentiality

All Laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain participant 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 participant, except as necessary for monitoring by the National Institute of Allergy and Infectious Diseases (NIAID), IRB, the Office for Human Research Protection (OHRP), or sponsor’s designee.

9.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, IRB or other government agencies as part of their duties to ensure that research participants are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of PACTG 1042s will be governed by PACTG policies.

11.0 BIOLOGICAL CONTAINMENT

As the transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and handling of all specimens in this study in a clinical or laboratory setting, as currently recommended by the Centers for Disease Control (CDC).

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations Packing Instructions 602. Please refer to individual carrier guidelines (ex., Federal Express, Airborne, etc.) for specific instructions.
12.0 REFERENCES


17. Sirois, PA, & Ingram, R. Resources for mental health services: A survey of PACTG site personnel (unpublished data).


## APPENDIX I
### SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Event</th>
<th>Pre-entry</th>
<th>Weeks</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(0) Entry</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>(+12 weeks)</td>
<td>(+8 weeks)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>(+/-8 weeks)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>(+/-8 weeks)</td>
</tr>
</tbody>
</table>

- **Consent X**

### NEUROPSYCHOLOGICAL EVALUATION (see Appendices II and II-A):

- Academic Achievement
- Attention
- Memory
- Language Comprehension
- Behavior

### P1042s QUESTIONNAIRES (see Appendix II):

- Adolescent Questionnaire
- Parent/Caregiver Questionnaire
- Health Beliefs Questionnaire

### ADHERENCE (see Appendix III):

- Instructions
- Four Week Pill Count
- PACTG 219C Adherence Module
APPENDIX I (Cont.)

SCHEDULE OF EVALUATIONS

1. The Neuropsychological (NP) Evaluations may be completed at the time of entry into P1042s or at any time within three months of the participant's regularly scheduled PACTG 219C and within 3 months of the regularly scheduled PACTG 219C neuropsychological assessment. All participants must receive the P1042s tests AFTER the PACTG 219C neuropsychological assessment. The 1042s NP evaluation may be completed in 2 sessions, if needed. A psychologist, neuropsychologist, or psychological examiner under the supervision of a psychologist must administer the 1042s NP tests and behavior questionnaire.

2. Wechsler Individual Achievement Test-II: Word Reading, Reading Comprehension, and Mathematics Reasoning

3. Children’s Memory Scale: Sequences (age 8- < 17) or Wechsler Memory Scale-III: Mental Control (age >= 17 - < 19)

4. Children’s Memory Scale: Stories and Family Pictures (age 8- < 17) or Wechsler Memory Scale–III: Logical Memory and Family Pictures (age >= 17 - <19)

5. Clinical Evaluation of Language Fundamentals—3d Edition: Concepts and Directions and Listening to Paragraphs (all ages)

6. Behavior Assessment System for Children—Parent Rating Scales and Self-report of Personality (all ages)

7. The study nurse will administer these questionnaires. Questionnaires should not be sent home with participants. Administer in a quiet room. Questionnaires should be completed independently by parents/caregivers and children/adolescents. Provide assistance with reading questions if necessary. Note: Participation of a caregiver in the questionnaires is not required in order for the child/adolescent to participate in the study, even when a caregiver must give consent for the child to enroll in PACTG 1042s. When participants are enrolled in the study, the Data Manager will record whether or not a caregiver is available and willing to complete the study questionnaires.

8. Administer only to adolescents who are aware of their HIV status. Administer to all parents/caregivers.

9. The Pill Count Instructions will be administered at entry and repeated at 4 (+/-8) weeks to prepare participants for the second pill count at 24 (+/-8) weeks after enrollment (see Appendix III). The study nurse will contact the participant or caregiver at the beginning of the second pill count to review instructions.

10. The pill counts will be scheduled at 4-12 weeks and 16-32 weeks, depending on the participants’ refill schedule, and may be scheduled at a PACTG 219C visit.

11. If PACTG 219C Adherence Module 1 was not administered as part of a PACTG 219C visit within one month before entry into PACTG 1042s, the study nurse should re-administer it at entry. Do not administer at the same time as the first pill count.

12. Allowable window to complete evaluations.

13. Adherence Module 1 will be administered by the study nurse at 24 (+/-8) and 48 (+/-8) weeks (may coincide with PACTG 219C visit) (See Appendix III).
APPENDIX II

NEUROPSYCHOLOGICAL EVALUATIONS

Purpose of Testing

The purpose of the P1042s cognitive/academic testing is both to examine correlates of medication adherence and as an outcome measure. Because the test results constitute critical variables for this protocol, it is essential that the test data be collected in a standardized manner. The P1042s team appreciates the efforts of the psychologists who participate in the conduct of this protocol and are committed to providing any guidance or assistance that is needed.

Team Contact Information:

Before the first testing at a site, the site psychologist should be in contact with the protocol chair, or one of the following team members (Drs. Malee, Sirois, or Kammerer) to insure that the procedures are clear and all the materials are available. Further questions regarding the scheduling of the neuropsychological evaluation, administration and scoring of tests or questionnaires, completion of CRFs, or purchasing of materials can be directed to the P1042s team by sending an email to ACTG.TEAMP1042s@fstrf.org.

Contact Site Psychologist:

Site study personnel will provide the psychologist a copy of the protocol as soon as site registration is completed. Some test materials may not be available at the site. Allow four weeks before testing begins for the psychologist to obtain new materials.

Measures

1. Clinical Evaluation of Language Fundamentals-Third Edition (CELF-3; Semel, Wiig, & Secord, 1995): Two subtests of this battery will be used to measure comprehension of material presented verbally. These subtests require children and adolescents to follow a series of spoken commands to point to particular stimuli and to answer questions about paragraphs that have been read to them.
   - Standardized for ages 6-21.
   - Both English and Spanish versions are available from the Psychological Corporation.
   - Administer the Concepts and Directions and the Listening to Paragraphs subtests for P1042.
   - Should be administered and scored by the site psychologist.

2. Children’s Memory Scale (CMS; Cohen, 1997): Subtests of this memory battery will be used to evaluate verbal and nonverbal memory and mental control in participants who are age
8-16. These subtests require the participant to listen to short stories read by the examiner and recall them in as much detail as possible, to recall spatial and content information from pictures, and to manipulate routine information mentally.

- Standardized for ages 6-16; use for participants through age 16 years 11 months.
- Available in English from the Psychological Corporation.
- Administer the Stories, Family Pictures, and Sequences subtests for P1042. Administer immediate, delayed and recognition components of Stories and immediate and delayed components of Family Pictures.
- Should be administered and scored by the site psychologist.

3. Wechsler Memory Scale - Third Edition (WMS-III; Wechsler, 1997b): Subtests of this memory battery will be used to evaluate verbal and non-verbal memory and concentration in participants who are over age 16. These subtests require the participant to listen to short stories read by the examiner and recall them in as much detail as possible, to recall spatial and content information from pictures, and to manipulate routine sequences mentally.

- Standardized for ages 16 through adulthood; use for participants age 17 years 0 months and older.
- Available in English from the Psychological Corporation.
- Administer the Logical Memory, Family Pictures, and Mental Control subtests for P1042. Administer immediate, delayed, and recognition components of Logical Memory and immediate and delayed components of Family Pictures.
- Should be administered and scored by the site psychologist.

4. Wechsler Individual Achievement Test-II (WIAT-II; The Psychological Corporation, 2001): Subtests will be administered to assess the participants’ ability to read and understand written material and to perform basic arithmetic tasks.

- Standardized for ages 6 through 19 years 11 months; use for all participants.
- Available in English from the Psychological Corporation.
- Administer the Word Reading, Reading Comprehension, and Mathematics Reasoning subtests.
- Should be administered and scored by the site psychologist.

5. Behavior Assessment System for Children (BASC). This questionnaire will be used to evaluate behavioral functioning. Parents/caregivers and participants complete different versions of the questionnaire.

- BASC Parent Rating Scale (PRS): Use the age-appropriate version, 6-11 or 12-18.
- BASC Self-Report of Personality (SRP): Use the age-appropriate version, 8-11 or 12-18.
APPENDIX II (Cont.)

- Available from American Guidance Service (AGS). The PRS is available in Spanish; the SRP is available only in English.
- The PRS and SRP are available in hand-scored and computer-scored formats. The computer-scored format is recommended to minimize personnel time and scoring errors and to increase the clinical usefulness of the test for sites.
- The questionnaires should be administered in person by the site psychologist and reviewed for completeness before the session is concluded.
- Younger participants or those with limited reading skills may need assistance to complete questions.
- The PRS and SRP should be scored by the site psychologist using the General norms.

P1042s Questionnaires: Three questionnaires were developed for P1042s to obtain information about responsibility for medications, problems related to adherence, physical and emotional well-being, and beliefs about HIV and its treatment.

6. P1042s Adolescent Questionnaire
   - An 11-item questionnaire, written at a 5th- to 6th-grade reading level. Administer to all participants.
   - Administer at the entry visit, or within 12 weeks of entry. Can be administered at a regularly scheduled PACTG 219C visit.
   - Study nurse will administer. Younger participants, or those with limited reading skills, may need assistance to complete the questions.
   - Review the questionnaire before the session ends to be sure that all questions are answered and that only one answer is provided for each question.

7. P1042s Parent/Caregiver Questionnaire
   - A parallel form of the Adolescent Questionnaire. Contains 11 items, written at a 5th- to 6th-grade reading level. Administer to all parents or caregivers if available.
   - Administer at the entry visit, or within 12 weeks of entry. Can be administered at a regularly scheduled PACTG 219C visit.
   - Should be administered by the study nurse. Adults with limited reading skills may need assistance to complete the questions.
   - Review the questionnaire before the session ends to be sure that all questions are answered and that only one answer is provided for each question.

8. Health Beliefs Questionnaire
   - A 20-item, Likert-type questionnaire, written at a 6th-grade reading level. The questions concern beliefs about HIV and its treatment and are, therefore, appropriate only for individuals who are aware of their HIV status.
APPENDIX II (Cont.)

- Administer at the entry visit, or within 12 weeks of entry. Can be administered at a regularly scheduled PACTG 219C visit.
- Administer to all parents or caregivers if available.
- Administer only to children and adolescents who are aware of their HIV status.
- Should be administered by the study nurse. Younger participants, or those with limited reading skills may need assistance to complete the questions.
- Review the questionnaire before the session ends to be sure that all questions are answered and that only one answer is provided for each question.

Test Administration:

Completion of the P1042s cognitive/academic tests and questionnaires involves a significant time commitment on the part of the participants and their families. It is essential that the data be gathered carefully to obtain the maximum research and clinical information. The following directions support accurate data collection and clinical use of data.

Examiner:

The cognitive/academic tests and the BASC should be administered by a psychologist, neuropsychologist, or licensed psychological examiner under the supervision of a licensed psychologist. “Psychologist” will be used to refer to the examiner for simplicity. The P1042s questionnaires will be administered by the study nurse.

Scheduling:

Given the importance of each test and questionnaire to the participant and study, it is essential that scheduling decisions be made to maximize cooperation, comfort and reliability of results. Refer to Appendix I.

Although most participants should be able to complete the P1042s tests and questionnaires in one session, a second session is allowed if the participant becomes fatigued. In order to allow for adequate time for testing, the family should be alerted to the possibility of two testing sessions for completion of the P1042s tests at the time of signing consent forms for the study. Completion of all parts of the P1042s cognitive/academic assessment must occur within 3 months of the PACTG 219C neuropsychology assessment.
Test Selection:

Many of the cognitive and academic tests that are part of P1042s can be used across all ages on the protocol. The memory tests, however, must be chosen according to the age of the participant. The Children’s Memory Scale (including Sequences, Stories, and Family Pictures) will be used at ages 8 through 16; the Wechsler Memory Scale (including Mental Control, Logical Memory, and Family Pictures) will be used at ages 17 to 19.

If a participant is having difficulty on any of the tests due to cognitive limitations, attempt to complete and score the test. If this is not possible (due to skills or frustration), the test can be stopped and the reason documented on the CRF form.

Language of Testing:

PACTG 1042s is appropriate for English speaking and Spanish speaking participants. For participants who speak Spanish or whose families speak Spanish, it is best to have a psychologist who is fluent in English and Spanish. If a bilingual psychologist is not available, an interpreter can be used, which should be noted on the CRF. If there is any question about the fluency of a participant in English, a bilingual psychologist (or interpreter) should be available. For primarily Spanish speaking participants, the CELF3 Spanish version should be used. For the Children’s Memory Scale/Wechsler Memory Scale, instructions for Sequences/Mental Control and Family Pictures should be interpreted carefully by the psychologist or interpreter. The Stories/Logical Memory subtest should not be administered to participants who do not have adequate facility in English. The Wechsler Individual Achievement Test materials are available only in English, which may be appropriate for students who are being educated in English. The psychologist should give the instructions for the test in Spanish and in English if this is more comfortable for the student. If a student is being primarily educated in Spanish or has only recently begun being educated in English, then this test is not appropriate and should be so noted on the CRF.

A Spanish version of the BASC PRS is available. For the SRP, the questions should be translated into Spanish by the psychologist or interpreter, and the child/adolescent should circle the response privately on the form.

Test Introduction:

The testing experience should be as positive as possible for the participant and the family. The testing should be explained to the family and child/adolescent, including the kind of feedback that will be made available to them. The proposed
schedule should be shared and coordinated with the family’s needs. The child/adolescent should be given the opportunity to ask any questions or voice concerns about the procedures.

Testing should occur in as quiet a place as possible with no interruptions. Regular positive reinforcement should be given for effort and engagement on the tasks. Given the length of the testing, breaks should be given when appropriate for comfort or clinical needs. Testing should be discontinued and rescheduled if the participant shows significant stress, discomfort, or fatigue.

Cognitive/Academic tests:

All cognitive and academic tests should be given according to standard administration as noted in examiner manuals. Psychologists who are not familiar with these tests should carefully study the procedures and practice the tests ahead of time to avoid adding time or errors during the testing time with a participant.

Particular caution is advised on the following tests:

- **CELF 3**: Spanish version is available when needed. Listening to Paragraphs requires matching the participant’s age to the appropriate paragraphs. Use the age appropriate paragraphs even when language skills may be below age level.

- **Children’s Memory Scale/Wechsler Memory Scale**: For Stories on the Children’s Memory Scale, different stories are read at different ages. For the 8 year olds, a separate report form is used. For the 9-16 year old, choose the age appropriate story from the 9-16 record form. The delayed recall and the recognition conditions of the Stories on the Children’s Memory Scale and Logical Memory from the Wechsler Memory Scale should be given following an approximate 30 minute delay. On Sequences/Mental Control, items must be scored carefully for time and accuracy, which are added for the total score for the item. On Family Pictures, scoring the responses quickly and accurately can be difficult. Responses should be taped to insure accurate scoring. Taping responses to the Stories and Logical Memory will also aid accuracy of scoring. Erase tapes immediately after scoring.

- **The Wechsler Individual Achievement Test (WIAT-II)**: The WIAT-II also requires starting at a specific point relative to the participant’s grade. For adolescents who are not in school, the last grade attended may be used. It is standard to go backwards if the participant is not succeeding at the appropriate grade level. Additional support and reassurance that academic
• testing is brief in this battery may be required for some participants for whom academics are a source of stress.

Test Prioritization:

After the PACTG 219C tests, in the same or separate session(s), the P1042s cognitive/academic tests should be given in the standard order given below. If this order is changed for any reason; please note this in the CRF. If it is clear that not all the cognitive/academic tests will be completed in one session, ensure that the immediate and delayed components of the memory tasks (Stories, Logical Memory, Family Pictures) are given in the same session.

Order of Administration:

In order to standardize data collection and the participants' testing experience, the assessment measures should be given in a standard order. Breaks are allowed if needed, but should be avoided between the immediate and delayed trials of the memory tests. Administration of additional subtests from the test batteries for clinical purposes is encouraged; however, sites are requested to administer these AFTER the P1042s battery so that the protocol testing is not invalidated.

1. CMS/WMS Stories/Logical Memory Immediate
2. CMS/WMS Family Pictures Immediate
3. CMS/WMS Sequences/Mental Control
4. WIAT-II Word Reading
5. WIAT-II Math Reasoning
6. CMS/WMS Stories/Logical Memory Delayed
7. CMS/WMS Family Pictures Delayed
8. WIAT-II Reading Comprehension
9. CELF-3 Concepts and Directions
10. CELF-3 Listening to Paragraphs
11. BASC Parent Rating Scale (PRS)*
APPENDIX II (Cont.)

12. BASC Self-Report of Personality (SRP)

*Note: If the parent/caregiver has no difficulty reading the questions, the PRS may be administered while the child/adolescent is engaged in testing with the examiner.
APPENDIX II-A

NEUROLOGICAL TEST ORDERING INFORMATION

(Prices may change over the length of the study)

Limited funding is available through a grant from the William T. Grant Foundation to help sites pay for testing materials. Research discounts are also available from the test publishers. Please contact the P1042s team for information about accessing William T. Grant Foundation Funding or receiving discounts.

The following tests are available from the Psychological Corporation (The Psychological Corporation, 19500 Bulverde Road, San Antonio, Texas 78259-3701, Phone: 1-800-872-1726, Fax: 1-800-232-1223, www.PsychCorp.com. The numbers and prices for test components are from the 2002 catalog.)

1. Clinical Evaluation of Language Fundamentals-Third Edition (1995) – Note: This study requires the CELF-3, not the recently released CELF-4, since the CELF-4 is not available in a Spanish edition.

   For Complete Kit (includes examiner's manual, 2 stimulus books, technical manual and a package of 12 record forms)
   015-8035-003-MP299 399.00*

   *Spanish Version available

   Complete Kit
   015-8035-305-MP299 399.00*

   To order forms separately:

   Record Forms
   015-8035-046-MP299, Pkg. of 12 30.00*  

2. Children's Memory Scale (1997)

   For Complete Kit
   Includes 25 record forms for both age levels, manual, 2 stimulus booklets, response grid, chips in pouch and 5 family picture cards
   015-8038-002-MP299 410.00*

   To order components separately:

   Record Forms only
   Ages 5-8
   015-8038-010-MP299 45.00*

   Record Forms only
   Ages 9-16
   015-8038-029-MP299 45.00*

* Prices quoted on 9-05-03
APPENDIX II-A (Cont.)


015-8981-715-MP299 461.00*

To order components separately:
Administration/Norms Manual
015-8981-723-MP299 82.00*

Record forms
015-8981-758-MP299, Pkg of 25 48.00*


For complete Kit (includes Stimulus Books 1 & 2, Record Forms (25), Response Booklets (25), Examiner's Manual, Scoring Normative Supplements
015-8983-505-MP299 340.00*

To order components separately:
Combination Record Forms/Response Booklets
015-8983-998-MP299, Pkg. of 25 each 63.00*

Stimulus Book 1
015-8983-513-MP299 91.00*

Stimulus Book 2
015-8983-481-MP299 91.00*

WIAT-II Examiner's Manual
015-8983-556-MP299 96.00*

* Prices quoted on 9-05-03
5. The following test is available from: American Guidance Service Inc. 4201 Woodland Road Circle Pines, MN, 55014-17961-800-328-2560, www.agsnet.com. Ordering information for the computer scoring version (recommended) follows. Forms are sold in packages of 25 minimum. Sites that would like to purchase fewer than 25 forms for particular age levels or respondents may contact Dr. Nichols, who will coordinate sharing of orders between sites or central purchasing of forms.


**BASC Plus Windows Starter Set**

- Includes: manual, Plus Windows CD-ROM Kit, One pkg (25) per age level of computer-entry format of Parent, Self, & Teacher forms, one pkg (25) of SOS and SDH forms

**BASC Plus Macintosh Starter Set**

- Includes: manual, Plus Macintosh CD-ROM Kit, One pkg (25) per age level of computer-entry format of Parent, Self, & Teacher forms, one pkg (25) of SOS and SDH forms

To order forms separately:

**Parent Report**

- 6-11 years
  - #AC3819, computer entry format, pkg. of 25
  - 19.95*

**Parent Report, Spanish version**

- 6-11 years
  - #AC3919, computer entry format, pkg. of 25
  - 19.95*

**Parent Report**

- 12-18 years
  - #AC3820, computer entry format, pkg. of 25
  - 19.95*

**Parent Report, Spanish version**

- 12-18 years
  - #AC3920, computer entry format, pkg. of 25
  - 19.95*

**Self-report of Personality**

- 8-11 years
  - #AC3821, computer entry format, pkg. of 25
  - 19.95*

* Prices quoted on 9-05-03
APPENDIX II-A (Cont.)

12-18 years
#AC3822, computer entry format, pkg. of 25 19.95*

BASC Manual
#AC3801 76.95*

6. The Parent/Caregiver, Adolescent and Health Beliefs Questionnaires will be provided in the Case Report Forms (CRFs)

* Prices quoted on 9-05-03
APPENDIX III

PILL COUNT INSTRUCTIONS

General instructions:

- Pill or medication ‘counts’ will be performed for a 20-30 day period for all antiretrovirals prescribed for participants in P1042s at two times:
  - 4 (+8) weeks after enrollment
  - 24 (+/-8) weeks after enrollment.
  
  Note: This window of time is provided to allow sites to coordinate pill counts with participants’ refill schedules as well as their clinical and/or PACTG 219C study visits.

- A visit should be scheduled at the end of the 20 - 30 day period so that research staff can complete the pill or medication ‘count’.

- The use of individual pill count data for clinical care is at the discretion of the site investigator.

- Initiate each pill count when the participant's antiretrovirals are due to be refilled, or dispensed by the research pharmacy.

- Begin the pill count when ART medications are dispensed if antiretrovirals are dispensed by the research pharmacy on site.

- Study coordinators should obtain a standard release of medical information at enrollment, so that a commercial pharmacy may be contacted if clarification (regarding dispensing amounts and dates) is needed for a pill count.

- Example cases and completed forms are available on the PACTG web site at: http://pactg.s-3.com.

- If a participant has a medically prescribed drug holiday initiated less than 20 days after the pill count is begun, reinitiate the medication count when medications are re-started if within window.

Caregiver/participant instructions:

- Written instructions (which can be copied from the box below) should be given to the caregiver/participant and reviewed at the time of enrollment. Participants should receive a reminder phone call or visit to review instructions at the beginning of each medication count.
Instructions for the medication counts for caregivers and children/adolescents in P1042s:

Medication counts are done to review how participants are taking their medications. We need your help to complete these assessments.

- Medication counts will be done twice
  - About 1-3 months after enrollment on: _______________________
  - About 6 months after enrollment on: _______________________
- You will need to bring all the medicine bottles to clinic on these two dates.
- You will start the medication count at home a month before the clinic visit to see how you are doing. Your doctor or nurse will explain the medication count when you get your refill bottles.
  - When you start a new bottle of medicine, write the date you began giving medicine from that bottle on the label.
  - Set aside any ‘old’ bottles containing the same medicine. Do not administer medicine from those ‘old’ bottles until the medication assessment visit happens.
  - If you/your child needs more than one bottle of medicine during the month before the medication count happens, write the date on the label that you ran out of meds on bottle #1. Write the date on the label of bottle #2 you began using that bottle.
  - Do not throw any bottles away, even empty ones.
  - Bring all bottles to clinic for the medication count visits.

Performing the pill counts:

1. Schedule the participant (per Appendix I) for the pill count 20-30 days after the antiretrovirals were due to be refilled.
2. Perform the medication count on the same day for all antiretrovirals. If medications are on different dispensing schedules, the interval may be shorter than the desired 20-30 days for one or some of the medications.
3. The Continuous Dosing CRF will be used for PACTG 1042s.
4. Enter each formulation separately. (e.g., a patient receiving 250 mg of Efavirenz would have data re the 200 mg caps entered and data re the 50 mg caps entered.).
5. Do not count pills or measure liquids in front of the participant or parent/caregiver.
6. For each formulation:
   a. Complete Drug Code and Drug Formulation
   b. Complete Dose. For each formulation, the Dose is the number of pills, cc’s, or scoops per dose.
   c. Complete Units (formulation information) and Number of Times per Day
   d. Enter Start Date (the date the participant wrote on bottle #1 of a formulation indicating they began dispensing from that bottle on that date).
   e. The Stop Date is the date the pill count is performed. Participants will be instructed to write the date they ran out of meds in a given bottle to facilitate late counts. Dates on interim bottles (if more than one bottle is used) are for the coordinator’s use and not for entry.
   f. Enter Number of Units Dispensed. This is the total dispensed for all bottles of a formulation (if applicable). If not indicated on the label, call pharmacy to verify.
   g. Measure Number of Units Remaining in the bottle currently in use (or the last bottle used if a late count).

Contact information for questions/queries specific to the P1042s pill count:
pactgteamp1042s@fstrf.org.
DIVISION OF AIDS
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)
SAMPLE INFORMED CONSENT
For protocol:
PACTG P1042s: Cognitive, Behavioral, and Psychosocial Correlates of Medication Adherence in Children and Adolescents with HIV-1 Infection Version ____ Date ____

SHORT TITLE FOR THE STUDY: Cognitive, Behavioral, and Psychosocial Correlates of Medication Adherence in Children and Adolescents

INTRODUCTION

You/your child are/is being asked to take part in this research study because you/ your child are infected with HIV and are enrolled in PACTG 219C. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your child to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to look at the relationship between language, memory, attention, behavior, and academic skills and how children cope with responsibility for taking medication. This study will help to find out what can help or make it difficult for you/your child to take your/their medicine. This study will look at:

- understanding language
- remembering
- paying attention
- how you/your child do/does in school
- how well you/your child do/does in following a medication schedule
- behavior and feelings

You are/your child is one of two hundred and eighty PACTG 219C participants who have been chosen at random (selected by chance) and will be offered the choice to take part in this study.
APPENDIX IV (Cont.)

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

If you enroll in PACTG P1042s, you/your child will have 2 hours of testing. Some of this testing will be written and some oral. You will keep track of your/your child’s medication, by writing the start and stop dates on the label of the bottle. You/your child will bring medicine bottles to the clinic. The testing and questionnaires can be done at PACTG 219C visits. You may have to make 1-2 extra visits to clinic. The P1042s protocol team will study some of the data collected on you/your child during the course of PACTG 219C. These data include age, sex, race, and HIV disease status, immunologic status (health of the immune system), medical and psychiatric diagnoses, and response to questionnaires administered as part of that study.

1). Neuropsychological Testing: You/your child will take written and oral tests of reading, mathematics, memory, and attention. Responses to some of these tests will be audiotaped. The tapes will be erased after the test has been scored. The neuropsychological testing will take 1 to 1½ hours and can be done in two visits. At any time you may request a break, or that testing be rescheduled. This testing will be administered by your/your child’s site psychologist.

2). P1042s Study Questionnaires: You/your child will complete questionnaires about who has responsibility for medication and medical treatment for you/ your child. You will also complete questionnaires about how medicine/treatments affect your/your child's life and about your/your child’s behavior. This will take approximately 30-40 minutes. For this study, both the child and the caregiver are asked to fill out similar questionnaires.

3). Pill Count: At 4 (+8) weeks after entry, and again 24 (+/-8) weeks after entry, you/your child will be asked to bring in your/your child's medication bottles to review how you have/your child has been taking the medications. You/your child will be reminded of instructions for the pill count by telephone.

If you decide to leave the study/remove your child from the study early, you can ask to meet with the psychologist to review the results of any testing that has been completed up until that point.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 200 children/adolescents and their parents/caregiver will take part in this study.

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

You/your child will be in this study for about 48 weeks.
WHY WOULD THE DOCTOR TAKE YOU/YOUR CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off the study early without your permission if:

- The study is cancelled by the National Institutes of Health (NIH), or the site's Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- You/your child are unable to attend study visits as required by the study.
- The study doctor decides that being in this study is harmful to your/your child's well-being.

WHAT ARE THE RISKS OF THE STUDY?

You/your child may become tired during the testing or be uncomfortable answering personal questions.

WHAT ARE THE RISKS RELATED TO PREGNANCY?

There are no related risks to pregnancy for participants in PACTG 1042s.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take(s) part in this study, there may be a direct benefit to you/your child, but no guarantee can be made. Information from PACTG P1042s study evaluations may be used in planning your/your child’s clinical care, or in school planning, with your permission, and will be reviewed with you by the psychologist at your request.

It is also possible that you/your child may receive no benefit from being in this study. 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 have the choice of:
APPENDIX IV (Cont.)

- not being in the study.
- having cognitive, behavioral, emotional testing/evaluations done independently.
- having no evaluations done.

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

WHAT ABOUT CONFIDENTIALITY?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this certificate, the researchers cannot be forced to disclose information that may identify you, 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, 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 or for information that must be disclosed.

People who review your records include: (insert name of site) IRB, National Institutes of Health (NIH), study staff, study monitors.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your 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 the information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: 1) in the case of suspected child abuse; 2) in the case of suspected harm to you/your child or others.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you/your child is/are taking part in a research study.
WILL I/MY CHILD RECEIVE ANY PAYMENT?

You/your child may receive compensation for being in this study, depending on a specific site and may include transportation cost, meals, or food vouchers.

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?

If you/your child is/are injured as a result of being on this study, you/your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or to the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

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

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study/take your child out of the study at any time. If you choose not to participate in PACTG P1042s, your participation in PACTG 219C will not be affected. You/your child will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your/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/DOES MY CHILD DO IF I HAVE/MY CHILD HAS 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/your child’s rights as a research participant, contact:

- 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 Consent Discussion (print)  Study Staff Signature and Date

Witness’ Name (print)  Witness’s Signature and Date
(As appropriate)
APPENDIX IV (Cont.)

The following section does not apply if participant signs above.

CONSENT FOR STUDY TEAM TO UTILIZE PACTG 219C DATA FOR PARTICIPANTS REFUSING PARTICPATION IN P1042S:

You have refused to participate in the P1042S study. We would like to ask your permission to use study data collected on you/your child during your participation in PACTG 219C. Your/your child’s PACTG 219C data is identified by code and personal information will not be revealed without your written consent.

The reason to study data on PACTG 219C participants who choose NOT to enroll in Protocol 1042S is to determine whether these children differ in any way from the children who are entered into Protocol 1042S. Differences in age, sex, race, HIV disease status, previous diagnoses, questionnaire responses, and immunologic status (health of the immune system) are some examples of data that may be examined. This may be important in designing future studies of HIV-infected children. Any use of PACTG 219C data is for research purposes only, and the results of these tests will not be sent back to research personnel, participants, or participant’s health care providers.

<table>
<thead>
<tr>
<th>Participant's Name (typed or printed)</th>
<th>Participant's Signature OR</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant's Legally Acceptable Representative or Representative</td>
<td>Legally Acceptable Representative's Signature</td>
<td>Date</td>
</tr>
<tr>
<td>Witness's Name (Typed or printed)</td>
<td>Witness's Signature</td>
<td>Date</td>
</tr>
</tbody>
</table>

NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

The Division of AIDS strongly encourages a witness for the participant's signature.