DIRECTLY OBSERVED THERAPY (DOT) IN HIV-1-INFECTED ADOLESCENTS

A Multicenter Center Pilot Study of the Pediatric AIDS Clinical Trials Group (PACTG)

Sponsored by:

The National Institute of Allergy
and Infectious Diseases

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PACTG P1036B PROTOCOL TEAM ROSTER

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DIRECTLY OBSERVED THERAPY (DOT) IN HIV-1-INFECTED ADOLESCENTS:
PART B-PILOT STUDY

DESIGN: Pilot study of DOT.

SAMPLE SIZE: A total of 24 subjects will participate at four different sites (4-8 subjects per site). The protocol is site restricted.

POPULATION: HIV-infected adolescents, ages 16 to < 22 years, who were infected after the age of 12 years.

STRATIFICATION: By site.

REGIMEN: Primary care physician prescribes the best once daily or twice daily Highly Active Antiretroviral Therapy (HAART).

STUDY DURATION: 24 weeks.

OBJECTIVES:

Primary:

1. To examine the feasibility of providing DOT to HIV-1-infected adolescents.

Secondary:

1. To assess subject satisfaction of the DOT intervention model developed in PACTG P1036A.

2. To evaluate the cost of the DOT model.

3. To explore the effective ratio of DOT facilitators to subjects, considering specific site factors (i.e., travel distance, local obstacles, etc.).

4. To explore the reproducibility of DOT implementation across sites.

5. To assess the impact of DOT on adherence to HIV medications.
6. To assess the impact of DOT on HIV viral load and CD4 count.

7. To assess beliefs about HAART and perceptions of self-efficacy (confidence) to adhere to HAART pre- and post-DOT.

8. To explore the prevalence of, and changes in, symptoms of depression, hopelessness, emotional and behavioral problems, coping style, perceived barriers to adherence via self-report, and substance abuse pre- and post-DOT, controlling for the occurrence of severe incident illness.

9. To explore the sustainability of DOT benefits.

Schema of DOT study development in HIV-infected adolescents

Part A (completed)
Focus groups (3 sites)

Part B (current protocol)
DOT pilot study (4 sites)

Part C (in planning stage)
DOT study questionnaire (All PACTG sites)
1.0 INTRODUCTION

1.1 Background

The continued detection of newly infected adolescents who have acquired HIV infection through sexual transmission, combined with the perinatally HIV-infected children who are approaching adolescence, has resulted in a growing population of HIV-infected adolescents. It is estimated that there are 40,000 new infections in the United States (U.S.) each year. At least half of these infections are among people under the age of 25 (1:2). As with many other chronic diseases, the problem of adherence to therapy for HIV infection has posed a major challenge in successfully achieving, and consistently maintaining, adequate control of the disease process in this population. Only 41% of HIV-infected adolescents, recruited from 13 U.S. cities into the Reaching for Excellence in Adolescent Care and Health (REACH) project, reported full adherence to HAART (3). A retrospective analysis of a smaller group of HIV-infected adolescents (ages 13-21 years) revealed that 72% of subjects receiving antiretroviral medications were non-adherent (4). Adolescents often cite forgetting to take their medications as the reason for poor adherence. In the REACH project, forgetting to take medications (some of the time or often) was one of the most commonly endorsed reasons for non-adherence (5). In a smaller study, which included 31 adolescents in Los Angeles, this was found to be a reason for poor adherence in 22% of the study population (6).

Implications of Poor Adherence

PACTG 381 demonstrated a more reduced virologic response to HAART than would be predicted based on adult studies (7). After 16-24 weeks of treatment, only 59% of HIV-infected adolescents in this study showed an undetectable viral load. Complete adherence to HAART was the only predictor of achieving undetectable viral loads (P<0.001). A direct correlation between adherence to antiretroviral therapy and virologic outcome has been demonstrated in other clinical studies as well (3;6;8;9). Additionally, it is well recognized that non-adherence accelerates the development of viral resistance to antiretroviral medications.

Poor adherence not only affects the individual in the form of clinical failure and development of resistance, but also has public health implications(10). The results of ACTG 076, occupational exposure studies, and studies in subjects infected via blood or blood products, support the assumption that successful antiretroviral therapy in adherent individuals can reduce the viral load in blood and genital secretions, which might result in diminished HIV transmission risk (11-14). Concern also remains regarding the possibility of transmission of a single
drug or a multi-drug resistant virus, resulting in primary infection with resistant HIV variant (15;16).

Recognizing the major impact of adherence to antiretroviral therapy on the magnitude and durability of therapeutic response, physicians have tried well recognized adherence strategies, such as educational support and enhanced social services, as well as newer approaches, such as the use of pagers, telephone reminders, specialized pill boxes, improved physician access after hours, financial incentives, outreach workers and pharmacist counselors. Despite the use of these strategies, non-adherence continues to be one of the major challenges to the successful management of HIV infection, especially in the adolescent population.

DOT for Tuberculosis

Many of the issues discussed so far are analogous to those faced in the treatment of tuberculosis (TB). To increase the probability of treatment compliance, DOT has been recommended as the standard of care for pulmonary TB (17;18). Based on a review of existing literature, the Public Health Tuberculosis Guidelines Panel concluded that treatment completion rates for pulmonary TB are most likely to exceed 90% when treatment is based on DOT with multiple facilitators and enhancers. This was felt to be unlikely using other, less intensive, interventions including unsupervised strategies and modified approaches to DOT. The Panel also concluded that DOT appears to be cost-effective, compared with self-administered therapy, although pertinent data were limited (18).

DOT for HIV Infection

An approach using a DOT strategy for HIV infection, and obtaining similar successful results as with DOT in TB, is limited by certain differences that exist between the two diseases. These include curability, mode of transmission, issues of confidentiality, complexity of medication regimens and duration of therapy (19). Over the past few years, there have been some studies using a total or partial DOT approach in the context of HIV infection. While many of them have targeted prisons or correctional facilities (20-23) or been incorporated into methadone maintenance programs (24-28), a few studies have looked into the feasibility of providing community-based DOT (29-34). In a non-randomized study of treatment-naïve adult subjects, comparing DOT in a Department of Corrections facility versus self-administered therapy in the clinic population, the DOT group had greater short and long-term virologic responses, when compared with those in the self-administered therapy group (20). There was no common treatment regimen between these subject groups. Using an intent to treat analysis, the proportion of subjects with HIV RNA < 400 copies/mL in the DOT versus the self-administered therapy group was: at week 16, 94% versus 77%; at week 24,
100% versus 76%; at week 48, 100% versus 81%; at week 64, 100% versus 81%; and at week 80, 95% versus 75% respectively. In another study aimed at providing DOT in the community setting, a modified DOT approach (i.e., one of the two daily doses of medication was given under observation 5 days a week) was adopted (29). Three months worth of study data were reported on 22 adult, HIV-infected, antiretroviral-exposed subjects, who were referred for self-reported non-adherence; these data showed increased compliance and decreased viral load (mean decrease 1.36 log) among study participants. The majority of these subjects felt that the outreach worker had helped them and they felt better about taking medication upon completion of the project. This is another potential benefit of DOT, especially in the adolescent population, where higher levels of depression were found, and were significantly associated with decreased adherence (3;35;36). Also, a lack of once-a-day HIV therapy had been one of the major obstacles to conducting properly designed, well-powered studies of DOT in the community setting. Over the past few years, the availability of new once-a-day antiretroviral medications such as atazanavir, emtricitabine, tenofovir, and fosamprenavir, combined with data to support once-a-day dosing of well-known agents, such as didanosine, and lamivudine, have increased our ability to put together potent once-a-day antiretroviral regimens which may be more amenable to being used in DOT programs.

The economic impact of administering DOT to HIV-infected subjects in the community has not been studied. Despite its greater initial cost, DOT, for the treatment of TB, was found to be a more cost-effective strategy than self-administered therapy (37). This analysis used a decision analysis model that included both the cost of initial therapy and the cost of treating disease that arises as a result of failure to initial therapy. Using a similar strategy, the cost-effectiveness of DOT, versus self-administered therapy, in the treatment of HIV infection needs to be evaluated, taking into account both the direct and indirect costs. This includes assessing not only the cost benefit of managing well-controlled disease in the subject, but also the cost averted, in terms of reduced transmission, decreased drug resistance, and improved quality of life.

The limited, but growing, literature on the potential of DOT in the treatment of HIV-infected patients seems promising, with feasibility and success demonstrated in small studies within special patient populations. Questions, however, still remain regarding duration of DOT, sustainability of benefits from DOT, and overall cost-effectiveness of such an intervention.

1.2 Rationale for Studying DOT for the Treatment of HIV in Adolescents

None of the studies previously mentioned have looked into the feasibility and impact of DOT in adolescents. Adolescents make up a unique population with special needs and challenges, both physical and emotional. They continue to be
significantly represented in the overall pool of newly HIV-infected individuals in the U.S. They have also demonstrated significant problems with adherence. For these reasons, conducting a well-designed study of DOT in this patient population is a high priority. Successful adherence to HAART through DOT would provide benefits to the adolescent, through better disease control, and also to the public, by potentially preventing the development and spread of viral resistance and reducing the risk of transmission.

While DOT has traditionally been viewed for its value in ensuring (even enforcing, in the case of DOT for TB) adherence to medication, an additional, though possibly indirect, benefit of DOT is the daily interaction with a health care provider or other DOT facilitator. The support provided by these interactions may improve one’s perceptions and beliefs about HAART (e.g. “taking medications as prescribed will keep me healthy”), and lead to increased perceptions about one’s ability to sustain adherence (e.g. “I am confident I can take my medication as prescribed”) once subjects are weaned from DOT and this supportive relationship. Consequently, improved adherence, as a result of these DOT interactions, may lead to an indirect improvement in subjects’ overall quality of life. This would include improvements in other co-morbid factors like depression, which directly or indirectly, influence adherence to treatment and overall outcome of the disease. The REACH study showed that HIV-infected adolescents with good social support structures and adaptive coping mechanisms had lower levels of depression (36). It is hypothesized that the daily interaction between the DOT facilitator and the subject could facilitate practical coping strategies around barriers to adherence that result in improved self-efficacy, reduced depressive symptoms, and improved adherence.

Recognizing the challenges of working with adolescents, and being cognizant of their unique needs, has led to a multi-step approach to designing a DOT study that is specific for this population. As a first step, adolescents were approached for their perspectives and ideas regarding the acceptability of DOT and the DOT process. This was done in PACTG P1036A, in a focus group setting. PACTG P1036B is being designed as a pilot study to examine the feasibility of implementing a community-based DOT model (which incorporates the information available from P1036A) in HIV-infected adolescents. This study is being conducted in preparation for future studies with appropriate sample size that address the timing, duration and cost-effectiveness of DOT as part of a multiple strategy intervention to improve adherence in adolescents with known adherence problems to HIV medications.

Results of P1036A – Focus Groups

P1036A was designed to obtain information from HIV-infected adolescents regarding the concept, design, and implementation of a DOT intervention model.
In this study, focus groups (5-10 participants each) were conducted at three sites within the PACTG. These sites were located in Los Angeles, CA; Miami, FL; and Memphis, TN. The three sites were selected through a site application process based on site experience with the conduct of focus groups, available population of patients with adherence problems, and an existing adolescent support group. The information that was obtained from P1036A was translated into specific recommendations which have been included in P1036B. The recommendations that emerged from the focus groups include the following:

Selection of the DOT Facilitator

The ideal candidate would:

- Be a young adult, preferably ≥ five years older than the subject;
- Regardless of HIV status, be knowledgeable (or available for training) about HIV infection and its treatments, including side effects and their management;
- Be skilled in interpersonal communication and be able to display empathy for the subject;
- Maintain a professional relationship and not invade the personal boundaries of the subject;
- Be someone selected from existing clinic staff with whom the adolescent is familiar. If this is not feasible, the adolescent should be provided with opportunities to meet with the DOT facilitator to establish familiarity, and build rapport, prior to initiating the DOT study; and
- Be trained in providing a link between the subject and his/her case manager, as a means of providing referral services for necessities and counseling, if needed.

Logistics of the DOT Interaction

- The DOT facilitator will be given a cell phone and the subject will be given a pager so that they are able to contact each other more easily. Some of the focus group participants cited the disadvantages of a pager and suggested providing a cell phone to the subjects; however, after careful consideration, due to logistical issues, the P1036 team decided to give subjects pagers, instead of cell phones, as part of the study plan. The DOT interaction should be scheduled, but allow for flexibility (if needed) by the subject.
- The plans for the interaction should be flexible, both as to where it occurs (and allow for alternate meeting locations on different days) and what time of day (within reason to accommodate drug schedules). Privacy is desired and should be considered in the selection of the location.
- If the subject does not show up at the scheduled place and time, the DOT facilitator should attempt to contact him or her after 15 minutes, using the
pager, as a reminder. If the DOT facilitator is unable to contact, or reschedule with the subject, he or she should wait a maximum of 30 minutes (15 minutes after paging the subject) before leaving the arranged location.

Rationale for Part B: Pilot Study

A DOT pilot study will help to better define an acceptable model of providing DOT that can be applied, in a standardized way, at various sites. The study can also begin to investigate the appropriate duration of DOT, the logistics of the DOT facilitator and subject interactions, subject satisfaction, and a strategy for the discontinuation of DOT. Finally, the study may be able to successfully estimate the cost of providing DOT to this unique population.

The population chosen for this pilot DOT study will consist of adolescents who are continuing, changing, or re-initiating HAART regimens and have demonstrated adherence problems. Since poor adherence to medication can be a major determinant in the success or failure of subsequent treatment regimens, it is important to study this type of intervention. The information obtained from this study will then form the basis for future clinical trials that can better answer the issues of efficacy of DOT, timing of DOT and cost-effectiveness of such an intervention. The objectives of future studies will likely be to examine DOT as an intervention that provides extra services to a patient over a defined period of time when they are showing poor adherence to medications. The hope would be that by doing this, patients build the skills to eventually assume self-care.

1.3 Behavioral Theories and the DOT Pilot Study Model

While previous DOT studies were based primarily on a Medical Model, the present pilot study depends on combined aspects of the Health Beliefs Model and Self-Efficacy Theory (Figure 1).

The Health Beliefs Model (HBM) was developed in an attempt to understand the failure of people to accept disease prevention or screening tests for asymptomatic diseases, but was subsequently applied to patients’ responses to symptoms, and adherence to prescribed medical regimens(38). The constructs of the HBM are derived from a group of well-established psychological and behavioral theories and models that hypothesize that health behavior depends largely on two key variables 1) the value an individual places on a particular outcome or goal; and 2) the individual’s estimation of the likelihood that a given action will lead to a particular outcome or goal.
Figure 1: Conceptual model of DOT - HBM and the Self-efficacy theory

The HBM posits that the most proximal determinants of an individual’s decision to adopt a recommended behavior or behavior change (e.g., to take his/her HIV medication) are a perceived threat of disease and a perception that the benefits of the recommended change or behavior far outweigh the perceived barriers to adopting the behavior or behavior change (see Figure).

*Perceived threat* represents beliefs about how susceptible people are to becoming ill with HIV disease and how severe that might be. *Perceived susceptibility* refers to the adolescent’s subjective evaluation of the likelihood of developing AIDS. *Perceived severity* is defined as the evaluation of the seriousness of leaving HIV untreated. *Perceived severity* also takes into account the medical/clinical consequences (e.g., hospitalizations, disability, and death) and the possibility of social consequences (e.g., the effects of the adolescent’s developing AIDS on family, school, and social relationships). The perceived benefits of action reflect the adolescent’s subjective evaluation of the effectiveness and feasibility of the
recommended health action. Thus, an action will unlikely be adopted, even in the face of significant threat, if it is not perceived to be an effective response. 

Perceived barriers include factors such as the cost of the recommended action, the associated risks (i.e., side effects), and unpleasant effects (i.e., inconvenience).

It is hypothesized that one engages in an informal cost-benefit analysis of the recommended actions to determine if the benefits outweigh the barriers. Together, one’s consideration of the benefits and barriers define the preferred course of action for responding to, or discounting, the health threat. According to the HBM, demographic, social, and psychological factors are thought to affect one’s likelihood of adopting recommended courses of action through their influence on perceptions of susceptibility, severity, benefits, and barriers. Demographics, social, and psychological variables, including a belief in personal incapacity, based on past failures or current life stresses, may also influence one’s health decision-making by directly affecting his/her perceived threat. In this framework, perceived threat does not necessarily lead to the adoption of a health recommendation, even when perceived benefits are high and perceived barriers are minimal.

The HBM contends that a cue to action must also be present. The cue to action in this study is the modified DOT. It is proposed that, by offering DOT intervention, adolescents will be encouraged to respond to the perceived threat of AIDS by adhering to HAART through a process of skill-building. It is expected that this will result in enhanced self-efficacy.

The Self-Efficacy Theory reflects upon one’s belief in his/her ability to engage in the desired behavior (adherence) and to sustain that behavior in the face of temptation not to (barriers to adherence). Self-efficacy will be further enhanced if the adolescent is able to maintain adherence as the cue to action (i.e. modified DOT) is gradually reduced, and ultimately stopped.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.11 To examine the feasibility of providing DOT to HIV-1-infected adolescents.

2.2 Secondary Objectives

2.21 To assess subject satisfaction of the DOT intervention model developed in PACTG P1036A.
2.22 To evaluate the cost of the DOT model.

2.23 To explore the effective ratio of DOT facilitators to subjects, considering specific site factors (i.e., travel distance, local obstacles, etc.).

2.24 To explore the reproducibility of DOT implementation across sites.

2.25 To assess the impact of DOT on adherence to HIV medications.

2.26 To assess the impact of DOT on HIV viral load and CD4 count.

2.27 To assess beliefs about HAART and perceptions of self-efficacy (confidence) to adhere to HAART pre- and post-DOT.

2.28 To explore the prevalence of, and changes in, symptoms of depression, hopelessness, emotional and behavioral problems, coping style, perceived barriers to adherence via self-report, and substance abuse, pre- and post-DOT, controlling for the occurrence of severe incident illness.

2.29 To explore the sustainability of DOT benefits.

3.0 STUDY DESIGN

Part B of P1036 will target adolescents, ages 16 to < 22 years who are continuing, re-initiating, or changing a HAART regimen and have demonstrated adherence problems. This pilot study of DOT will look at the feasibility of providing DOT to HIV-1-infected adolescents at a location chosen by the subject. The DOT model used in this pilot study is based on information obtained from adolescents who participated in focus groups as part of P1036A. The information obtained in P1036B will help determine the acceptability of DOT in adolescents, as well as the logistics of providing such care, including cost. This information, combined with feedback on the chosen DOT model, obtained from a larger and more diverse population of adolescents in a companion protocol (P1036C), will help construct a more concrete model for providing DOT to this age group; this model will be included in the development of future studies with appropriate sample size that address the timing, duration and cost-effectiveness of DOT as part of a multiple strategy intervention to improve adherence to HIV medications in adolescents with demonstrated adherence problems.

A study overview is provided in Appendix II. Subjects who meet the entry criteria, and agree to participate in the DOT study, will have baseline evaluations and assessments, including a viral load and CD4 count, performed. Subjects will then receive eight weeks of DOT. In the first two weeks of the study, DOT will be provided every day for one dose of medication per day. Subjects who are on a twice-per-day regimen will self-administer their second dose. After the initial two weeks, DOT will be provided once-a-day, for five days a week, with the remaining doses being self-administered.
While on DOT, subjects will be provided with pagers to facilitate communication between the DOT facilitator and the subject, and to optimize the logistics of delivering DOT.

After completion of eight weeks of DOT (two in which DOT was provided daily, and six in which DOT was provided five days a week), a repeat viral load and CD4 count will be obtained, and the plan for further DOT will be decided based on the subject’s adherence to antiretrovirals over the past four weeks (directly observed and self-administered doses) and subject input. Clinic personnel will make assessments of adherence using information provided by the DOT facilitator. The site investigator will make a recommendation for the subject to either continue DOT according to the current schedule, or to reduce or escalate therapy, based on the subject’s level of adherence. The subject will have the option to either accept or refuse the investigator’s recommendation. The need for ongoing DOT will be revisited with the subject at monthly clinic visits. Subjects who feel comfortable switching to self-administered therapy will continue to be reassessed for the need for resuming DOT at every clinic visit. Total duration of the study will be 24 weeks.

There is no specified HAART regimen for this pilot study. Subjects will be given prescriptions by their primary care physicians for the most appropriate regimens, based on the standard of care. Whenever possible, a QD (daily) regimen is preferable. Changes in HAART regimen will be permitted during the trial, provided that the new regimen can be administered in either a QD or BID (twice daily) manner. Changes in regimen will be at the discretion of the primary care physician, following notification of the study team. At each DOT interaction, the DOT facilitator will bring a dose of medicine that he/she will observe the subject swallow, as well as doses for the subject to take unobserved prior to the next scheduled DOT interaction. The subject will also be provided with a five day emergency supply of medicine that is to be used in the case of an unforeseen event that precludes the subject’s ability to show up for a DOT interaction. If this occurs, the used doses from the emergency supply will be refilled at the next DOT interaction. It will be the subject’s responsibility to notify the DOT facilitator of any unforeseen events.

Self-reports, assessing symptoms of depression; hopelessness; emotional and behavioral problems; coping style; beliefs about medication; and perceived barriers to adherence, will be administered at baseline, after 12 weeks of DOT, and at the end of the study (24 weeks, or upon premature study withdrawal).

3.1 Site Selection

This protocol will be restricted to four clinical sites. All NIAID and NICHD PACTG sites may apply to conduct this study. Interested sites should complete the PACTG P1036B Site Application Form. Four sites will be selected by the PACTG P1036 team using the following criteria:
• Site availability of staff with experience in adolescent health care and psychosocial support staff who can address concerns identified on the depression and hopelessness self-reports.
• Site estimates of the scope and determinants of antiretroviral drug non-adherence in adolescents 16 to < 22 years of age.
• Brief description of site plans to recruit DOT facilitators, as described in section 1.2, if approved to participate in P1036B. Potential existing resources should be mentioned.
• Ability of the site to coordinate dispensing subject-specific medicine aliquots to the DOT facilitator, who will then take them to the subject.

Each of the above requirements will be equally weighted and a global assessment of each site based on the above criteria will be used to choose the final four.

A list of interested sites will be reviewed by the protocol team and four sites will be chosen to participate. Members of the team whose sites are under consideration will be excluded from the selection process. There is no preference given to sites which have already participated in P1036A.

Following site selection, a conference call will be scheduled to review the study process and to answer site questions. This call will include site personnel, the protocol chair, and the protocol psychologist. The DOT facilitators will be trained by site staff from the selected sites and supplemented by start-up conference calls led by the protocol chair.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 HIV-1-infected subjects 16 to < 22 years of age.

4.12 Subjects HIV-1-infected after the age of 12 years.

4.13 Subjects with a confirmed diagnosis of HIV-1 infection, defined as two positive assays from two different samples. Historical data may be used to determine HIV-1 infection. Source documentation must be available. Testing will be performed on site if no source documentation of previous tests is available. The two results may be in any combination of the following:

• at any age: DNA PCR, RNA PCR, or HIV culture; and/or
• Licensed ELISA with confirmatory Western Blot.
4.14 Parent or legal guardian is able and willing to provide informed consent (if requirement is not waived). Assent of the minor subject should be obtained where required.

4.15 Subjects who are either continuing, changing, or re-initiating a QD or BID HAART regimen and have demonstrated adherence problems (less than 85% of prescribed doses taken, as clinically disclosed, on two consecutive occasions, at least one month apart).

4.16 Female subjects who are sexually active and able to become pregnant who are using adequate birth control methods.

4.17 Subjects who have demonstrated an ability and willingness to swallow medication.

4.18 Subjects who, or sites that, have access to HAART therapy.

4.2 Exclusion Criteria

4.21 Subjects who are currently pregnant or breastfeeding.

4.22 Subjects who have any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the opinion of the investigator, would require a much closer follow-up and frequent monitoring (as compared to what would generally be done for any other HIV-infected patient of that age).

4.23 Subjects whose HAART regimens include medications that are taken more often than BID.

4.3 Allowed Medications

Subjects are allowed to receive approved antiretroviral agents, prophylaxis for opportunistic infections, and other medications required for acute or chronic medical conditions.

4.4 Disallowed Medications

Investigational agents (HAART or other medications) administered as part of other research protocols are not allowed while on this protocol.
4.5 Enrollment Procedures

Protocol registration for PACTG P1036B 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 entry. Once it has been determined that the subject may qualify for the protocol, the study details will be discussed, questions will be answered, and written informed consent and assent (where applicable) will be obtained from the subject, the parent, or the legal guardian before any study-related procedures are performed.

4.6 Co-enrollment Guidelines

Given the relatively short study duration, and a target population that has documented problems with adherence, the protocol team discourages co-enrollment with other research protocols. The protocol team must be notified, and approval obtained, prior to the subject enrolling into any other PACTG, AACTG, ATN, or pharmaceutical company-sponsored study. Subjects already on PACTG 219C will continue to remain on this protocol.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration, and Duration

Primary care physicians should select the most effective combination of antiretroviral agents for the individual subject, based on past medication history and/or genotyping. If possible, a once-daily regimen should be selected.

The current once-a-day regimens can include a choice from column A and a choice from column B. Literature to support some of these combinations is minimal; therefore, the current protocol does not recommend or endorse any specific combination or combinations.

<table>
<thead>
<tr>
<th>Column A – Combination NRTI</th>
<th>Column B – PI or NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddI + emtrictabine</td>
<td>efavirenz</td>
</tr>
<tr>
<td>ddI + lamivudine</td>
<td>nevirapine</td>
</tr>
<tr>
<td>abacavir + lamivudine</td>
<td>atazanavir + ritonavir</td>
</tr>
<tr>
<td>tenofovir + lamivudine</td>
<td>saquinavir/amprenavir</td>
</tr>
<tr>
<td>tenofovir + emtricitabine</td>
<td>fosamprenavir + ritonavir</td>
</tr>
<tr>
<td>ddI + abacavir</td>
<td></td>
</tr>
</tbody>
</table>

Standard BID regimens, as recommended by the Health and Human Services (HHS) Guidelines (http://www.aidsinfo.nih.gov/guidelines/), are also suggested.
5.2 Drug Supply, Distribution, and Pharmacy

There are no protocol-specified or supplied study drugs. Subjects will be given prescriptions by their primary care physicians for the most appropriate regimens, based on the standard of care, and subject medications will be provided, as per site specific resources and policy. Each site will describe its medication management plan to comply with the guidelines outlined in this protocol (section 6.115), applicable state laws, and site capability.

6.0 SUBJECT MANAGEMENT

In this study, the subject will receive initial and follow-up behavioral and laboratory assessments. All medical conditions are to be managed at the discretion of the site investigator/clinician. Severe or life-threatening HIV and non-HIV-related illnesses and hospitalizations should be reported to the team on study Case Report Forms (CRFs) at the time points specified in the Schedule of Evaluations (Appendix I). Any adverse events should also be reported to the Institutional Review Board (IRB), according to local IRB policies.

6.1 Study Management Plan

6.11 Pilot Study

This study will be offered to all HIV-infected patients (16 to < 22 years) who are either continuing, changing, or re-initiating their HAART regimens and have demonstrated adherence problems (less than 85% of prescribed doses taken, as clinically disclosed, on two consecutive occasions, at least one month apart). Subjects willing to participate in this study and meeting the eligibility criteria will be enrolled.

6.111 Selection and training of the DOT Facilitator

The ideal candidate would:

6.1111 Be a young adult, preferably ≥ five years older than the subject;

6.1112 Regardless of HIV status, be knowledgeable (or available for training) about HIV infection and its treatments, including side effects;

6.1113 Be skilled in interpersonal communication and be able to display empathy for the subject;
6.1114 Maintain a professional relationship and not invade the personal boundaries of the subject;

6.1115 Be someone selected from existing clinic staff with whom the adolescent is familiar. If this is not feasible, the adolescent should be provided with opportunities to meet with the DOT facilitator, to establish familiarity and build rapport, prior to initiating the DOT study; and

6.1116 Be trained in providing a link between the subject and his/her case manager, as a means of providing referral services for necessities and counseling, if needed.

It is recommended that the DOT facilitator only observe the subject as he/she takes his/her medication and not actually administer the medication. Institutional, local, and state regulations regarding the dispensing and administration of prescription drugs must be considered.

Sites will follow specific guidelines for training the DOT facilitator. An outline of these guidelines is provided in Appendix III; an accompanying training manual will also be provided.

6.112 Location for Administering DOT

6.1121 Within reasonable limits, and provided that the DOT facilitator does not perceive a threat to personal safety, the subject will select the location where DOT will be administered. The plans for the interaction should be flexible, both as to where it occurs (and allow for alternate meeting locations on different days) and what time of day (within reason, to accommodate drug schedules).

6.1122 Privacy is desired and should be considered in the selection of the location. Potential venues for administering DOT include the subject’s home, a restaurant, the mall, or some other location identified in the community. The subject can choose to receive DOT in the clinic on some, or all, of the days in which DOT is administered. Under
these circumstances, transportation, or basic reimbursement for transportation, will be provided.

6.113 Logistics of the DOT Interaction

Each subject will have his/her own pager for the duration of the study while he/she is on DOT. The DOT facilitator will be provided with a cell phone. Given the mobility of adolescents, this is a necessary expense in order to help facilitate communication with this subject population. After each DOT interaction, the DOT facilitator will set a time with the subject for the next DOT interaction. The DOT facilitator will page the subject 30-60 minutes prior to the meeting. The subject will be instructed to call back only if he/she requires a change in the time or location of the DOT interaction. Failure to receive a call back will imply that the DOT interaction will occur at the predetermined time. This will allow last minute changes in the schedule, if required, as well as decrease the chance of failed DOT interactions. While the DOT interaction should be scheduled, reasonable changes, if needed by the subject, will be allowed.

Note: DOT facilitators will not contact subjects except for scheduled visits or to answer calls/questions they receive from the DOT subjects during their working hours.

The subject will be allowed to call the DOT facilitator on his/her cell phone for DOT interaction-related questions during the working hours of the DOT facilitator. After his/her working hours, the DOT facilitator will have the option to turn off his/her cell phone, and the participant will be instructed to use the site’s regular channels of communication for triage of any questions that they may have. The DOT facilitator will meet with each subject once-per-day, with the number of days that DOT is administered being dependent on the study week. If a subject is on a BID regimen, the second dose of the regimen will be self-administered. For each DOT interaction, the DOT facilitator will bring a dose of medicine that is to be taken during that interaction, as well as the dose that the subject will be taking on his/her own (if on a BID regimen) prior to the next interaction. The subject will also be provided with a five day emergency
supply of medicine that is to be used in the case of an unforeseen event that precludes the subject’s ability to show up for a DOT interaction. If this occurs, the used doses from the emergency supply will be refilled at the next DOT interaction. It will be the subject’s responsibility to notify the DOT facilitator in the case of any unforeseen events. Pagers will be programmed for subjects to receive reminders for the unobserved doses using an internet-based medication reminder system. If a subject does not show up at the designated time and place for the DOT interaction, the DOT facilitator will wait at the pre-determined site for 15 minutes. After 15 minutes, the DOT facilitator will page the subject again and wait for an additional 15 minutes. If no contact is established, or the subject does not arrive within 30 minutes of the scheduled time, the DOT facilitator will record the event as a missed interaction. The following day, the DOT facilitator will page the subject to remind him/her, as usual, about his/her next visit 30-60 minutes prior to the interaction. If contact is established, the DOT facilitator will meet the subject at the designated time and place. In addition to administering DOT, the DOT facilitator will inquire about, and document, the reason for the missed interaction and keep a log of his/her notes on the subject. The DOT facilitator will utilize this information to work with the subject, in order to reduce missed interactions in the future. He/she will also provide feedback that can be used for the ongoing development of a stronger model to be used for providing DOT.

If the DOT facilitator is unable to contact the subject for the next DOT interaction, attempts will be made to contact him/her at his/her alternative contact telephone number. If no contact is established, a letter requesting that the subject contact the clinic will be mailed to his/her contact address. Incentives to adhere to DOT interactions may be provided at the site’s discretion. Information regarding the incentives will be collected in the P1036B Site Survey.

Each site will apply its routine policy to ensure that subjects are aware of their clinic visits and will follow up with those who have missed their scheduled visits. A window period
of plus two or minus one week(s) will be set up for each subject, to enhance scheduling flexibility for clinic visits.

6.114 Content of the DOT Interaction

A typical DOT facilitator-subject interaction will last approximately 15-20 minutes and will comprise of:

- Inquiring about the subject’s health, including medication side effects;
- Observing the subject swallow the dose of medication that is due at that time of the day;
- Inquiring about whether the subject has experienced any difficulties with the unobserved dose, obtaining an assessment of adherence, and identifying potential barriers to adherence; and
- Setting a time and place for the next DOT interaction within the guidelines regarding safety and appropriateness, as defined by the focus groups.

Following the DOT interaction, the DOT facilitator will triage any questions or concerns that came up during the course of this interaction and provide them to clinic staff. Any adverse events reported by the patient to the DOT facilitator will be triaged by the site staff to the social worker, clinician or others depending on the nature of the event reported. Appropriate follow-up based on the sites’ standard of care will then occur. This may involve telephone follow-up with the patient or a clinic visit. The DOT facilitator will keep a log of all interactions for each subject, including information on adherence to the unobserved doses. Additionally, at the time of study entry, each subject will be informed that the DOT facilitator can help facilitate actions to address problems related to housing, transportation, or food. Subjects will also be told that they can obtain condoms from the DOT facilitator if they choose to. This information will also be conveyed to subjects at every clinic visit. By doing this, the facilitator will be in a position to respond to subject requests regarding any of the above referenced matters, while not giving the impression of invading the subject’s privacy,
through detailed inquiries about the subject’s specific needs at every DOT interaction.

6.115 Medication Management While on DOT

This study requires the DOT facilitator to deliver enough medication for one directly observed dose and any other scheduled doses until the next DOT interaction. The DOT facilitator will act as a courier for delivering the medication. Additionally, the subject will be provided with a five day emergency supply of medication, to be used in cases of any unforeseen events and missed interactions/visits. This supply will be replenished, as needed. Please note that, beyond what is specified above, the subject does not maintain an “extra supply of medication.” This is to maximize the accountability of medications, optimize adherence to DOT interactions, and monitor adherence to the unobserved doses.

Operationalization of the above recommendations is left to individual sites to allow for modifications based on applicable state laws and site capabilities. This will involve defining the logistics of where the subjects’ medications will be stored, how they will be dispensed to the DOT facilitator, and maintenance of a drug accountability log. All of this information will be requested in the Site Application Form.

6.116 Continuation of DOT After the First Eight weeks

At week eight, and at each subsequent clinic study visit, a decision will be made about how the subject will continue DOT. The site investigator will make recommendations regarding the continuation of DOT based on the subject’s adherence to antiretroviral medication doses (directly observed and self-administered) over the previous four weeks. Adherence will be estimated at each DOT interaction, based on adherence to the DOT interactions, along with the subject’s self-report about the unobserved doses; this information will be recorded in the DOT facilitator log.

For convenience, adherence will be measured according to the following levels. Each level is determined based on subject adherence during the previous four weeks. Adherence levels are as follows:
- Adherence Level 1 - Adherence is greater than 93% (missing ≤ 2 days worth of medication in 4 weeks);

- Adherence Level 2 - Adherence is between 86% and 93% (missing > 2 and ≤ 4 days worth of medication in 4 weeks);

- Adherence Level 3 - Adherence is less than 86% (missing > 4 days of medication in 4 weeks).

Recommendations on DOT frequency will be based on level of adherence in the previous four weeks and will be determined at week eight, and at every subsequent visit. DOT frequencies are defined as follows:

- Frequency 1 - self-administered therapy
- Frequency 2 – DOT three days per week
- Frequency 3 – DOT five days per week
- Frequency 4 – DOT seven days per week

At week eight, and at each subsequent visit, if adherence is at level 1, it is recommended that the subject be weaned from DOT by moving down one frequency level (e.g., at week 8, if adherence is 96%, the subject should be weaned from Frequency 3 to Frequency 2). If adherence is at level 2, it is recommended that the subject maintain the same DOT frequency. Alternatively, if adherence is at level 3, it is recommended that the subject be escalated to the next (higher) frequency level of DOT (e.g., if the subject is at week 16 and is currently being administered DOT 3 days per week with adherence at 50%, it is recommended that the subject be increased to Frequency 3, which includes DOT 5 days per week).

The site investigator will make the recommendation regarding DOT frequency, with the final decision being made by the subject. Subjects who elect to discontinue DOT and begin self-administered therapy prematurely, will continue to be followed for the study duration. A subject
who discontinues DOT at week eight, or any subsequent visit, will be asked to fill out the Exit Survey Instrument (Appendix IV) and to return the pager.

6.2 Criteria for Taking a Subject off Study

Subjects will be taken off study early for the following reasons:

- The subject or legal guardian refuses further participation/observation and/or follow-up evaluations.
- The subject fails to comply with the study requirements, so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The subject declines to continue taking his/her HAART regimen.
- The subject is hospitalized for greater than two weeks while receiving DOT.
- The subject is found to be pregnant while receiving DOT.†
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.

†Subjects taken off study because of a diagnosis of pregnancy while receiving DOT will be replaced by an equal number of new accruals.

Note:

- Although pregnancy is an exclusion criterion for study entry and an off-study criterion for subjects who are receiving DOT, subjects who become pregnant after coming off DOT, while on study, can remain on study and will be followed as per the study schedule.
- For any subject taken off study because of a diagnosis of pregnancy while the patient was receiving DOT, the site will assess that subject’s dependency on DOT and develop a transition plan to help the patient wean off DOT and get the standard of care.
- Except for those subjects who meet the criteria to be taken off-study, subjects who are prematurely taken off DOT will remain “on-study” and continue to be followed, as per the study schedule. This will include participating in follow-up behavioral assessments.
• When a subject comes off-study early, reasonable attempts will be made to complete all of the assessments listed in Appendix I under “premature discontinuation.” The Exit Survey Instrument will be completed only in the case of premature discontinuation while the subject was receiving DOT.

6.3 Management of Subjects who are Hospitalized

Subjects will be temporarily taken off of DOT if hospitalized for less than two weeks while receiving DOT. After the subject is no longer hospitalized, DOT interactions and study visits will resume based on where the subject was on the study schedule, prior to hospitalization. Subjects hospitalized for greater than two weeks will be taken off-study.

6.4 Study Assessments and Evaluations

6.41 Adherence

Subject on DOT: While a subject is receiving DOT, information about adherence to the observed doses will be obtained from the DOT facilitator log. Additionally, at each DOT interaction, the DOT facilitator will inquire about the subject’s adherence to all unobserved doses since the last DOT interaction. This information should be elicited in a non-judgmental manner. Any potential barriers to adherence, identified in the process, will be addressed with the help of clinic staff. Since the primary objective of the study is to explore the feasibility of providing DOT to HIV-infected adolescents, as measured by adherence to DOT interactions, the provision for the DOT facilitator to elicit information about adherence to medication is unlikely to bias the study results. Adherence information will be shared with each subject by clinic staff. If a subject is found to be non-adherent, site personnel will also assess barriers to adherence and offer suggestions to overcome them, such as by using reminder watches, pill boxes, and scheduling the medication doses around the subject’s normal daily activity. Additional interventions to improve adherence will be documented, and accounted for, in the study analysis.

Subject no longer receiving DOT and on self-administered therapy: Monthly adherence will be measured, based on subject four-week recall. Additionally, at the last study visit (week 24), a pill count will be done to get an objective estimate of the subject’s adherence to medication during the last month of the study. Sites will have to make the necessary arrangements to facilitate the end of the study pill count, based on where the subject gets his/her prescriptions filled. For subjects who get prescriptions filled at outside pharmacies, information about the date the prescription was filled, the number of pills dispensed, and the day the
subject started using the medication will be obtained from the subject and the dispensing pharmacy. Additionally, the subject should be reminded that he/she has to bring medication bottles to the clinic for his/her last study visit. Despite all efforts, if a reliable pill count cannot be obtained at the last study visit, adherence will be calculated, based on subject four-week recall.

Adherence to psychotropic medications will be measured using monthly four-week recall throughout the study. Adherence to these medications will be kept in mind when reviewing the changes in the various behavioral assessments done as part of this study.

6.42 All Additional Assessments/Evaluation Tools

The following assessments will be administered at baseline (entry), 12, and 24 weeks, and at the time of (in the case of) premature discontinuation. All instruments, with the exception of the Beliefs About Medicine Scale and Patient Assessment Tool, are commercially available. All instruments, except for the Patient Assessment Tool - Part II (Appendix VI) will be administered in an interview format. In order to optimize patient response and maintain confidentiality, the Exit Survey Instrument (Appendix IV) will be administered by a site staff member who is not directly involved in the conduct of P1036B at that site. The Patient Assessment Tool - Part II (Appendix VI) should be filled out by the subject when possible, with confidentiality maintained. For a) those with reading difficulties; or for b) those that prefer that items be read to them, assistance from someone not part of the subject’s clinical care or study team is preferable.

6.421 Depression

Severity of depression experienced by each subject will be assessed using the Beck Depression Inventory – Second Edition (BDI-II, 1993) (39). This is a 21-point scale that is appropriate for children and adolescents ≥13 years of age. This instrument has shown a high content, construct, and factorial validity. Immediately following completion of all questionnaires, site staff will need to pay particular attention when reviewing the subject’s endorsement of item 9 regarding suicide.

Subjects who choose option 2 or 3 in item 9 of the BDI-II will require immediate follow-up with a social worker for further assessment of intent and severity; in this situation, appropriate
intervention, or referral, will be provided according to institutional guidelines.

6.422 Coping

Coping strategies related to medication adherence will be assessed using the Coping Responses Inventory (CRI), which includes separate Youth and Adult versions (40;41). The CRI-Youth questionnaire is appropriate for subjects 12 to < 18 years of age, and the CRI-Adult version is used for subjects who are ≥ 18 years of age. T scores are obtained for eight different subscales (see below) – each corresponding to a different coping style. Both of these scales have been well validated (40;41).

### 8 Coping Domains

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Approach Coping</th>
<th>Avoidance Coping</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Logical Analysis</td>
<td>5. Cognitive Avoidance</td>
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<tr>
<td>2. Positive Reappraisal</td>
<td>6. Acceptance or Resignation</td>
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<tr>
<td>Behavioral</td>
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<tr>
<td>4. Problem Solving</td>
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<td>8. Emotional Discharge</td>
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6.423 Hopelessness

Hopelessness will be measured using the Beck Hopelessness Scale (BHS) (42). The BHS is a 20-item self-report scale that measures degree of feeling hopeless in three domains: feelings about the future, loss of motivation, and expectation. The authors recommend that scores of 9 or more be assessed further clinically. The instrument is valid and reliable for ages ≥ 17 years, and is considered acceptable for use in research for adolescents as young as 13 years of age (42).

6.424 Emotional and Behavioral Problems

Emotional and behavioral problems will be assessed using the Youth Self-Report (YSR)/Adult Self-Report (ASR) (43;44). The YSR (ages 11 to ≤ 18 – for 18-year-olds who live with a parent/guardian) and ASR (ages ≥ 18 years – for 18-year-olds who live independently) are well-established measures of self-reported emotional and behavioral problems among adolescents and young adults. The YSR consists of 112 items and the ASR contains 126 items scored on a 3-point scale (0 = Not True, 1 = Sometimes True, 2 = Often True). Reliability and validity of each measure have
been demonstrated and are reported in the administration and scoring manuals (43;44). Each questionnaire is comprised of internalizing and externalizing scales and clinical subscales (see below). Numerous studies have found strong relationships between mood disorders and medical adherence, as well as maladaptive coping (i.e. aggression/acting out, and rumination/inattention) and adherence among chronically ill adolescents and adults, including, but not limited to, persons infected with HIV (45-48).

Scales:

Both: Internalizing Symptoms
Externalizing Symptoms
Total Problems

ASR: Anxious/Depressed            YSR: Anxious/Depressed
Withdwon                            Withdrawn
Somatic Complaints                   Somatic Complaints
Thought Problems                       Thought Problems
Attention Problems                    Attention Problems
Aggressive Behavior                  Aggressive Behavior
Rule-Breaking Behavior               Delinquent Behavior
Intrusive Thoughts/Behavior          Social Problems

ASR Diagnostic and Statistical Manual (DSM)-oriented scales:
Depressive Problems; Anxiety Problems; Somatic Problems;
Avoidant Personality Problems; Attention Deficit/Hyperactivity Problems; and Antisocial Personality Problems.

6.425 Perceived Barriers to Adherence

Perceived barriers to adherence will be assessed using the instrument included in Appendix V (the Patient Assessment Tool, which is being used with permission from the ATN 023B team) and the Beliefs About Medicine Scale (2002) (Appendix VIII) (49), which is provided for this study with the author’s permission. Given the potential impact of certain high risk behaviors, such as substance abuse, on the subject’s ability to adhere to treatment, some relevant information will be collected using the Patient Assessment Tool – Part II, included in Appendix VI.
6.426 Exit Survey Instrument

Subject feedback will be obtained when a participant completes the prescribed course of DOT or elects to discontinue DOT prematurely using the Exit Survey Instrument included in Appendix IV.

7.0 EXPEDITED ADVERSE EVENTS (EAE) REPORTING

This study uses the targeted level of expedited AE reporting as defined in the DAIDS EAE Manual. This pilot study involves a behavioral intervention and does not have any specified “study drugs”. The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual), dated May 6, 2004. AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form). The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December, 2004 must be used for grading toxicities. The above-referenced DAIDS EAE Manual, the EAE Reporting Form, and the DAIDS Table for Grading Adverse Events are all available on the RCC website at http://rcc.tech-res-intl.com/.

AEs must be reported on an expedited basis at the TARGETED LEVEL during the Protocol-defined EAE Reporting Period, which is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

Additionally, sites should consult with their IRBs on local reporting requirements, if any. Adverse drug events that are severe, life-threatening, or lead to hospitalization or death should be reported by the investigator directly to the FDA through the MedWatch system.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

P1036B is a pilot study to determine the feasibility of administering DOT in an adolescent population which has demonstrated adherence difficulties. Results of this study will be used to plan future studies with appropriate sample size that address the timing, duration and cost-effectiveness of DOT as part of a multiple strategy intervention to improve adherence to HIV medications in patients with known adherence problems. A total of 24 subjects, from four different sites, will
be enrolled in this pilot study. Accrual will be stratified by site, with four to eight subjects from each of the four sites.

Since there is no precedent for a structured DOT intervention for HIV-infected adolescents, this study will primarily focus on assessing the feasibility of DOT, rather than on an evaluation of its effectiveness. This study will provide moderate precision to estimate the true percentage of study subjects who are adherent to DOT interactions. The adherence proportion is likely to be estimated within +/- 22%. It is anticipated that a full evaluation of this intervention in future studies with sufficient sample size will address more than one domain including, but perhaps not limited to, adherence to the DOT interaction, adherence to medication during the weaning periods, impact on virologic and immunologic parameters, improvement in self-efficacy, and a decrease in mental health problems.

8.2 Outcome Measures

8.21 Primary Outcome Measures

The primary outcome is the subject’s adherence to the prescribed DOT intervention, as measured by:

- The proportion of completed DOT facilitator-subject interactions, among all scheduled interactions, for each subject during the second four-week period on study; and

- The number and proportion of subjects who were able to complete the recommended duration of DOT.

8.22 Secondary Outcome Measures

The following secondary outcome measures for enrolled subjects will be used to address the secondary objectives:

- Subject satisfaction with DOT will be assessed using the Exit Survey Instrument (Appendix IV).

- Cost of implementing DOT per subject will be evaluated.

- The effective ratio of DOT facilitators to subjects will be determined by the calculation of the actual time spent by the DOT facilitator. This includes transportation, time required to contact and track subjects, and the actual DOT interaction.
• Reproducibility of DOT implementation across sites will be evaluated. Subjects’ adherence to DOT interactions and ability to complete the prescribed duration of DOT will be compared across sites.

• Adherence for each subject will be categorized as > 93%, 86-93%, and < 86% of all medicine in the four-week period prior to a study visit; this will be determined at weeks 8 and 12 by subject self-report and adherence to DOT interactions; and by pill count and subject four-week recall at week 24.

• Virologic outcomes will be defined by the suppression of HIV-1 RNA to:
  o > 1.5 log decrease from baseline at weeks 8, 12, and 24;
  o < 400 copies at week 8, 12, and 24; and
  o change in HIV-1 RNA copy number from baseline to week 24.

• Immunologic outcome will be defined by a change in absolute CD4 count from baseline to week 24.

• Self-efficacy (confidence) will be assessed using responses obtained from the Patient Assessment Tool – Part I (Appendix V) and Beliefs About Medicine Scale (Appendix VIII).

• Beliefs about HAART will be assessed using the Beliefs About Medicine Scale (Appendix VIII). Scores will be reported in terms of the four identified subscales: *Perceived Threat (13 items) *Positive Outcome Expectancy (20 items) *Negative Outcome Expectancy (13 items) *Intent (7 items)

• Severity of depression experienced by each subject will be assessed using the BDI-II (39). Scores will be interpreted according to manual guidelines.

• Hopelessness will be measured using the BHS (42). Scores obtained on the BHS will be interpreted according to manual guidelines.

• Emotional and behavioral problems will be assessed using the YSR/ASR (43;44). Scores will be interpreted according to manual guidelines utilizing transformed T-scores, with a mean of 50 and standard deviation of 10. Scores 65-69 will fall in the borderline
clinical range; and Scores ≤70 will fall in the clinically significant range.

- Coping of each subject will be assessed using the CRI-Youth and CRI-Adult (40;41). Scores will be interpreted according to manual guidelines using transformed T-Scores with a mean of 50 and a standard deviation of 10.

- Perceived barriers to adherence will be assessed at baseline, week 12, and at week 24 using the instrument included in Appendix V (Patient Assessment Tool – Part I) and the Beliefs About Medication Scale (2002) (Appendix VIII).

- Substance abuse will be assessed, while maintaining confidentiality, at baseline, week 12, and at week 24 using the instrument included in Appendix VI (Patient Assessment Tool – Part II).

- Sustainability of DOT benefits will be assessed as the proportion of subjects adherent at week 24 (defined as > 93% adherence to medication over the past 4 weeks) among those who successfully complete the first eight weeks of DOT, and are taken off DOT at 12 weeks.

8.3 Randomization and Stratification

8.31 Randomization

There is no randomized assignment of treatments in this study.

8.32 Stratification

Four to eight subjects will be enrolled at each of the four sites. This stratification is for analysis purposes only.

8.4 Sample Size and Accrual

8.41 A total of 24 subjects, from four different sites in the U.S. (4-8 subjects from each site), is deemed by the protocol team to be an appropriate number of subjects in order to meet study objectives. Choosing four different sites will have the advantage of allowing the protocol team to observe the applicability of the DOT model in subject populations with differing risk factors and barriers to adherence. It will also provide some information on the logistics of introducing the DOT concept in locations
with different infrastructures and resources. A total of 24 subjects was chosen so that, if all 24 subjects successfully complete the prescribed duration of DOT (including a gradual weaning of DOT), the lower bound of the two-sided 95% confidence interval (CI) for the true success rate will be over 85%.

Subjects taken off study because of a diagnosis of pregnancy while receiving DOT will be replaced by an equal number of new accruals.

The following table shows the 95% CI for the true percentage of subjects successfully completing the prescribed 12 weeks of DOT (includes a gradual weaning of DOT) for given numbers of subjects observed to succeed. The first column, labeled “Sample Rate” refers to the number of subjects (out of 24) successfully completing 12 weeks of DOT.

**TABLE 1: True Proportion of Subjects Successfully Completing the Total 12 Weeks of DOT for Given Numbers of Successes Observed**

<table>
<thead>
<tr>
<th>Sample Rate (number of successes observed/number of subjects in study)</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>24/24</td>
<td>0.8575</td>
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<tr>
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<td>0.0103</td>
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<tr>
<td>0/24</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

The percentage of subjects successfully completing 12 weeks of DOT (including a gradual weaning of DOT) is likely to be estimated within +/- 22%.
8.42 Accrual

Accrual for this study is expected to be completed within six months.

8.5 Monitoring

8.51 Routine Monitoring

A monitoring plan will be developed for the 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 the team will review, and what the timing of such routine reviews will be. Monthly conference calls will be held by the study team to assess accrual, losses to follow-up, completeness of data collection, and timely and appropriate referrals in the case of mental health problems. More extensive monitoring reports may be produced, if deemed necessary by the study team, as indicated by team assessment of monthly reports.

8.52 Interim Analysis

There will be no interim analysis.

8.6 Analysis

8.61 Analysis for Primary Outcome Measure

Analysis for the primary outcome measures include:

- Tabulating the proportions of completed DOT facilitator-subject interactions for all subjects; and

- Calculating the number and proportion of subjects able to adhere to the prescribed course of DOT (including the weaning from DOT, based on adherence to medication). An exact 95% CI will be calculated to show the precision of the estimated proportion.

In addition to analyzing all subjects together we will summarize the primary outcomes separately for subjects starting new therapies and those continuing on existing ones.
8.62 Analysis for Secondary Outcome Measures

- Subject satisfaction with DOT: results of the Exit Survey Instrument (Appendix IV) will be tabulated. Responses to open-ended questions will be reviewed using exploratory analysis for qualitative data.

- Cost of implementing DOT will be estimated.

- Effective ratio of DOT facilitators to subjects will be determined by the calculation of actual time spent by the DOT facilitator. This includes transportation, time required to contact and track subjects, and the actual DOT interaction.

- Reproducibility of DOT implementation across sites will be assessed. Subjects’ adherence to DOT interactions, and ability to complete the prescribed duration of DOT, will be compared across sites. Given the sample size, this analysis will be exploratory.

- Adherence: the proportion of subjects with adherence > 93%, 86-93%, and < 86% will be estimated with the respective CI calculated using the exact method.

- The number and proportion of subjects with a > 1.5 log decrease in HIV RNA, as compared to baseline, and those achieving suppression of HIV-1 RNA to <400 and <50 copies/mL at weeks 8, 12, and 24 will be calculated. Exact CIs will be calculated to show the precision of the estimated proportions.

- Change in absolute CD4 count and logarithmic HIV-1 RNA copy from baseline will be described at both weeks 12 and 24.

- Responses related to self-efficacy will be tabulated. Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.

- Severity of depression scores at baseline, week 12, and week 24 will be tabulated. Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.

- Hopelessness scores at baseline, week 12, and week 24 will be tabulated. Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.
• Self-report of behavioral and emotional problems will be tabulated at baseline, week 12, and week 24. Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.

• Coping scores at baseline, week 12, and week 24 will be tabulated. Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.

• Perceived barriers to adherence and the Beliefs About Medication Scale (2002) will be assessed at baseline, week 12, and at the end of the study using the instruments included in Appendices V (Patient Assessment Tool – Part I) and VIII (Beliefs About Medicine Scale). Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.

• Substance abuse will be assessed at baseline, week 12, and week 24 using the instrument included in Appendix VI (Patient Assessment Tool – Part II). Descriptive statistics will be presented. Week 12 and week 24 assessments will be compared with baseline values using the Wilcoxon test.

• Logistic regression will be used to correlate adherence with depression, coping, hopelessness, and beliefs about medication, controlling for the occurrence of severe incident illness.

• Sustainability: the proportion of subjects adherent at week 24 (defined as > 93% adherence to medications over the past 4 weeks) among those who successfully complete the first eight weeks of DOT, and are taken off DOT at 12 weeks, will be estimated with a CI calculated using the exact method.

• Duration of initial and subsequent DOT cycles will be tabulated.

Objectives 1, 2, and 3 involve descriptive analysis and will be achieved as part of this pilot study. Objectives 4 to 9 involve exploratory analysis that will be informative but less likely to be statistically significant. Additionally, some information that will be useful for power and sample size calculations for future DOT related clinical trials will be obtained from such exploratory analysis.
9.0 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.

9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent document (Appendix XII), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee (EC) responsible for the oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age, unless waived by the reviewing IRB). The subject's assent must also be obtained. 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 subject (or parent or legal guardian).

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45 – Public Welfare, Part 46 – Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR resigns the consent. The plan should follow all IRB, local, and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

Parental Permission

The study team is requesting the waiver of parental permission for minor participation based on 45 CFR 46.408, which provides that the IRB may waive parental permission under the same circumstances that it may waive individual consent, as described in 45 CFR 46.116 (d): (1) the research involves no more than minimal risk to subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. This research clearly meets requirements 1 & 2. Since many HIV positive adolescents access medical care services independently of parental involvement, the requirement to involve parents may adversely affect the minor’s decision to participate and thereby potentially bias the sample.
9.2 Subject Confidentiality

All laboratory specimens, 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 from the subject, except as necessary for monitoring by the NIAID, IRB or the Office of Human Research Protection (OHRP).

9.3 Study Discontinuation

The study may be discontinued at any time by the IRB, NIAID, PACTG, or the Office of Human Research Protection (OHRP).

10.0 PUBLICATION OF RESEARCH FINDINGS

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

11.0 BIOHAZARD 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 shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

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


49. Reikert KA, Drotar D. Beliefs about medicine scale: Development, reliability and validity. Journal of Clinical Psychology in Medical Settings 2002;177-84.
APPENDIX I

SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Entry&lt;sup&gt;9&lt;/sup&gt;</th>
<th>*On Study Week/Visit&lt;sup&gt;10&lt;/sup&gt;</th>
<th>Premature Discontinuation&lt;sup&gt;11&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>Informed Consent</td>
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<td></td>
<td>4 8 12 16 20 24</td>
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</tr>
<tr>
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<td>X</td>
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</tr>
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<td>Patient Assessment Tool – Part I</td>
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<td>Beck Depression Inventory - II</td>
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<tr>
<td>Beck Hopelessness Scale</td>
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<tr>
<td>Coping Responses Inventory</td>
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<tr>
<td>Beta HCG (urine)&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td>HIV RNA</td>
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<td>5mL 5mL 5mL</td>
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<td>Lymphocyte subsets (CD4)</td>
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<td>CBC&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>TOTAL BLOOD VOLUME (ml)</td>
<td>11mL</td>
<td>5mL</td>
<td>11mL 11mL</td>
<td>11mL 11mL</td>
</tr>
</tbody>
</table>
*DOT will be administered for eight weeks for subjects who meet study entry criteria and have completed all baseline evaluations and assessments. In the first two weeks of the study, DOT will be provided every day for one dose of medication per day (subjects who are on a twice-per-day regimen will self-administer their second dose). After the initial two weeks, DOT will be provided once a day, for five days a week, with the remaining doses being self-administered. After completion of eight weeks of DOT, the plan for further DOT will be decided, based on the subject’s adherence to antiretrovirals over the past four weeks (directly observed and self-administered doses) and subject input.

1. History – a. Demographic information (refer to the Supplemental Demographics form);  b. History of current and previous HIV-related diagnoses, severe or life threatening non-HIV related illnesses, mental health illnesses, and moderate or worse, chronic, non-HIV-related diagnoses (e.g. diabetes); c. History of current and previous antiretroviral and psychotropic medications.

2. Behavioral Assessments - Administration of Patient Assessment Tools (Appendix V and Appendix VI), Beliefs About Medication Scale (Appendix VIII), Beck Depression Inventory – II (BDI-II), Beck Hopelessness Scale (BHS), Coping Responses Inventory (CRI) and Youth Self-Report (YSR)/Adult Self-Report (ASR). All instruments, except for the Patient Assessment Tool – Part II, will be administered in an interview format. The Patient Assessment Tool – Part II should be filled out by the subject, with confidentiality maintained. For those with reading difficulties, or who prefer that items be read to them, assistance should be provided by someone not part of the subject’s clinical care or study team, if possible.

3. Adherence – Adherence to antiretroviral medications and psychotropic medications will be assessed using the four-week recall at study entry and monthly clinic visits. Adolescent Adherence Module II will be administered whenever a history of missed medications is obtained on the four-week recall. Adherence based on pill count will be estimated at the end of study visit (week 24) or at premature discontinuation.

4. Exit Survey Instrument (Appendix IV) - This will be administered in an interview format when the subject successfully completes the prescribed course of DOT or elects to discontinue DOT.

5. Documentation of Support Services (Appendix X) – This will include information elicited from the subject by the social worker.

6. Additional urine/serum pregnancy test should be obtained at any time during the study if pregnancy is suspected.

7. Lymphocyte subsets can be performed locally in a CLIA accredited laboratory. Only absolute and percent CD4 count are required.

8. CBC includes WBC, differential, and platelet count and/or other hematology indices required by clinicians.

9. Screening and entry can be done on the same day, or within a maximum of two weeks. DOT should be initiated within seven days of the entry visit.

10. The window period for study visits are plus two weeks or minus one week. If the subject comes to the clinic beyond two weeks after the scheduled study visit, the protocol team should be contacted to determine if a study visit can be performed.

11. In the case of premature discontinuation, subjects will be asked to complete all of the assessments listed in this column at one final study visit. The Exit Survey Instrument will be completed only in the case of premature discontinuation while the subject was receiving DOT.
APPENDIX II – STUDY OVERVIEW

Patient meets inclusion criteria and is willing to participate in the study.

Informed consent. Pregnancy screen where applicable.

Baseline assessments done at entry visit. Plans to coordinate site-based medication dispensing to the subject are made.

Directly Observed Therapy (i.e. ONE observed dose a day [DOT]) provided seven days a week for two weeks.

Frequency of DOT reduced to five days a week for six weeks.

Week 8 clinical and behavioral assessments completed. Adherence Level (adherence over the past 4 weeks) assessed at week 8 clinic visit and frequency of DOT recommended as shown. Decision to accept or not accept DOT recommendation is left to the subject.
Adherence Level 1 (> 93%) – Frequency 1 (i.e., DOT 3 days a week)
Adherence Level 2 (86-93%) – Frequency 2 (i.e., DOT 5 days a week)
Adherence Level 3 (< 86%) – Frequency 3 (i.e., DOT 7 days a week)

Week 12 clinical and behavioral assessments completed. Adherence Level assessed at week 12 and at each subsequent monthly clinic visit and frequency of DOT adjusted as shown. Subject preference is respected. Decision to accept or not accept DOT recommendation is left to the subject.
Adherence Level 1 – Reduce frequency of DOT. Those already on Frequency 1 stop DOT and start self-administered therapy.
Adherence Level 2 – Keep same frequency of DOT as the past four weeks.
Adherence Level 3 – Increase frequency of DOT by one level (i.e., those on frequency 2 go to frequency 3).

Reevaluate adherence level and frequency of DOT every four weeks.

Week 24 end of study clinical and behavioral assessments completed.
APPENDIX III

Guidelines for DOT Facilitators

I. Overview: Directly Observed Therapy (DOT) has been used successfully to deliver therapy for tuberculosis (TB) and has been evaluated with HIV-infected adults. This protocol will examine the feasibility of providing DOT to HIV-infected adolescents. The frequent subject contacts in a community setting may result in potential problems for the DOT facilitator and the study team. The additional complexity of clinical research with adolescents demands that there are adequate training and safety procedures in place for the DOT facilitators.

II. Preparation: For discussion of the required characteristics of the DOT facilitators, please see section 6.111 of the protocol.

a. Training of DOT Facilitators: DOT facilitators should undergo a formal orientation, prior to initiating any fieldwork. It is preferred that they have some outreach experience and are comfortable in the field setting. Training/discussions should be in the following main areas:

i. HIV Training:
   1. DOT facilitators should have basic training in HIV pathogenesis.
   2. DOT facilitators should have additional training in medications used to treat HIV and their common side effects.
   3. DOT facilitators should be trained in complications of HIV and STD’s.
   4. DOT facilitators should understand the rules regarding state medication assistance programs.
   5. DOT facilitators should have training in infection control.

ii. Understanding DOT – DOT facilitators should have an understanding of the following:
   1. Adherence;
   2. Definition of DOT;
   3. Case management;
   4. Barriers to completion of therapy;
   5. Building rapport and communicating effectively;
   6. How to ensure that the subject swallows the observed dose; and
   7. Patient education.
iii. Cultural Competency – DOT facilitators must be able to:

1.8. Address a variety of cultural issues (youth, race/ethnicity, sexual identity) and foster respect and acceptance towards all persons;
2.9. Understand cultural norms and biases, and the effect these may have on people’s decision making; and
3.10. Discuss cultural differences in beliefs towards medication and western medicine.

iv.iii. Logistics of Providing DOT in P1036B – DOT facilitators should:
2. Review the procedures for handling subject medications.
3. Review charting and reporting procedures, including documentation in the DOT facilitator log.

v.iv. Research- DOT facilitators should understand/have knowledge of:
1. General topics, including human subjects training, understanding the importance of following the protocol, basic research terminology, integrity of data, parental waiver, confidentiality, and HIPAA.
2. Specific training in protocol delivery and documentation.

vi.v. Legal Issues – DOT facilitators should:
1. Review and understand the state regulations regarding HIV, confidentiality, partner notification, etc.;
2. Understand the state regulations and their obligations regarding child abuse and domestic violence;
3. Review the state laws surrounding minors, emancipated minors and rights to seek medical care; and
4. Review the legal boundaries of outreach workers; Outreach workers cannot dispense medications and should not attempt to diagnose or treat medical problems.

vii.vi. Safety Issues - DOT facilitators should:
1. Review the planning process, prior to going in the field;
2. Review emergency procedures;
APPENDIX III (Cont.)

3. Discuss the boundaries of the DOT facilitator/subject relationship; and
4. Review general safety procedures (see below).

Community/Programmatic Resources:
1. DOT facilitators should spend time with case managers and social workers on the team to understand the importance of their role. They should be trained in communicating back to the case manager when the subject requests assistance or would like to discuss issues and concerns.
2. DOT facilitators should be introduced to other outreach workers who may be a source of information and support.
3. Social workers can increase the DOT facilitator’s awareness of available resources within the community, including food banks, state and county offices, mental health facilities, and job training.

Practical Training - DOT facilitators should:
1. Participate in a conference call with experienced HIV DOT facilitators at other sites; and
2. Arrange to spend at least a week accompanying an experienced community outreach worker, such as a case manager or a TB DOT worker, if they have minimal field experience.

III. Supplies: DOT facilitators should be supplied with a cell phone, maps of the areas that they are visiting, appropriate study forms, and a list of emergency contacts.

Safety procedures for DOT Facilitators

These guidelines are meant to help guide DOT facilitators through their professional interaction with subjects and with their behavior in the community.

Before each DOT interaction, DOT facilitators should:

- Know where they are going to meet the DOT subject. If they are unfamiliar with the area, they should ask their supervisor, or another outreach worker, to help them with directions and to assess the safety of the area;
- Be sure that their supervisor, or someone in the office, knows their itinerary for the day;
APPENDIX III (Cont.)

- Be sure that their cell phone is charged and that they bring all necessary forms or equipment. They should always have emergency numbers available, such as the home office number, and number for the police department. They should be reachable at all times;

- Carry official picture identification (I.D.) at all times; I.D. should include the name of their organization, their name, and their title; and

- Not look “too professional” or wear flashy clothing and/or expensive jewelry that may call attention to themselves.

When at a DOT interaction, DOT facilitators should:

- Be sure to assess the entrances and exits of the home or private area. They should also beware of dogs that may be aggressive;

- Choose an area where privacy can be ensured, however, safety is a priority. They should leave the area if there is perceived or actual tension or violence, or for any other reason that the area may be (or feel) unsafe;

- Avoid any confrontations and/or debates with the DOT subject or other companions;

- Not lend money to a DOT subject;

- Not become too personal with a DOT subject and share secrets, etc.;

- Not drink alcoholic beverages or buy, receive, or sample drugs while at a DOT interaction; and

- Not attempt to diagnose a DOT subject who has symptoms, or administer medical care; in a case like this, subjects should be referred to the clinic.
APPENDIX IV

EXIT SURVEY INSTRUMENT

Introductory remarks (read to the participant by the interviewer):

As you are aware, you have been receiving Directly Observed Therapy (DOT). This therapy has been designed to help people who have difficulty taking all of their medicine. We would like to understand your experience with directly observed therapy. Your honest opinion about your experience will be incredibly helpful for researchers to think of ways to improve care for patients in the future. YOUR RESPONSES ARE CONFIDENTIAL and are not read by anyone in the clinic. Thank you so much for your help.

Beginning of Questionnaire:

Thinking about your experience with DOT, can you complete the following statements:

1a. Choosing a place to meet the DOT facilitator was ____________________?

1 2 3 4 5
Very difficult Difficult Don’t Know Easy Very Easy

1b. Can you explain why this was (difficult or easy)? Room for open-ended response

2a. Remembering to meet the DOT facilitator was ________________?

1 2 3 4 5
Very difficult Difficult Don’t Know Easy Very Easy

2b. Can you explain why this was (difficult or easy)? Room for open-ended response
APPENDIX IV (Cont)

3a. Being paged made remembering to meet the DOT facilitator ____________?

1  2  3  4  5
Very difficult  Difficult  Don’t Know  Easy  Very Easy

3b. Can you explain why this was (difficult or easy)? *Room for open-ended response*

4a. Choosing a place where I felt comfortable meeting the DOT facilitator was _______?

1  2  3  4  5
Very difficult  Difficult  Don’t Know  Easy  Very Easy

4b. Can you explain why this was (difficult or easy)? *Room for open-ended response*

5a. Meeting with the DOT facilitator at the place I chose was _________________?

1  2  3  4  5
Very difficult  Difficult  Don’t Know  Easy  Very Easy

5b. Can you explain why this was (difficult or easy)? *Room for open-ended response*

6a. Taking the medicine in front of the DOT facilitator was ____________________?

1  2  3  4  5
Very difficult  Difficult  Don’t Know  Easy  Very Easy
6b. Can you explain why this was (difficult or easy)? *Room for open-ended response*

7a. Talking to the DOT facilitator about how well I took my medicine was 
___________________________?

1) Very difficult  2) Difficult  3) Don’t Know  4) Easy  5) Very Easy

7b. Can you explain why this was (difficult or easy)? *Room for open-ended response*

*These questions are about how DOT affected you.*

8a. Did participation in DOT change your motivation to taking the medication?
1) No
2) Yes

8b. How did your motivation change?

1) Less motivated to take medication  2) No change  3) More motivated to take medication

9a. Did participation in DOT change how regularly you take the medications?
1) No
2) Yes

9b. How did you change?

1) Took medicine less regularly  2) No change  3) Took medicine more regularly
APPENDIX IV (Cont)

10a. Would you recommend DOT to a friend who was having problems taking HIV medications regularly?
1) No
2) Yes

10b. Why (would or wouldn’t) you recommend DOT? *Room for open-ended response*

11a. Did the DOT facilitator help you in other ways besides taking your medicine regularly? Examples of “other ways” includes “provided support, provided encouragement, was someone I could talk to, etc."
1) No
2) Yes

11b. If Yes, please tell us how the DOT facilitator was helpful or not helpful? *Room for open-ended response*

12. Should DOT be offered to anyone who is having problems taking HIV medications?
1) No
2) Yes

13a. Was it helpful to gradually reduce the frequency of DOT from 5 days a week DOT to 3 days a week DOT before completely stopping it?
1) No
2) Yes

13b. In what ways was this gradual reduction helpful or not helpful? *Room for open-ended response*

14a. When DOT ended did you feel sad or let down about DOT ending?
1) No
2) Yes
APPENDIX IV (Cont)

14b. Can you explain more? *Room for open-ended response*

15a. When DOT ended will you miss seeing the DOT facilitator?
1) No
2) Yes

15b. Can you explain more? *Room for open-ended response*

16. If you had the choice would you like to continue or restart DOT?
1) No
2) Yes

17a. What did you like about DOT? *Room for open-ended response*

17b. What did you dislike about DOT? *Room for open-ended response*

18. Tell us how we can improve DOT. *Room for open-ended response*
APPENDIX V

PATIENT ASSESSMENT TOOL – Part I

(This instrument has been obtained from the ATN 023 team and modified to include questions regarding high risk behaviors)

Instructions to the Interviewer
1. Read each statement/question to the subject. Record the subject's response in the box next to, or below, the statement/question; or by checking the Yes or No box.
2. For questions 1 and 2, show the corresponding laminated “Likert Scale” card to the subject.

1. I am going to read a list of situations that could occur during your treatment. Please indicate how confident you are that you can do each of the following using the scale from 0 to 10, with 0 being "Not At All Confident" and 10 being "Completely Confident".

<table>
<thead>
<tr>
<th>Not At all Confident</th>
<th>Moderately Confident</th>
<th>Completely Confident</th>
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<tbody>
<tr>
<td>0</td>
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<td>8</td>
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<td>9</td>
<td>10</td>
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How confident are you that you can:

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>SUBJECT RESPONSE (0-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Stick to taking your medicine even when side effects begin to interfere with daily activities?</td>
<td>☐</td>
</tr>
<tr>
<td>b) Make taking your medication part of your daily routine?</td>
<td>☐</td>
</tr>
<tr>
<td>c) Take your medication even when it means taking medication in front of people who don't know you are HIV-infected?</td>
<td>☐</td>
</tr>
<tr>
<td>d) Stick to taking your medication even when your daily routine is disrupted?</td>
<td>☐</td>
</tr>
<tr>
<td>e) Stick to taking your medication even if you aren't feeling well?</td>
<td>☐</td>
</tr>
<tr>
<td>f) Stick to taking your medication when it means changing your eating habits?</td>
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APPENDIX V (Cont.)

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<tr>
<td>g) Continue to take your medication even when you are not sure that it is working?</td>
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<tr>
<td>h) Continue to take your medication even when getting to your clinic appointments is a major hassle?</td>
<td></td>
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<tr>
<td>i) Continue to take your medicine even when your family does not support you?</td>
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<tr>
<td>j) Continue to take your medicine even when you are dealing with family problems? <em>(Family problems could be anything that the subject thinks is a problem.</em>)</td>
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</table>

2. For the following statements, please tell me how much you agree or disagree with what is being said, with 1 being “Strongly Disagree” and 5 being “Strongly Agree”.

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>SUBJECT RESPONSE (1-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) If I take my antiretroviral medication as prescribed, it will help me stay well.</td>
<td></td>
</tr>
<tr>
<td>b) If I take my antiretroviral medication as prescribed, the medication might do more harm than good.</td>
<td></td>
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<tr>
<td>c) If I take my antiretroviral medication as prescribed, then I will experience troublesome side effects.</td>
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<tr>
<td>d) If I take my antiretroviral medication as prescribed, then I feel depressed about being HIV-infected.</td>
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<tr>
<td>e) If I do not take my antiretroviral medication as prescribed, my body will develop resistance to HIV medications.</td>
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<tr>
<td>f) Having a positive outlook about my HIV infection is more important to my health outcome than taking my antiretroviral medication.</td>
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<tr>
<td>g) If I feel healthy, then I don't need to take antiretroviral medication even if my doctor says I should.</td>
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</table>
APPENDIX V (Cont.)

3. Do you face any of the following problems that make it difficult for you to take your HIV medication?

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>SUBJECT RESPONSE</th>
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</thead>
<tbody>
<tr>
<td>a) Do you always have someplace to sleep at night?</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>b) Do you have problems with medical insurance? (Explain as needed “Medical insurance is a way to pay for your medical visits, your blood tests, and your medication”.)</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>c) Do you have problems with transportation to pick up your medicine?</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>d) Do you have problems with transportation to get to the clinic for your visit with your primary care provider?</td>
<td>□ Yes □ No</td>
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<tr>
<td>e) Do you have problems getting your medication prescriptions filled? (Give the following examples as needed: “There’s a problem with your medical insurance, the pharmacy ran out of the medication, or the pharmacy did not have the dose your doctor prescribed”.)</td>
<td>□ Yes □ No</td>
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<tr>
<td>f) Do you have problems related to your job or your school?</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>g) Do you have problems dealing with your family or taking care of your children, either your own or someone else’s children?</td>
<td>□ Yes □ No</td>
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Interviewer: 
Date:
APPENDIX VI

PATIENT ASSESSMENT TOOL – Part II

The information you provide below is CONFIDENTIAL and the clinic staff will not see it. This information will be helpful in understanding how Directly Observed Therapy (DOT) helps patients. Please put the completed form in the envelope provided, and seal it, after you have completed filling out the information. Your honest opinion is very important.

1. During the past 30 days, how often have you had 5 or more drinks of alcohol (e.g. beer, wine, wine coolers, malt liquor, or liquor) in a row over 2-4 hours?

   Daily  Nearly  3 or 4 Times  One or Two  Once  Never
   every day  a Week  Times a Week  a Month

2. In the past 30 days, how often have you used the following (please circle the frequency):

2a. Marijuana?

   Daily  Nearly  3 or 4 Times  One or Two  Once  Never
   every day  a Week  Times a Week  a Month

2b. Cocaine (powder, crack, freebase injections)?

   Daily  Nearly  3 or 4 Times  One or Two  Once  Never
   every day  a Week  Times a Week  a Month

2c. Heroin?

   Daily  Nearly  3 or 4 Times  One or Two  Once  Never
   every day  a Week  Times a Week  a Month
### APPENDIX VI (Cont.)

2d. Amphetamines (speed)?

<table>
<thead>
<tr>
<th>Daily</th>
<th>Nearly every day</th>
<th>3 or 4 Times a Week</th>
<th>One or Two Times a Week</th>
<th>Once a Month</th>
<th>Never</th>
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2e. Sniffing organic solvents, glues or thinners?

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<th>Daily</th>
<th>Nearly every day</th>
<th>3 or 4 Times a Week</th>
<th>One or Two Times a Week</th>
<th>Once a Month</th>
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2f. Other? If so specify.

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<th>Daily</th>
<th>Nearly every day</th>
<th>3 or 4 Times a Week</th>
<th>One or Two Times a Week</th>
<th>Once a Month</th>
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APPENDIX VII
P1036 B SITE SURVEY

This survey is intended to obtain specifics about how your site conducted the study and what resources were used.

1. Description of site:
   a. Address:
   b. How many HIV-infected adolescents receive care at your site?
   c. What is the racial background of your HIV-infected adolescent patient population?
   d. Approximately what percentage of your HIV-infected adolescent population is known or suspected to use intravenous drugs?
   e. Approximately what percentage of your HIV-infected adolescent population is known or suspected to have been incarcerated in the past year?
   f. Does your site provide or assist with providing transportation to your patients?
   g. Do you have an on-site pharmacy or do patients get their medications from pharmacies in the community?

2. DOT facilitator
   a. How many DOT facilitators did your site use?
   b. What were their work hours?
   c. What was the maximum number of subjects that a DOT facilitator could provide DOT to in one day?
   d. How did you recruit the DOT facilitators and what were their backgrounds? Specifically mention if the DOT facilitators had previous experience with fieldwork, and for how long.
   e. Did the DOT facilitators use their own transportation, or was transportation provided by your site?
   f. Please include any other specifics regarding the DOT interaction that you feel were unique to your site:

3. Suggestions: Based on your site’s experience of providing DOT, please provide your comments and/or suggestions regarding future DOT programs.
APPENDIX VII (Cont.)

4. Incentives:
Please provide the details of any incentives that your site used to encourage subjects to adhere to the DOT interactions.

a. Type of incentive:

b. Criteria set for a subject to qualify for this incentive:

c. Frequency at which the incentive was given:

d. Site comments on the use of this incentive(s), including the pros and cons (if any), and whether incentives would be recommended for use in the future.

5. Please provide the following information for each DOT facilitator. This information is to be filled out by the site principal investigator, in conjunction with the site personnel supervising the DOT facilitators.

**DOT facilitator identifier (print initials):**

Age: ___ in years

Sex: Male/Female

Education:
___ less than high school
___ high school graduate or GED
___ some or completed junior college
___ some four year college
___ college graduate
___ graduate school; specify:

Experience in health field:
APPENDIX VII (Cont.)

Has worked at a community-based organization:

___ no

____ yes; how many months?_____

Has worked at a medical clinic:

___ no

____ yes; how many months?_____

Has had job responsibilities involving direct community outreach:

___ no

____ yes; how many months?_____

Has had job responsibilities of providing direct services to youth 12-18 years of age:

___ no

____ yes; how many months?_____

Baseline HIV knowledge

HIV (virus, testing, disease course, transmission)

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HIV Treatment (medications, side effects, adherence, resistance)

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HIV Services (available in the area)

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APPENDIX VII (Cont.)

Post-Training HIV knowledge

HIV (virus, testing, disease course, transmission)

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HIV Treatment (medications, side effects, adherence, resistance)

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HIV Services (available in the area)

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Personal Empathy

Did the site staff become aware of any situation in which this DOT facilitator failed to be appropriately empathetic with study subjects?

Professional Conduct

Did the site staff become aware of any situation in which this DOT facilitator failed to be appropriately professional or invaded the personal boundaries of subjects?

Was this person part of the clinic staff before recruitment as a DOT facilitator?

Were the DOT subjects already familiar with the DOT facilitator from previous interactions, or were they introduced after initiating the study?

Did this DOT facilitator receive training for all of the elements listed in Appendix III?

___yes

___no. If not, list which ones were not included in the training for this DOT facilitator and the reason(s) why:
ID Number

APPENDIX VIII

BELIEFS ABOUT MEDICINE SCALE- ADOLESCENT VERSION

PLEASE RATE HOW MUCH YOU AGREE OR DISAGREE WITH EACH STATEMENT USING THE FOLLOWING RATING SCALE:

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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<tbody>
<tr>
<td>Disagree Completely</td>
<td>Disagree Mostly</td>
<td>Disagree a Little</td>
<td>Neither Agree Nor Disagree</td>
<td>Agree a Little</td>
<td>Agree Mostly</td>
<td>Agree Completely</td>
</tr>
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</table>

1. My friends think I should take my medicine the way the doctor says I should. ______

2. When I take my medicine the way the doctor says I should, I feel like I am doing something good for my health. ______

3. I do not think my illness is a serious illness. ______

4. If I take my medicine the way the doctor says I should, it gets in the way of me living my life the way I want to. ______

5. The side effects of my medicine are so bad that I do not want to take it. ______

6. My illness gets in the way of finishing my job, or schoolwork, or other responsibilities. ______

7. I worry about health problems I might have if I do not take my medicine the way I should. ______

8. I am sure that I can take my medicine the way the doctor says I should. ______

9. If I do not take my medicine the way I should, I will get sicker. ______

10. I worry that my illness may get in the way of me doing the things I want to do in the future. ______

11. If I take my medicine the way the doctor says I should, it makes me feel sicker. ______

12. As long as I feel well, my illness is not a problem. ______

13. It is often annoying for me to take my medicine the way the doctor says I should. ______

14. Even if I got sicker, it would not change my life very much. ______

15. My family thinks I should take my medicine the way the doctor says I should. ______
APPENDIX VIII (Cont.)

16. It is embarrassing for me to take my medicine in front of people I do not know well. 

17. It is stressful to take my medicine the way the doctor says I should. 

18. I worry about getting sicker than I am right now. 

19. My illness gets in the way of me having fun with my friends. 

20. People in my life care if I take my medicine the way I should. 

21. It takes too much time to take my medicine the way the doctor says I should. 

22. I worry less about my health if I take my medicine the way I should. 

23. My illness gets in the way of me doing things I want to do. 

PLEASE RATE HOW MUCH YOU AGREE OR DISAGREE WITH EACH STATEMENT USING THE FOLLOWING RATING SCALE:

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<tbody>
<tr>
<td>Disagree</td>
<td>Completely</td>
<td>Mostly</td>
<td>a Little</td>
<td>Neither Agree</td>
<td>Agree</td>
<td>Agree</td>
<td>Agree</td>
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<tr>
<td>Agree</td>
<td>Agree</td>
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</table>

24. I am sure that I can take my medicine the way the doctor says I should even if there are other things I want to do. 

25. If I do not take my medicine the way I should, I could die. 

26. I feel different from other teenagers because I have to take medicine. 

27. It is easy for me to take my medicine the way the doctor says I should. 

28. I feel pressure from my friends to skip taking my medicine. 

29. Other people with my illness get very sick even if they take their medicine the way the doctor says they should. 

30. I have a lot to gain from taking my medicine the way the doctor says I should. 

31. Taking my medicine the way I should makes me miss out on doing fun things. 

32. I am sure that I can take my medicine the way the doctor says I should even when my life is stressful. 

33. It upsets me to have to take medicine. 

34. Even if people pressure me to skip a dose of my medicine, I will still take it.
APPENDIX VIII (Cont.)

35. If I take my medicine the way the doctor says I should, it will keep me from getting sicker. ______
36. I want to take my medicine the way the doctor says I should because it matters to people I care about. ______
37. When I think about my illness I feel scared. ______
38. I do not feel better even when I take my medicine the way the doctor says I should. ______
39. My family helps me take my medicine the way the doctor says I should. ______
40. The good things that come from taking my medicine the way I should make the side effects worth it. ______
41. If I take my medicine the way the doctor says I should, it helps keep me feeling well. ______
42. My illness gets in the way of me getting along with my family. ______
43. I miss a lot of school, or work, or other daily responsibilities because of my illness. ______
44. Taking my medicine will keep me from having to go to the hospital. ______
45. Friends who are important to me care if I take my medicine. ______
46. I get out of doing things I do not want to do because I have to take medicine. ______

PLEASE RATE HOW MUCH YOU AGREE OR DISAGREE WITH EACH STATEMENT USING THE FOLLOWING RATING SCALE:

1 2 3 4 5 6 7
Disagree Disagree Disagree Neither Agree Agree Agree Agree
Completely Mostly a Little Nor Disagree a Little Mostly Completely

47. Taking my medicine the way the doctor says I should puts me in a bad mood. ______
48. My family knows if I take my medicine the way the doctor says I should. ______
49. When I take my medicine the way I should, I feel well enough to do things I enjoy. ______
50. I think I will become sicker than I am right now. ______
51. My friends help me take my medicine the way the doctor says I should. ______
52. If I take my medicine the way I should, I miss fewer days of school, or work, or other daily responsibilities. ______
APPENDIX VIII (Cont.)

Part II: Please answer the following questions about the NEXT TWO WEEKS.

53. I plan to take my medicine the way the doctor says I should.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely Do Not</td>
<td>Mostly Do Not</td>
<td>Somewhat Do Not</td>
<td>Don’t Know Somewhat</td>
<td>Mostly Do</td>
<td>Definitely Do</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

54. What are the chances that you will miss at least one dose of your medicine?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely Not Likely</td>
<td>Mostly Definitely Not Likely</td>
<td>Somewhat Not Likely</td>
<td>Don’t Know Somewhat Likely</td>
<td>Mostly Likely</td>
<td>Definitely Likely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

55. I intend to take almost every dose of my medicine the way the doctor says I should.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely Do Not</td>
<td>Mostly Do Not</td>
<td>Somewhat Do Not</td>
<td>Don’t Know Somewhat</td>
<td>Mostly Do</td>
<td>Definitely Do</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

56. How likely is it that you will take every dose of your medicine the way the doctor says you should?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely Not Likely</td>
<td>Mostly Not Likely</td>
<td>Somewhat Not Likely</td>
<td>Don’t Know Somewhat Likely</td>
<td>Mostly Likely</td>
<td>Definitely Likely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

57. How likely is it that you will miss at least half of your doses of medicine?

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely Not Likely</td>
<td>Mostly Not Likely</td>
<td>Somewhat Not Likely</td>
<td>Don’t Know Somewhat Likely</td>
<td>Mostly Likely</td>
<td>Definitely Likely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VIII (Cont.)

58. I want to take every dose of my medicine the way the doctor says I should.

<table>
<thead>
<tr>
<th>Definitely</th>
<th>Mostly</th>
<th>Somewhat</th>
<th>Don’t Know</th>
<th>Somewhat</th>
<th>Mostly</th>
<th>Definitely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do Not</td>
<td>Do Not</td>
<td>Do Not</td>
<td>Do</td>
<td>Do</td>
<td>Do</td>
<td>Do</td>
</tr>
</tbody>
</table>

59. What are the chances that you will miss almost all of your doses of medicine?

<table>
<thead>
<tr>
<th>Definitely</th>
<th>Mostly</th>
<th>Somewhat</th>
<th>Don’t Know</th>
<th>Somewhat</th>
<th>Mostly</th>
<th>Definitely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not</td>
<td>Not</td>
<td>Not</td>
<td>Don’t Know</td>
<td>Likely</td>
<td>Likely</td>
<td>Likely</td>
</tr>
<tr>
<td>Likely</td>
<td>Likely</td>
<td>Likely</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE.
APPENDIX IX
DOT INTERACTION LOG

Patient Number: Date of Patient Visit:

INSTRUCTIONS:

• To be completed at each scheduled DOT visit.
• Use the 24-hour clock where 00:00 is midnight.

1. Scheduled location:

2. Time Scheduled (hh:mm):

3. Was the participant paged?
   a. Time of first page:
   b. Time of second page:

4. Did subject arrive?
   a. Did the participant call back to reschedule?
     b1. Time arrived (hh:mm):
     b2. Time completed:

5. Did the participant report illness and/or medication side effects:
   If Yes List:
   ___________________________________________________________
   ___________________________________________________________

6. Did the participant ask for any assistance? NOTE: DOT facilitator asks each question and checks all that apply.
   If No go to question 7.
   If Yes, check any/all that apply.
   a. Housing:
   b. Transportation:
   c. Food:
   d. Condoms:
   e. Other, specify:
APPENDIX IX (Cont.)

7. Was previous DOT interaction missed?
   If Yes, specify reason:

8. Date of last DOT interaction performed (mmm/dd/yyyy):
APPENDIX IX (Cont.)

INSTRUCTIONS to PARTICIPANT
Participants sometimes forget to take some or many doses of their medications. Knowing the exact amount of medicines that were taken by a participant is very important for treatment planning. This information is often hard to remember beyond the past few days. To obtain accurate information we will maintain a regular calendar of medication doses. We understand if you have missed doses but obtaining accurate information helps us provide the best treatment to you. Let us fill in the blanks between your last meeting with me and today.

INSTRUCTIONS to DOT FACILITATOR
The information entered below is on medication doses taken since the last DOT visit (use additional forms if needed) including today’s DOT dose. Do not enter previous DOT dose information here. Partial doses (i.e., not all medications due at that time were taken) are NOT counted as doses taken.

<table>
<thead>
<tr>
<th>Date of Dose</th>
<th>Scheduled Total doses</th>
<th>DOT or SAT*</th>
<th>Total Doses Taken</th>
<th>Participant Self-Report About Reason(s) for Missed Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXAMPLE: 4/22/05</td>
<td>2</td>
<td>SAT</td>
<td>1</td>
<td>forgot to take p.m. dose</td>
</tr>
<tr>
<td>EXAMPLE: 4/23/05</td>
<td>1</td>
<td>SAT</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>EXAMPLE: 4/23/05</td>
<td>1</td>
<td>DOT</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

a. 
b. 
c. 
d. 
e. 
f. 
g. 
h. 
i. 
j. 

*SAT = self administered therapy (i.e., subject took his/her dose unobserved by the DOT facilitator)

9. Did the participant receive all doses needed until the next scheduled DOT interaction?
APPENDIX IX (Cont.)

10. Does the participant report having a complete emergency supply? (sufficient doses to cover 5 days)

____________________________________     ______________________________
Initial (DOT Facilitator)/Date           Initial (Participant)

Part III: The following information should be entered at the end of each day that DOT is administered:

1. How many subjects were you scheduled to provide DOT to today?

2. How many subjects showed up to receive DOT?

3. What mode of transportation did you use to provide DOT today?

4. If you used a car, how many miles did you travel while providing DOT today?

5. Specify the total amount of time you spent providing DOT today? This includes traveling time, as well as the time spent completing the DOT interaction.

6. Any specific incidents, concerns, or suggestions that you have, based on your experience of providing DOT today?

__________________________________
Initial (DOT Facilitator)/Date
APPENDIX X

Documentation of Use of Support Services

Record of support services used by the subject since the last clinic visit:

This form is completed by the clinic staff and should also include information received from the DOT facilitator.

<table>
<thead>
<tr>
<th>Category</th>
<th>Services used over the past month</th>
<th>Did the DOT facilitator coordinate this service?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Health Services</td>
<td>Yes/No</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Food Assistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housing/Rental Assistance</td>
<td></td>
<td></td>
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<tr>
<td>Utility Assistance</td>
<td></td>
<td></td>
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<tr>
<td>Case Management</td>
<td></td>
<td></td>
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<tr>
<td>Substance Abuse Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child Day Care, Baby Care Items</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transportation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legal Assistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# APPENDIX XI – VIROLOGY

## COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
</table>
| Quantitative HIV-1 RNA PCR (Roche Amplicor-v. 1.5 - Ultrasensitive) | Minimum of 5.0 mL blood collected by venipuncture | 5.0mL Tripotassium EDTA Vacutainer® (Lavender top tube) | • Gently invert tubes several times to mix. Do not shake.  
• Label primary specimens with patient ID, protocol, site, visit, date and time of collection, specimen type, anticoagulant  
• Specimen should be kept at room temperature (18°-24°C) and processed within 4-6 hours of collection. |
| Test Code: HIVRNARU | | | |

**SPECIMEN PROCESSING:**
- Centrifuge blood at 800 x g for 10 minutes at 18°-24°C.
- Transfer plasma to a centrifuge tube; re-centrifuge at 800 x g for 10 minutes to completely remove platelets and cell debris.
- Aliquot at least 2 x 0.6mL plasma into sterile cryovials. Log specimens into the LDMS and label aliquots with standard ACTG labels. Store at -60° to -80°C until samples are shipped. RNA assays will be run real time.

To minimize RNA degradation, all plasma samples must be processed and stored at -60° to -80°C within 48 hours of collection. Although the required processing time has been increased from 4-6 hours to 48 hours, sites are encouraged to continue to process HIV-1 RNA samples as soon as possible.

**DESIGNATED LABORATORY:** All HIV RNA assays will be performed in the Laboratory of Dr. Steven Spector @ UCSD

**SHIPPING ADDRESS:**
- Primary Physician: Dr Steven Spector MD
- Primary Contact: c/o Carol Mundy
- Address: University of California, San Diego
  Room 427
  9500 Gilman Dr.  Mail Stop 0672
  San Diego, CA 92093-0672
- Contact E-mail: cmundy@uscd.edu
- Telephone: 858-534-7465
- Fax: 858-534-7411
- Lab Code: 008
DIRECTLY OBSERVED THERAPY IN HIV-1-INFECTED ADOLESCENTS

SHORT TITLE FOR THE STUDY: Directly observed therapy (DOT) pilot study

INTRODUCTION

You are/your adolescent is being asked to take part in this research study because you are/your adolescent is infected with HIV and you/your adolescent is having difficulty taking HIV medications regularly. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of the study at this site is: (insert name of Principal Investigator). Before you decide if you want to be/want your adolescent 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 to you about this study. You are free to ask questions at any time. If you agree to/let your adolescent 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 find a Directly Observed Therapy (DOT) program that will help adolescents take their antiretroviral medicine on time. For this study Directly Observed Therapy means that you/your adolescent will take some doses of your/your adolescent’s medications in the presence of a study staff (DOT helper) at a place in the community chosen by you/your adolescent. Not only will the study staff (DOT helper) help you/your adolescent take his/her medicines on time but he/she will also provide any additional support that you/your adolescent may need.
APPENDIX XII (Cont.)

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

Screening Visit

If you are/your adolescent is able to take part in the study and you/your adolescent decide(s) to take part, you will be asked to sign this consent form. If you are/your adolescent is able to become pregnant (menstruating), a urine sample will be collected to test for pregnancy. This test must be negative in order for you/your adolescent to take part in this study.

You should know that while participating in this study, you/your adolescent may not enroll in another study involving an experimental drug.

Entry Visit

At this visit, you/your adolescent will be asked questions about your/his/her background. This includes asking about any illnesses that you/your adolescent may have had (or currently have). Also, you/your adolescent will be asked about any medicine that you have/your adolescent has taken in the past 6 months (if you/your adolescent take(s) them regularly).

You/your adolescent will be asked to complete a number of questionnaires. Some of these questionnaires will ask questions about:

- your/your adolescent’s mood and emotions;
- your/your adolescent’s use of alcohol and other substances such as marijuana, cocaine, etc. (this questionnaire will be given to you/your adolescent to fill out in private);
- how often and how you/your adolescent take(s) your/his/her medicine;
- your/your adolescent’s thoughts about HIV medicines;
- if you/your adolescent have/has used any support services (such as mental health services, food and housing aid and/or others);

Most questionnaires will be given to you/your adolescent like an interview. As stated above, the questionnaire about your/your adolescent’s use of alcohol and other substances will be given to you/your adolescent to fill out in private. If you/your adolescent need(s) help with reading these questionnaires, you /your adolescent should let study staff know.

About 2 teaspoons of blood will be drawn from a vein in your/your adolescent’s arm for laboratory tests. These tests include finding out the amount of HIV in your/your adolescent’s blood, finding out the number of special cells in your/your adolescent’s blood that fight HIV (known as CD4+ cells), and other routine blood tests.

The entry visit will take about 2 – 2 ½ hours to complete.
On-Study Visits

DOT Meetings

You/your adolescent will be in this study for 24 weeks. During this time, DOT meetings will be scheduled once a day, every day, for the first 2 weeks, and 5 days a week for the next 6 weeks. After that, depending on how well you are/your adolescent is taking the HIV medication, the DOT meetings may be decreased to 3 days a week. DOT will then either be stopped or your/your adolescent’s doctor may recommend continuing DOT. The final decision on whether to continue DOT will be left up to you/your adolescent.

The following things will take place at every DOT meeting:

- you/your adolescent will be asked to take one dose of HIV medicine in front of a member of the staff (DOT helper).
- the DOT helper will ask about your/your adolescent’s health, including questions about any medication side effects.
- the DOT helper will give you/your adolescent extra doses of HIV medication that you/your adolescent may have to take before your/your adolescent’s next DOT meeting.
- you/your adolescent and the DOT helper will set a time and place for the next DOT meeting. The location of each meeting can be decided on by you/your adolescent and the DOT helper.

As part of this study you/your adolescent will be given a pager that will remind you/your adolescent when it is time to take HIV medicine (the dose of medicine that you/your adolescent will take without the DOT helper if you/your adolescent take(s) more than 1 dose a day). Also, the DOT helper will page you/your adolescent 30-60 minutes before each DOT meeting. You/your adolescent will be told to call back only if a change to the time or place of the DOT meeting is needed. If the DOT helper does not receive a call back, the meeting will happen at the decided time and place.

You/your adolescent can call the DOT helper on his/her cell phone for DOT-related questions during the working hours of the DOT helper. For safety and legal reasons, the DOT helper is not allowed to give you/your adolescent any money or a ride anywhere. He/she will let your/your adolescent’s case manager know about any needs that you/your adolescent may have so that you/your adolescent may get help from the case manager.
Clinic Visits

In addition to the DOT meetings, you/your adolescent will also be asked to come to the clinic for 6 more visits every 4 weeks at weeks 4, 8, 12, 16, 20, and 24. At each Clinic visit, you/your adolescent will be asked to fill out questionnaires about how often and how you/your adolescent take(s) your/his/her medicine. During the clinic visits at week 8, week 12 and week 24, about 1 or 2 teaspoons of blood will be drawn from a vein in your/your adolescent’s arm to find out the amount of HIV in your/your adolescent’s blood and measure the number of special cells in your/your adolescent’s blood that fight HIV (known as CD4+ cells).

At weeks 12 and 24 visits, you/your adolescent will be asked to fill out questionnaires just like the ones at the Entry visit.

Whenever DOT is stopped we will ask how you/your adolescent feel(s) about DOT using a questionnaire.

Early Discontinuation

If you/your adolescent decide(s) at any time that you/he/she would no longer like to take part in this study, you/your adolescent can let the study staff know. You/your adolescent will be asked to come to the clinic for 1 more study visit. At this visit, you/your adolescent will be asked questions about your/his/her background. You/your adolescent will also be asked about any illnesses that you/your adolescent may have had (or currently have). Also, you/your adolescent will be asked about any medicine that you have/your adolescent has taken since your/your adolescent’s last visit.

You/your adolescent will be asked to fill out questionnaires just like the ones at the Entry visit. Most questionnaires will be given to you/your adolescent like an interview. One questionnaire about your/your adolescent’s use of alcohol and other substances will be given to you/your adolescent to fill out in private, just like at the Entry visit. If you/your adolescent require(s) help with reading these questionnaires, you/your adolescent should let study staff know.

If you/your adolescent decide to stop receiving DOT but agree to remain on study, you/your adolescent will continue to be followed as per the schedule of events. If you/your adolescent decide you no longer want to take part in this study, about 2 teaspoons of blood will be drawn from a vein in your/your adolescent’s arm for laboratory tests. These tests include finding out the amount of HIV in your/your adolescent’s blood, finding out the number of special cells in
APPENDIX XII (Cont.)

your/your adolescent’s blood that fight HIV, and other routine blood tests. The study visit will take about 2 – 2 ½ hours to complete.

The results of routine tests done during the study will be made available to you/your adolescent. You will also be told if we are concerned about depression or hopelessness seen from the information you tell us in the questionnaires. These concerns will be dealt with by trained study staff. The information you tell us about use of alcohol and other substances in a questionnaire you fill out in private is not read by your clinic staff. You will not be given any advice about use of these substances unless you specifically ask for it.

HOW WILL MY MEDICINES BE PROVIDED?

Each site fills out their own plan regarding how the patient obtains his HIV medications, provides them to the study site and obtains refills.

OTHER INFORMATION:

The information and knowledge that comes out of doing this study may be used for other research related to HIV disease and approved by the PACTG. The summaries and conclusions about the different things looked at by this study may be used in designing future research studies about HIV disease that are similar to the problems studied in this research. No individual information in the PACTG study records will be looked at or used for this purpose.

HOW MANY ADOLESCENTS WILL TAKE PART IN THIS STUDY?

About 24 adolescents at 4 different sites in the U.S. will take part in this study.

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

You/your adolescent will be in this study for 24 weeks.

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

The study doctor may need to take you/your adolescent off the study early, without your permission, if:
APPENDIX XII (Cont.)

- 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 subjects.)
- A Data Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study.)
- You are/your adolescent is not able to attend the study visits as required by the study.
- You/your adolescent stop taking the HIV medicine.
- You are/your adolescent is in the hospital for two or more weeks.
- You/your adolescent become(s) pregnant while receiving DOT.

If you are taken off the study, you will be asked to come to the clinic for 1 more study visit, just as described above under “Early Discontinuation.”

WHAT ARE THE RISKS OF THE STUDY?

Blood drawing is routinely done to check how well HIV in your body is controlled and to look for medication side effects. Blood drawing may cause some discomfort, bleeding or fainting. It also may cause a feeling of lightheadedness. Sometimes, bruising, a minor infection or a small blood clot may form where the needle enters the body. There are no additional risks related to blood drawing that are specific to this study.

Many people choose to keep their HIV status confidential. It is possible that the meetings with the DOT helper in a public place may risk this confidentiality. The study staff will do their best to keep your/your adolescent’s HIV status confidential.

There are no certain medicines required to be in this study except that the medicine chosen by your/your adolescent’s doctor must be given either once or twice per day. The possible side effects of the medicine will be explained to you/your adolescent by your/your adolescent’s primary care doctor.

You/your adolescent may become tired when filling out the questionnaires. Because some of the questions are personal, you/your adolescent may feel uncomfortable answering all of the questions. If this occurs, you/your adolescent should let the study staff know.

ARE THERE RISKS RELATED TO PREGNANCY?

Pregnant women require other medical care and clinic appointments. Pregnancy is also linked to emotional changes. This makes it difficult for us to provide DOT and to measure its response.
APPENDIX XII (Cont.)

For these reasons, if you are/your adolescent is having sex that could lead to pregnancy, you/your adolescent must agree not to become pregnant. You/your adolescent or your/your adolescent’s partner must use some method of birth control regularly that you/your adolescent discuss(es) with the study staff. You/your adolescent may choose one of the birth control methods listed below. If you are/your adolescent is taking certain HIV medications like efavirenz, you must use two of these methods. Your HIV doctor will discuss this with you.

- Hormonal birth control drugs that prevent pregnancy given by pills, shots, or placed under the skin. Some HIV medications can cause hormonal birth control methods to not work as well. Therefore it is important to talk to your HIV doctor about different kinds of birth control.
- Male or female condoms with, or without, a cream or gel that kills sperm.
- Diaphragm or cervical cap with a cream or gel that kills sperm.
- Intrauterine device (IUD).

If you think you/your adolescent may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you/your adolescent about your/her choices.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your adolescent take(s) part in this study, there may be a direct benefit to you/your adolescent, but no guarantee can be made. The DOT meetings may help you/your adolescent remember to take your/his/her medicine. Also, you/your adolescent may find the DOT meetings helpful in talking about other problems, if you/your adolescent wish(es). This study may help us decide if DOT is helpful to others like you/your adolescent. It is also possible that you/your adolescent may receive no benefit from being in the study.

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

Instead of being in this study, you have/your adolescent has the choice of:
- Treatment with prescription drugs available to you/your adolescent
- Treatment with experimental drugs, if you/your adolescent qualify(ies)
- No treatment

Please talk to your/your adolescent’s doctor about these and other available choices. Your/your adolescent’s doctor will explain the risks and benefits of these choices.
APPENDIX XII (Cont.)

WHAT ABOUT CONFIDENTIALITY?

Your/your adolescent’s records will be kept confidential. A code number will be used to identify you/your adolescent. Only the study staff will know your/your adolescent’s name.

To help us protect your/your adolescent’s privacy, we have a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to release information that may identify you/your adolescent, 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/your adolescent, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States (U.S.) Government that is used for auditing or evaluation of federally funded projects.

People who may review your/your adolescent’s records include: (insert Name of Site) IRB, NIH, study staff, and study monitors.

You should understand that a Certificate of Confidentiality does not stop you/your adolescent or a member of your/your adolescent’s family from willingly giving out information about you/your adolescent or your/your adolescent’s participation in this research. If an insurer, employer, or other person gets your/your adolescent’s written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to refuse to give that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing willingly, without your/your adolescent’s consent, information that would identify you/your adolescent as a participant in the research project if the study staff learns of possible child abuse and/or neglect or risk of harm to you/your adolescent, or others. In such cases, we will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME/MY ADOLESCENT?

There is no cost to you/your adolescent for the DOT meetings or the study visits. 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 adolescent are/is taking part in a research study.
APPENDIX XII (Cont.)

WILL I/MY ADOLESCENT RECEIVE ANY PAYMENT?

A payment chosen by your/your adolescent’s site may be provided to you/your adolescent for not missing any DOT meetings (at the site’s discretion – this information should be removed if the site is not providing any incentives).

WHAT HAPPENS IF I AM/MY ADOLESCENT IS INJURED?

If you are/your adolescent is injured as a result of being in this study, you/your adolescent will be given immediate treatment for your/his/her injuries. The cost for this treatment will be charged to you or your/your adolescent’s insurance company. There is no program for reimbursement either through this institution or the NIH. You will not be giving up any of your legal rights by signing this consent form.

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

Taking part in this study is completely voluntary. You may choose not to take part/let your adolescent to take part in this study or leave this study/take your adolescent out of this study at any time. You/your adolescent will be treated the same no matter what you/he/she decide(s).

We will tell you about new information from this or other studies that may affect your/your adolescent’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/DOES MY ADOLESCENT DO IF I/WE 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/your adolescent’s rights as a research subject, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
APPENDIX XII (Cont.)

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you/your adolescent agree(s) 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)

______________________________          ______________________________
Father’s Name           Father’s Signature and Date
(As appropriate)