DIRECTLY OBSERVED THERAPY (DOT) IN HIV-1 INFECTED ADOLESCENTS:
PART A-FOCUS GROUPS

A Limited Center Trial of the Pediatric AIDS Clinical Trials Group

Sponsored by:
The National Institute of Allergy
and Infectious Diseases

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Version 1.0
FINAL
January 28, 2004
PACTG P1036 - PART A PROTOCOL TEAM ROSTER

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APPENDICES

I. SCHEDULE OF EVALUATIONS

II. INVITATION TO THE FOCUS GROUP - SCRIPT

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SCHEMA

DIRECTLY OBSERVED THERAPY (DOT) IN HIV-1 INFECTED ADOLESCENTS:
PART A - FOCUS GROUPS

DESIGN: Focus group to inform the Directly Observed Therapy (DOT) intervention model.

SAMPLE SIZE: A minimum of 15 and a maximum of 30 subjects will participate in three focus groups, at three different sites (5-10 subjects per site). The protocol is site restricted.

STRATIFICATION: By study site.

POPULATION: HIV-infected adolescents, age 16 to <22 years of age.

REGIMEN: This study does not involve any treatment regimen.

STUDY DURATION: One two hour session.

OBJECTIVE: To obtain information for a DOT intervention model that will be accepted by adolescents.

SCHEMA OF DOT STUDY DEVELOPMENT IN HIV-INFECTED ADOLESCENTS

PACTG P1036 - PART A - Focus groups (3 sites)
(The following design for possible future trials if feasibility is proven in this study)

Part B
DOT pilot study (3 sites)

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

1.1 Background

The continued detection of newly HIV-infected adolescents who have acquired HIV infection through sexual transmission combined with approaching adolescence for the existing perinatally infected children have resulted in a growing population of HIV-infected adolescents. As of December 1999, in the 32 states that report cases of HIV-1 infection, people aged 13-24 years formed 17.5% of the total HIV infected population. It is estimated that 50% of all newly infected people are in this age group. As with many other chronic diseases, the problem of adherence to therapy for HIV-1 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 REACH (Reaching for Excellence in Adolescent Care and Health) project reported full adherence to highly active antiretroviral therapy (HAART) (1). A retrospective analysis of a smaller group of HIV-infected adolescents (13-21 years) revealed 72% of subjects receiving antiretroviral medications were non-adherent (2). Adolescents often cite forgetting to take their medications as the reason for poor adherence as evidenced by data from the REACH project. The practice of forgetting to take medications was found in 67% of subjects as a reason for non-adherence (Personal communication, ME Belzer). Additionally, 22% of subjects in a smaller study of 31 adolescents in Los Angeles demonstrated this as a reason for poor adherence (3).

Implications of poor adherence

Preliminary results from PACTG 381 demonstrated a reduced virologic response to HAART than would be predicted based on adult studies. Using intent to treat analysis at 16 weeks, only 59% of HIV infected adolescents in this study showed an undetectable viral load. Although not achieving statistical significance, this short term virologic success was positively associated with perfect adherence in this study. In other clinical studies, a direct correlation between adherence to antiretroviral therapy and virologic outcome has been demonstrated (1, 4, 5). 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 viral resistance but also has public health implications (6). The results of PACTG 076, occupational exposure studies, and studies in subjects infected via blood or blood products, support the assumption that successful antiviral therapy in adherent individuals can reduce the viral load in blood and genital secretions which might result in diminished HIV transmission risk (7-10). There
also continues to remain a concern of transmission of a single drug or a multi-drug resistant virus resulting in primary infection with resistant HIV variant (11, 12).

Recognizing the major impact of adherence to antiretroviral therapy on the magnitude and durability of therapeutic response, physicians have tried highly 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 these strategies, non-adherence continues to be one of the major challenges to the successful management of HIV-1 infection, especially in the adolescent age group.

Directly Observed Therapy (DOT) for Tuberculosis

Many of the adherence issues faced in the treatment of HIV are analogous to those faced in the treatment of tuberculosis (TB). To increase the probability of treatment compliance, directly observed therapy has been recommended as the standard of care for pulmonary TB (13, 14). 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 directly observed therapy with multiple enablers and enhancers. This success rate was felt to be unlikely using other less intensive interventions including unsupervised strategies and modified approaches to directly observed therapy (DOT). The panel also concluded that DOT appears to be cost effective when compared to self-administered therapy, although pertinent data were limited (14).

DOT for HIV infection

Using a DOT strategy for HIV infection and obtaining similarly successful results as with DOT in tuberculosis 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 (15). There have been a few studies using a total or partial directly observed therapy approach in the context of HIV-1 infection (16-20). A majority of these studies have targeted prisons or correctional facilities and have shown promising results (16-19). In a non-randomized study of treatment naïve adult subjects, comparing DOT in a Department of Corrections facility versus self-administered therapy (SAT) in the clinic population, the DOT group had greater short and long-term virologic responses compared with those in the SAT group (16). 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 SAT group was as follows:
- week 16 (94% vs. 77%),
- week 24 (100% vs. 76%),
- week 48 (100% vs. 81%),
- week 64 (100% vs. 81%) and
- week 80 (95% vs. 75%).

In another open label, nonrandomized, single arm study in antiretroviral naïve incarcerated adults, after 24 weeks of twice-daily abacavir plus Combivir, 93% of subjects remaining on therapy had viral loads below 400 copies/mL in an intent to treat analysis (19). These studies demonstrate the benefit of directly observed antiretroviral therapy in certain special settings such as prisons. None of them have a randomized design.

There is only one published study that provided DOT in the community setting. In this study, a modified DOT approach (one of the two daily doses of medication was given under observation 5 days a week) was adopted (20). The three-month data reported on 22 adult HIV-1 infected, antiretroviral exposed subjects in this study, referred for self-reported non-adherence, showed increasing compliance and decreased viral load (mean decrease 1.36 logs). The majority of these subjects felt the outreach worker helped them and they felt better about taking medication upon completion of the trial. 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 (1, 21, 22). Also, the REACH study showed that HIV infected adolescents who had a good social support structure and adaptive coping mechanisms had lower levels of depression (22). Thus, we hypothesize that the daily interaction between the DOT enabler and the subject could facilitate practical coping strategies that could result in reduced depressive symptoms and improved adherence.

A lack of once a day HIV therapy has been one of the major obstacles to conducting properly designed, well powered studies of DOT in the community setting. A recent adult trial of once daily didanosine (400mg), emtricitabine (200mg), plus efavirenz (600mg) has demonstrated short term efficacy in controlling viral load (23). A safety and efficacy study using this regimen in 40 previously untreated HIV-1 infected adults demonstrated 98% of subjects achieved an undetectable viral load (<400 copies/mL) 24 weeks into treatment. Adverse drug reactions led to a permanent drug discontinuation in only one subject. An evaluation of the pharmacokinetics and safety of a single oral dose of emtricitabine (FTC) in HIV-1 infected or exposed children revealed plasma AUC of FTC at 120mg/m² (∼ 6mg/kg) which was comparable to the median value of the AUC seen in adults given a 200 mg dose (24). There were no severe adverse events seen. A phase II trial of FTC in children less than 17 years of age is currently in development.
The economic impact of providing DOT for HIV-1-infected subjects in the community has not been studied. Despite its greater initial cost, DOT for the treatment of tuberculosis was found to be a more cost effective strategy than SAT (25). This evaluation of DOT used a decision analysis model that included both the cost of initial therapy and cost of treating disease that arises as a result of failure to the initial therapy. Using a similar strategy, we will try to estimate the cost-effectiveness of DOT versus SAT in the treatment of HIV-1 infection taking into account the direct and indirect costs. These include 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 improvement in quality of life.

There are examples of cost effectiveness analysis using a probabilistic decision model in the literature pertaining to HIV-1. One model compared elective Cesarean Section versus vaginal delivery with model outcomes including total lifetime cost, quality adjusted life expectancy, HIV transmission rate and incremental cost effectiveness ratios (26). A study to evaluate the cost-effectiveness and cost benefit of school based HIV, other STDs, and pregnancy prevention program, used the Bernoulli model of HIV transmission (27). This model is a cumulative probability equation that estimates the probability of HIV infection based on 4 variables:

- number of sexual partners,
- number of sexual contacts with each partner,
- HIV prevalence
- probability of transmission.

Because DOT enablers can also reinforce safe sexual practices, reduction in pregnancies or incident of sexually transmitted diseases may also be seen.

1.2 Rationale for a DOT Study

There is an urgent need to explore the potential benefits of DOT based on its success in the management of pulmonary TB, despite the differences between these two conditions. There are currently no studies that have addressed this issue with an adequate sample size in a randomized trial comparing the current standard of self-supervised care. The long-term outcome of HIV-1 infected subjects after completion of DOT is unknown. There is also a need to determine the cost effectiveness of this approach that should take into account both the direct and indirect costs, to the individual and to society. The availability of newer regimens that demonstrate success with once a day dosing has made consideration of DOT in HIV-infected subjects a reality (23).

Successful adherence to HAART through DOT would provide benefits to the individual, through better disease control, and to the public, by potentially preventing development and spread of viral resistance as well as reducing the risk of
transmission. An additional benefit of DOT is the daily interaction with a health care provider or DOT enabler. The emotional support provided by this interaction may improve overall quality of life and help address other co-morbid factors like depression, which directly or indirectly influence adherence to treatment and overall outcome of the disease. HIV-1 infected adolescents would form an excellent targeted population to assess using DOT.

1.3 Rationale for P1036-Part A: Focus Groups

In this part of the study, we will attempt to define the characteristics of a DOT intervention model that will be acceptable to adolescents. The model developed will attempt not only to deliver HAART therapy to the individual, but to help adolescents adopt good medication taking behavior. In addition, the DOT enabler will provide individual support for the adolescents. The study will consist of three focus groups that will be conducted at three PACTG sites (one focus group per site). The purpose of the focus groups will be to obtain input from adolescents at those sites into the design of the DOT intervention model. The adolescents will provide guidance in the following areas:

- the identification of the characteristics of the DOT enabler;
- guidance regarding the possible locations, times of day, and other parameters for the DOT intervention;
- the specific objectives that are to be achieved during the DOT encounter and their phased timing, and,
- the incorporation of features that render the encounter acceptable to adolescents.

Additionally, this exercise will permit a more precise and appropriate listing of factors that adolescents consider important in DOT in order to better develop the design of the DOT intervention model. The DOT intervention model, as developed, will then be launched as a pilot study of DOT in HIV-infected adolescents (PACTG P1036-Part B). This focus group process will also form the basis for the development of a survey to be used in a larger group of adolescents in all PACTG sites in a companion protocol (PACTG P1036-Part C). The objective of this companion protocol will be to assess the acceptability of the DOT intervention across more diverse populations of adolescents. Based on the results of these studies, a randomized clinical trial comparing DOT to SAT is anticipated.

Focus group interviews are advantageous for their reasonable costs and are often desired since more subjects can be included (27). Focus group methods are also especially useful in rapidly evolving fields of study, like HIV/AIDS, since data can be obtained quickly. Focus group methods are broadly conceptualized as the use of:
1.0 INTRODUCTION

This study is designed to collect information from HIV-1 infected adolescents for the development of a possible study that will use a DOT intervention model. Three focus groups will use interviews to define the DOT intervention model. Specific details that will be discussed in Section 5.2 include the characteristics of the DOT enabler, guidance regarding the possible locations, times of day, and other parameters for the DOT intervention, the specific objectives that are to be achieved during the DOT encounter and their phased timing, and the incorporation of features that render the encounter acceptable to adolescents. A minimum of 15 and a maximum of 30 subjects will participate in three focus groups at three different sites (5-10 subjects per site). The age groups used for this study will include adolescents aged 16 to <22 years. The protocol will be site restricted for participation. The interviews will then be used to provide a detailed description of the DOT intervention model, including guidelines for selection and training of DOT enablers. The DOT intervention model defined in this study may then be used in a pilot study (P1036-Part B) looking at the feasibility of successfully providing DOT to HIV-1 infected adolescents at a site in the community chosen by the subject, the acceptability of such an intervention in adolescents, as well as the logistics of providing such care, including cost. All this will help construct a more concrete model of providing DOT to this age group, which will be assessed in a larger and more diverse population of adolescents in a companion protocol (P1036-Part C). Long term goals include the development of a larger randomized clinical trial of DOT versus SAT.

Following completion of Part A, we will also develop Part C which will be designed to have broader input into the feasibility of DOT. We recognize that in Part A, which targets only 15 – 30 subjects, and Part B, which will target 24 subjects, we will have a very limited response to the concept of DOT in the adolescent population. Part C is planned to occur concurrently with Part B. It is planned as a questionnaire targeting subjects aged 16 to < 22 years at all PACTG sites, primarily describing the details of the DOT intervention.

2.0 STUDY OBJECTIVE

2.1 Primary Objective

To obtain information that may be used to design a DOT intervention model that will be accepted by adolescents.

3.0 STUDY DESIGN

This study is designed to collect information from HIV-1 infected adolescents for the development of a possible study that will use a DOT intervention model. Three focus groups will use interviews to define the DOT intervention model. Specific details that will be discussed in Section 5.2 include the characteristics of the DOT enabler, guidance regarding the possible locations, times of day, and other parameters for the DOT intervention, the specific objectives that are to be achieved during the DOT encounter and their phased timing, and the incorporation of features that render the encounter acceptable to adolescents. A minimum of 15 and a maximum of 30 subjects will participate in three focus groups at three different sites (5-10 subjects per site). The age groups used for this study will include adolescents aged 16 to <22 years. The protocol will be site restricted for participation. The interviews will then be used to provide a detailed description of the DOT intervention model, including guidelines for selection and training of DOT enablers. The DOT intervention model defined in this study may then be used in a pilot study (P1036-Part B) looking at the feasibility of successfully providing DOT to HIV-1 infected adolescents at a site in the community chosen by the subject, the acceptability of such an intervention in adolescents, as well as the logistics of providing such care, including cost. All this will help construct a more concrete model of providing DOT to this age group, which will be assessed in a larger and more diverse population of adolescents in a companion protocol (P1036-Part C). Long term goals include the development of a larger randomized clinical trial of DOT versus SAT.

Following completion of Part A, we will also develop Part C which will be designed to have broader input into the feasibility of DOT. We recognize that in Part A, which targets only 15 – 30 subjects, and Part B, which will target 24 subjects, we will have a very limited response to the concept of DOT in the adolescent population. Part C is planned to occur concurrently with Part B. It is planned as a questionnaire targeting subjects aged 16 to < 22 years at all PACTG sites, primarily describing the details of the DOT intervention.
model that is developed from the feedback of the focus groups (Part A). The idea behind this is to check the acceptability of the DOT concept developed at three PACTG sites to a much more diverse patient population in all PACTG sites. The feedback obtained as part of this questionnaire (Part C) combined with the experience in the pilot study (Part B) will provide a comprehensive picture of the logistics of providing DOT to adolescents. This will be helpful in deciding the feasibility of conducting a randomized clinical trial comparing DOT with SAT.

Site Selection

Any NIAID and NICHD PACTG site may apply to conduct this study. Interested sites should complete the PACTG P1036 Site Application Form. Three sites will be selected by the PACTG P1036 team using the following criteria:

- site availability of staff with experience in adolescent health care (includes a group facilitator and a second person to take notes) and the conduct of focus groups, and
- site availability of a functioning support group for only HIV-1-infected adolescents with regular adolescent attendees, and
- site estimates of the scope and determinants of antiretroviral drug non-adherence in adolescents 16 years of age and older, and
- limited site description of efforts to promote adherence and their estimated success rates.

A list of interested sites will be reviewed and three sites will be chosen by the protocol team. Members of the team whose sites are under consideration will be excluded from the selection process. Following identification of site selection, sites must complete the protocol registration process.

Following the site selection, a conference call including the facilitator, the protocol chair, and the protocol psychologist will be scheduled to review the process, the script for the focus group, and to answer questions.

Chain of Custody for the Audio-tape

Following the completion of the focus group, the facilitator will label the tape with the site and date. The tapes, along with the notes taken by the facilitator’s assistant, will be sent via Federal Express to the protocol chair. The site will notify the protocol chair prior to sending. When not in use, the tapes and notes will be stored in a locked cabinet. The tapes of the focus groups will be transcribed at the protocol chair’s direction, with the notes for clarification, as necessary. If any names are inadvertently used during the session, they will be omitted in the transcripts. Following transcription, the protocol psychologist and the protocol chair will listen to the tapes to validate the transcript and to
note the tone of the participants. Once assurance is made that the transcription is valid, the tapes and notes will be destroyed. The protocol chair will maintain a log of tape and note locations and destruction.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

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

4.12 HIV-1 infection transmission due to high-risk behaviors as identified by subject records.

4.13 Subject is able and willing to provide informed consent.

4.14 If the subject is less than the legal age of consent, the parent or legal guardian should be available to provide parental permission unless waived by the local IRB. Assent of the minor subject should be obtained where required.

4.15 Subject should be a regular attendee of his/her local HIV adolescent support group.

4.16 Subject is currently prescribed antiretrovirals or has a history of prior antiretroviral therapy.

4.2 Exclusion Criteria

4.21 Subject report of current pregnancy.

4.22 Subject report of current breastfeeding.

4.23 Subject who is visibly distraught or visibly emotionally unstable (i.e. depressive mood, or exhibiting manic, suicidal or violent behavior, etc.) in the opinion of the local site.

4.24 Documented or suspected perinatal HIV infection.

4.3 Allowed Medications

There are no medication restrictions for participation in the trial.

4.4 Disallowed Medications

There are no medication restrictions for participation in the trial.
4.5 Enrollment Procedures

Protocol registration for PACTG P1036-Part A 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 and the study details are discussed, questions will be answered, and written informed consent will be obtained from the subject and the parent or the legal guardian (if required by the local IRB) before any study related procedures are performed.

4.6 Co-enrollment Guidelines

There are no co-enrollment restrictions for the focus group participants in this study.

5.0 SUBJECT MANAGEMENT

5.1 Toxicity Management

Not applicable. This is a one session study involving participation in a focus group by adolescents already participating in local HIV-1 support groups.

5.2 Study Management Plan

5.21 Focus Groups

A sample of HIV-1 positive adolescents who have disclosed their HIV-1 status to, and are regular attendees of, their local HIV-1 adolescent support group will be invited to participate in a focus group to be held at their clinical care site or other site determined by site personnel. These focus groups can be scheduled at the time of choosing for site personnel. We will attempt to have a minimum of five and a maximum of ten adolescents at each of three sites to voluntarily participate in the focus group. The group will be facilitated by a staff member who has some prior experience with focus groups, who is knowledgeable about HIV infection, has some understanding of the problems of non-adherence to medication, and who is not otherwise affiliated with the development of PACTG P1036A. Suggested personnel include social workers, nurse practitioners, psychologists, or other qualified personnel. The focus group leader should have credentials acceptable to the PACTG P1036A team and experience working with adolescents. A second individual to take notes is also required. The PACTG P1036A team recognizes that volunteers will have variable experiences with adherence
difficulties and that not all adolescents engaged in support groups will have perfect adherence.

5.211 Invitation to Participate

During a regularly scheduled support group meeting, the support group facilitator will announce another session that focuses on gathering the opinions of adolescents around a proposed adherence intervention. The date, time, and location will be announced and all present will be invited to attend. Those adolescents who are regular attendees of the support group not in attendance on the day of the announcement will be contacted by their support group facilitator and invited to attend the focus group. A scripted invitation is contained in Appendix II. If more than 10 adolescents are willing to participate in the focus group and are found to meet the study eligibility criteria, 10 will be selected by the site staff and the others will be thanked for their willingness to participate.

5.212 Focus Group Procedures

Focus groups will be run by a member of the study staff using a focus group script developed by the PACTG P1036-Part A team (Appendix III). The focus groups will be led by one facilitator and will last approximately two hours. A second person will assist the facilitator by taking notes, although the groups will also be audio-taped to assure all salient information provided by the groups is captured. A minimum of five participants must be present to conduct the initial focus group. If, after 45 minutes, a minimum of five participants are not present, the facilitator will thank participants for coming and let them know that the group will be rescheduled. It will be particularly important to ensure a sufficient number of participants as required for the study. Participants will be asked not to use names that might identify those in the group. Incentives to participate in the focus group, including money, food, transportation, child-care, or others are permitted, but will be determined by the site and local IRB, and should be included in the site-specific consent form.

5.213 Measures

- Participants will be presented with and react to the DOT strategy, discuss characteristics of the DOT enabler, the venue, the context and the procedure.
• An anonymous, self-administered, demographic checklist including age, gender, race, ethnicity, education, prior and current experience with ARV therapy, and the presence of adherence problems will be collected for the purpose of describing the participants in the focus groups. If the participant has difficulty completing the checklist, the facilitator can assist. This checklist will be placed into an envelope and sealed by the participant to ensure confidentiality. The envelope will be sent via Federal Express directly to the DMC.
• Time estimate for the completion of the focus group is two hours.

6.0 SERIOUS ADVERSE EXPERIENCE REPORTING

This is a one session study involving participation in a focus group by adolescents already participating in local HIV support groups. No issues regarding disclosure of diagnosis or confidentiality are anticipated. Personnel, such as a social worker, case manager, or psychologist will be available in case the content of the discussion group causes emotional distress. Because this study is observational and will not involve any treatment, SAE reporting will not be required.

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design Issues

This is a study to determine the characteristics of a DOT intervention model in an adolescent population that is either naïve to antiretroviral therapy or has demonstrated adherence difficulties. Focus groups will be conducted at three predetermined sites. The information gained from these focus groups will be used to refine the DOT intervention model proposed in a pilot DOT protocol that will follow this study. Fifteen to thirty participants will attend the focus groups at the three study sites.

7.2 Outcome Measures

7.21 Primary Outcome Measures

The primary outcome is the opinions expressed by the focus group participants on the DOT strategy, including characteristics of the DOT enabler, the venue, the context, and the procedure of the DOT intervention.
7.3 Stratification

This study will be stratified by site. There will be 3 strata.

7.4 Sample Size and Accrual

Sample Size

7.41 For this study (focus group) a minimum of 5 subjects and a maximum of 10 subjects will be included at each of the three participating sites. Targeted accrual will be 15-30 subjects total.

7.42 Accrual

Not applicable. Focus group participants will be comprised of established subjects at the three study sites.

7.5 Monitoring

This study involves one session to participate in the focus group and will not require any ongoing monitoring. There will be no interim analysis.

7.6 Analysis

7.61 Analysis for Primary Outcome Measure

Following the focus groups, the facilitator will label the tape with the site and date. The tapes will be sent via Federal Express, along with the notes taken by the facilitator’s assistant, to the protocol chair. The tapes of the focus groups will be transcribed, with the notes used for clarification, as necessary. The site will notify the protocol chair prior to sending. When not in use, the tapes and notes will be stored in a locked cabinet. Should any names be inadvertently used during the session, they will be omitted in the transcripts. Following transcription, the protocol psychologist and the protocol chair will listen to the tapes to validate the transcript and to note the tone of the participants. Once assurance is made that the transcription is valid, the tapes and notes will be destroyed. The protocol chair will maintain a log of tape and note locations and destruction.

The transcript will then be assessed by qualitative software to assess repeating themes. The reviewers will note recommendations from the adolescents regarding the identification and characteristics of the DOT enabler, and recommendations regarding the locations and times for meetings. They will also note the features that adolescents would accept in a
DOT enabler and a set of specific objectives that should be covered in the DOT visit. After review of the tape, transcript, and results of the qualitative search, the protocol psychologist and the protocol chair will summarize the results. The summary will also be broken down by site. Information collected by the self-administered checklist, including the demographic characteristics of the study subjects, their experiences with ARV therapy and the presence of adherence problems will be summarized both by site and for the whole study. The summaries will be reviewed and then discussed by the team.

8.0 HUMAN SUBJECTS

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

8.1 Institutional Review Board (IRB) Review and Informed Consent

Written Informed Consent

Waiver of written informed consent will be requested based on the finding that the focus group process in this context involves no more than minimal risk and involves procedures that would not require written consent outside the research setting (45 CFR 46.117c). The participants will be provided with a written summary of the purpose of the focus group and the process. Only the listed demographic and antiretroviral therapy/adherence information will be obtained. The names of the participants will not be used nor will any identifiers be contained in the information forwarded to the protocol psychologist and the protocol chair. A model informed consent is included in Appendix V in the event that the local IRB does not waive the requirement for written informed consent.

Parental Permission

The study team is also requesting the waiver of parental permission for minor participation in the focus groups 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.

The informed consent process 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/legal guardian) as determined by the IRB.

The site will follow the direction of the local IRB in obtaining informed consent:

(a) If both written informed consent and parental permission are waived, the site must document the subject’s willingness to participate in the study in the medical record. In situations where parental permission is waived, the subject will be provided with additional pertinent information about the study.

(b) If the local IRB allows waiver of written documentation of informed consent but not parental permission, verbal permission from the parent or legal guardian is required and must be documented in the medical record.

(c) If the local IRB allows waiver of parental permission but not written documentation of informed consent, the subject must review and sign the written informed consent document.

(d) If neither the request to waive written documentation of informed consent nor parental permission is granted, written informed consent must then be obtained from the subject or parent/legal guardian of subjects who are below the legal age of consent. The minor subject's assent must also be obtained (this qualification is unnecessary since such a person could not function in the focus group).

8.2 Subject Confidentiality

Demographic data sheets will be collected without any identifying information. These sheets will be placed by the study subject in an envelope and sealed to protect confidentiality. All sheets from the session will be sent via Federal Express to the DMC. These data sheets and the focus group audio-tapes will only be identified by the city and date of the focus group. Participants in the focus groups will be asked not to use names during the audio-taped sessions. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only.

8.3 Study Discontinuation

The study may be discontinued at any time by the DAIDS.
9.0 **PUBLICATION OF RESEARCH FINDINGS**

Publication of the results of this trial will be governed by PACTG policies. Any presentation, abstract, or manuscript will be reviewed according to PACTG policy prior to submission.
10.0 REFERENCES


APPENDIX I

SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen*</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform about focus groups</td>
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<td></td>
</tr>
<tr>
<td>Determine eligibility</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Focus group invitations</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Informed consent**</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Focus group session</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Self –Report Demographic and Adherence Information Collection Form</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Screen within 30 days of focus group interview session.
** May not be appropriate if waived.
APPENDIX II

INSTRUCTIONS FOR INVITATION TO THE FOCUS GROUP

During a regularly scheduled support group meeting of HIV-1-infected adolescents only, the leader will announce the following:

“I wanted to let you know about a new research study that is being done in the Pediatric AIDS Clinical Trials Group (PACTG). The PACTG, for those who may not know, is a group of people from all over the country who research new drugs for children and teens with HIV. They also try to find ways to help make it easier to take HIV medicines, as well as try to make sure that young people are taking their medications correctly.

This research study involves a one session focus group. A focus group is a small group of people that meet to discuss a certain topic. There is a leader in the group that helps to keep the group discussion on track. The reason for having this focus group is to find out ways to help young people to keep taking their HIV medicines at the times that they are supposed to take them so that the medicines will have the best chance of working. One way that health care workers have thought to do this is through Directly Observed Therapy or DOT. Basically, with DOT, someone would actually watch the person take his/her HIV medication. The purpose of this focus group is to find out the most acceptable way to use DOT in teens.

The group will be held after our usual support group (or alternate time and location). We will need 5 to 10 volunteers to participate. The focus group will take about 2 hours and only meet once. In addition to the leader or facilitator there will be someone to help take notes about what is said. The session will also be audio-taped, but not video-taped. Once the group is finished, the audio-tape and notes will be mailed to two members of the study team so that they can listen and gather the information. Focus groups will be conducted at three PACTG sites across the US. After the researchers listen to the discussions from the tapes, the tapes and notes will then be destroyed. To protect everyone’s privacy, we will ask you not to use any names on the tape. Should anyone use a name by accident, this information will not be written in the report of the focus group. There will be one brief questionnaire for you to answer, but it will not have your name on it. The questionnaire will be placed directly in an envelope and sent to a center to have the answers entered into a computer.

If you are interested, you must agree to stay an extra 2 hours (or for a 2 hour session if not adjacent to the regular support group). For your participation ________ (Insert language if meals, transportation, incentives are available).

To participate, you must be between 16 years and up to your 22nd birthday, have first become HIV infected as a teenager, you must be taking or have taken HIV medications at some time, and you must not be pregnant or breast-feeding. If you are interested, please let me know.”
(Add any necessary site-specific language re the consent process).
APPENDIX III

FOCUS GROUP MONOLOGUE AND QUESTIONS

Opening: (5 minutes for introduction, 15 minutes to complete demographics sheet)

The facilitator will thank the group for participating in the focus group.

I would like to thank each of you for agreeing to be a part of this focus group. My name is ___________________ and I will be leading the focus group session today. This is ____________________ whose only role here today will be to help me by taking notes about your opinions. We will also audio-tape the discussion so that we will be certain not to miss writing down any of your ideas. This tape, along with the notes, will be sent to researchers in Memphis, Tennessee where it will be listened to and more notes will be taken. The reason for doing this is so that we do not miss any of your thoughts or ideas that you present here today. After the tape is listened to at the center in Memphis, it will be destroyed, along with the written notes that were taken here today.

Most of you here may already know each other from your usual support group. However, during today’s focus group we want your thoughts and ideas to be anonymous, so I will ask you not to use anyone’s name, including your own, during the discussion. We will not ask directly about your own experience with taking HIV medications but ask that you think about what it might be like for someone like you who is prescribed HIV medications. If you forget and call someone by name or talk about yourself, we will remind you not to use names or talk about your own experience with medications for HIV.

Before we get started with our discussion, there are several questions the researchers would like you to answer for them (Note: Facilitator will pass out the data sheets while talking to the group). Because they want your answers to be anonymous, please do not put your name on the sheet. Please read and answer each of the questions. The reason for collecting the information asked in these questions is so the researchers will know some information about those who participated in the focus group and get an idea if your background and experiences are similar to the adolescents that the researchers want to study in the research program that they are developing. If you do not understand a question or need help reading the questions, please let us know so we can help you. (Note: a list of prescribed antiretroviral medications will be made available to assist the participants with identifying and responding to the question about their medication(s)/history).

FACILITATOR: START AUDIO-TAPING NOW

Introduction (5 minutes): The focus group will be informed that the purpose is to help a group of researchers develop a new program to help HIV-infected adolescents with adhering to their medication regimen in the following manner:
APPENDIX III (Cont.)

The reason that we are having this focus group is so that you can provide your input for a research program that researchers are trying to develop that will help other adolescents do better at taking their medications as prescribed. The program that we will talk about is called “Directly Observed Therapy” or “DOT” for short. As the name says, this is a program where someone would meet with an adolescent daily for a certain number of days to watch him/her take each of his/her medication doses. The researchers are only considering this program for adolescents who know they have trouble taking their HIV medications as prescribed and would like help OR for subjects that are just being started on HIV therapy for the first time and are unsure if they will be able to take their medications as prescribed.

Facilitator:

What were the first thoughts that came to your mind when thinking about the term “Directly Observed Therapy”?

Transition (10-15 minutes): The facilitator will ask the participants to list reasons that HIV-infected adolescents may not take their medications as directed. These will be listed on a white/blackboard or flip chart to refer to later in the focus group. The items listed in the demographic sheet will already be listed on the board/flipchart.

Facilitator:

Before getting more into discussing DOT, I think it would be helpful if we could make a list of some of the reasons that adolescents may have trouble with taking their medications. If you will look at the board/flip chart I’ve already listed the same items that were on your sheet. These are things that we have learned from other groups of adolescents. What do you think about these being good reasons?

(If there is no spontaneous discussion, the facilitator can ask directly about each item on the list).

Facilitator: Are there any other reasons you can think of as to why an adolescent would not take his/her medications as prescribed? (Any additional items mentioned by the participants should be added to the list).

Facilitator: These are all very important ideas because the researchers can use them when they are thinking about the best way to develop the DOT program.
Key Questions (60 minutes, approximately 5 minutes on each question): The facilitator will then lead into the key questions for the focus group.

Facilitator: *We now have a few very important questions that the DOT researchers would like your answers on.*

1. *Do you think that meeting someone every day to watch you take your medications would help you/someone be more adherent? Why or why not?*

2. *If there was a DOT program, what sort of person, we'll call them DOT enablers, would be best to meet the needs of the DOT participant? Describe the characteristics that you think would be important.*

   (Facilitator probes: if not otherwise brought up by the group, query for preferred age, gender, HIV status, ethnicity, affluence, education, communication style, availability, willingness to meet at what kind of locations.)

3. *If you are to take your medications twice a day, and you meet with the DOT enabler once a day, how do you think meeting with the enabler will affect/influence you taking your later dose(s)? If not meeting with the DOT enabler for each dose, what things would help someone remember to take the second or second and third doses of medications?*

   (Facilitator probes: if not otherwise brought up by the group, ask about automated medication reminders on beepers.)

4. *One of the things that we would be especially concerned about is the safety of both the DOT enabler and the person he/she was meeting. Can you think of places or situations that we should avoid in trying to set up the meeting of the teen and the DOT enabler?*

   (Facilitator probes: if not brought up, ask about gang activity and locations and times that would be unacceptable to meet.)

5. *Where would the best place for the DOT participant to meet the DOT enabler be? Should the DOT participant or the DOT enabler be the person to choose or should they both participate in the decision? Should it always be the same place? Or, would it be better to meet in the place where the adolescent most frequently would take his/her medication?*

   (Facilitator probes: if not otherwise brought up by the group, ask about home, school, community center, clinic, business, workplace as acceptable places)
6. How would the DOT participant and the DOT enabler communicate with each other? (e.g., how would they arrange to meet, or talk about change of plans, or important issues that come up)

(Facilitator probes: if not otherwise brought up by the group, ask about beepers and cell phones and who should have them available, and who should call who.)

7. Presuming that the DOT participant is given a beeper and the DOT enabler has a cell phone:

a. What should be expected of the DOT participant if he/she is unable to reach the meeting place on time?

b. What should be expected of the DOT enabler if he/she does not find the DOT participant at the meeting place?

8. What sorts of issues or problems related to medication adherence should the DOT enabler be able to help with?

(Facilitator probes: The list of reasons for non-adherence generated in the transition should be referred to here. Also, if not otherwise mentioned, the facilitator should ask about general health inquiries, condom availability, housing, food, and transportation for the next clinic appointments).

Is there anything you think he/she should not help with?

9. How many days, weeks, or months do you think the DOT enabler should meet with the DOT participant?

(Facilitator probes: once answers are provided: If it was you, do you think you realistically would continue to meet with your enabler for that (going through each duration provided) long?

10. What kinds of problems can you see happening with the DOT program?

(Facilitator probes: If not otherwise addressed, probe regarding school officials’, parents’, friends’ recognition of the DOT interaction.)

11. If you were having problems with taking HIV medications as prescribed, would you consider DOT as an option? If not, can you tell me some of the reasons that it wouldn’t be helpful to you?
APPENDIX III (Cont.)

Ending (10 minutes): The facilitator will close the meeting and thank the participants.

Facilitator: If you had advice to give about the DOT program to these researchers, what would it be?

Facilitator: The DOT researchers and I thank you very much for your time. I know this information will be very helpful to the researchers. Even though they are not here, I know that they would also like to thank you for being so open about this important issue.

As a final question, is there is anything you wanted to say but did not get a chance to say?

Thank you once again for your participation!
APPENDIX IV

DIVISION OF AIDS
PEDiatric AIDS CLINICAL TRIALS GROUP (PACTG)

SAMPLE DEMOGRAPHIC COLLECTION FORM

Demographic Information Collection Form

City: ___________________________ Date: __________________________

1. How old are you? ___________ (yr/month)

2. What is your gender? (Circle correct answer)
   Male    Female

3. What is your race/ethnicity? (Circle correct answer)
   African-American
   African/Caribbean/Non-Latino
   Latino
   White/Non-Latino
   Asian
   Other

4. What is the last grade that you completed in school? ________________

5. Are you currently prescribed anti-HIV medications? (Circle correct answer)
   Yes    No

6. If yes, can you list the names of the medications?

7. If you are not taking anti-HIV medications now, have you ever taken anti-HIV medications (if female, at a time other than while you were pregnant)? (Circle correct answer)
   Yes    No
APPENDIX IV (CONT)

8. If you have ever been prescribed anti-HIV medicines, have you ever had any problems taking your medications? (Circle correct answer)
   Yes     No

9. If you have had problems taking your medications, please indicate all those reasons below that may have been reasons why you had problems taking your medications as prescribed? (Please circle correct answer for each item below.)

   Confused about what and/or when to take the medications  Yes   No
   Felt like the medication was toxic or harmful      Yes   No
   Felt like the medication had no positive effect     Yes   No
   Wanted to avoid the side effects of the medication Yes   No
   Felt healthy, so did not take                      Yes   No
   Taking the medication reminded you of having HIV  Yes   No
   Felt sick or ill                                   Yes   No
   Problem with special instructions about taking the medications Yes   No
   Had too many pills to take                         Yes   No
   Did not like the taste/texture                     Yes   No
   Already missed medications – blew it for the day  Yes   No
   Did not want others to notice the medications     Yes   No
   Prescription not refilled                          Yes   No
   Busy with other things                             Yes   No
   Fell asleep or slept through dose time             Yes   No
   Change in daily routine                           Yes   No
   Did not have medication with you                   Yes   No
**APPENDIX IV (CONT)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simply forgot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not have a set daily routine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Could not swallow pills because they were too big</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not want to take them/ Didn’t feel like it</td>
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</table>

Thank you very much for completing this information and being a part of the focus group.
APPENDIX V

DIVISION OF AIDS
PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG)

SAMPLE INFORMED CONSENT

P1036A Version 1.0

DIRECTLY OBSERVED THERAPY (DOT) IN HIV-1 INFECTED ADOLESCENTS:
PART A - FOCUS GROUPS

SHORT TITLE FOR THE STUDY: DOT in Adolescents-Part A: Focus Group

INTRODUCTION

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

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

WHY IS THIS STUDY BEING DONE?

The purpose of the study is to help researchers design a directly observed therapy program (DOT) that will help adolescents with taking their antiretroviral medications on schedule. DOT is when a special person “watches” as you take your medications every day to make sure you have taken your medications that day.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you are eligible and decide to take part in the study, you will be asked to sign this consent form. You will then be asked to attend the group session that will last approximately 2 hours. Each person may participate in only one group. The group session will be held at __________.
If it becomes necessary to reschedule the group (for example, if not enough people attend, if recording equipment should break, or if the group moderator's schedule needs to be changed), the session will be rescheduled and you will be contacted and asked to participate for the next time.

After everyone has arrived, you will be asked questions about yourself, your HIV medical history and any HIV medications you are currently taking or have taken in the past. You will place this questionnaire in an envelope and seal it. It will then be mailed directly to a data center in New York. This will help protect your confidentiality. After completing this questionnaire, the moderator will remind everyone that the group discussion is to be private and confidential. Only the group participants, a person taking notes, and the moderator can remain after the discussion begins. Each person will agree to protect the privacy of all the group members. You will be asked to discuss how you would respond to working with someone to assist you in taking your medications, what kind of person you would like for them to be, and where you would feel most comfortable meeting with them. So that you and others feel free to openly discuss your feelings, you will be asked to maintain the privacy and confidentiality of all the other study volunteers. You must agree to keep the discussion private and not to reveal the name or HIV status of other group participants. Once at the location, you can decide not to actively take part in the discussions. If at any time you decide that you no longer wish to participate, you are free to leave the session.

The group discussions will be audio-taped so that the researchers can record comments completely and accurately. The moderator will secure the interview tapes. The identity of the study volunteers will not be revealed in any presentations or publications that result from the study. The group sessions will NOT be video-taped.

Participating in this study will not keep you from participating in additional research studies at the same time.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

Between 15 and 30 adolescents will participate in this study.

**HOW LONG WILL I BE IN THIS STUDY?**

You will be in this part of the study for only one session that will last about 2 hours.
WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- the study is cancelled by the National Institutes of Health (NIH), or the site’s Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- you are not able to attend the study session as required by the study
- your behavior is disruptive to the group discussion.
- you become pregnant

WHAT ARE THE RISKS OF THE STUDY?

Because of the personal nature of some of the questions and/or discussions, you may feel very uncomfortable during the discussions. Even with the precautions taken to protect your confidentiality, you still may feel uncomfortable. You may find it difficult to maintain the privacy of each group participant's identity and stories, but this is required.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You will receive no direct benefit from being in this part of the study. Information learned from this study may help others who have HIV.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the (insert name of site) IRB, National Institutes of Health (NIH), study staff, and study monitors supporting this study. Having a Certificate
of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

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

WHAT ARE THE COSTS TO ME?

There are no costs to you for participating in this study.

WILL I RECEIVE ANY PAYMENT?

You may be paid by the local site for being a part of this focus group, or meals may be provided. Transportation expenses will be reimbursed.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. We will have counselors available at the time of the focus group to discuss any problems with you. They will also be available to help you after the study if you feel that this is needed. There is no program for compensation either through this local institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

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

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.
APPENDIX V (Cont.)

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

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

For questions about your 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
SIGNATURE PAGE

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

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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<th>Participant’s Legal Guardian (print) (As appropriate)</th>
<th>Legal Guardian’s Signature and Date</th>
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<th>Study Staff Conducting Consent Discussion (print)</th>
<th>Study Staff Signature and Date</th>
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<th>Witness’ Name (print) (As appropriate)</th>
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