IMPAACT P1080
(DAIDS Document ID 10768)

A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents

A Multicenter, US Domestic and International Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

This file contains all documents related to Version 1.0 of IMPAACT P1080, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #2, dated August 22, 2011
- Clarification Memorandum #5, dated August 19, 2011
- Clarification Memorandum #4, dated April 21, 2011
- Letter of Amendment #1, dated February 16, 2011
- Clarification Memorandum #3, dated November 29, 2010
- Clarification Memorandum #2, dated August 25, 2010
- Clarification Memorandum #1, dated July 27, 2010
- Protocol Version 1.0, dated June 17, 2010
TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in P1080
FROM: P1080 Protocol Team
DATE: August 22, 2011
DAIDS ES #: 10768

THE FOLLOWING INFORMATION IMPACTS THE P1080 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR REVIEW. THIS LETTER OF AMENDMENT MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

UPON RECEIVING FINAL IRB/EC AND ANY OTHER APPLICABLE REGULATORY ENTITY (RE) APPROVAL(S) FOR THIS LOA, SITES SHOULD IMPLEMENT THE LOA IMMEDIATELY. SITES ARE STILL REQUIRED TO SUBMIT A LOA REGISTRATION PACKET TO THE DAIDS PROTOCOL REGISTRATION OFFICE (DAIDS PRO) AT THE REGULATORY SUPPORT CENTER (RSC). SITES WILL RECEIVE A REGISTRATION NOTIFICATION FOR THE LOA ONCE THE DAIDS PRO VERIFIES THAT ALL THE REQUIRED LOA REGISTRATION DOCUMENTS HAVE BEEN RECEIVED AND ARE COMPLETE. A LOA REGISTRATION NOTIFICATION FROM THE DAIDS PRO IS NOT REQUIRED PRIOR TO IMPLEMENTING THE LOA. A COPY OF THE DAIDS PRO LOA REGISTRATION NOTIFICATION ALONG WITH THIS LETTER AND ANY IRB/EC CORRESPONDENCE SHOULD BE RETAINED IN THE SITE'S REGULATORY FILES.

This letter of amendment can be obtained from the P1080 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the P1080 web page you will have the option to click the PSWP tab.

This Letter of Amendment (LOA) serves to make the following changes in P1080, Version 1.0:

1. The exclusion criteria have been updated to allow subjects who are taking other routine psychiatric medications which are not included in the disallowed medications list (section 4.5) to enter the study. Additionally, psychiatric medications prescribed for occasional use are not restricted in the week prior to the PK visit.
   - Section 4.32 is deleted.

2. Section 4.5, Disallowed Drugs, has been updated as follows:
   - In Section 4.53, the following drugs have been added to the list of disallowed medications for subjects in the amphetamine/dextroamphetamine arm:
     - Fluoxetine
     - Paroxetine
     - Quinidine
   - Bupropion has been removed from the list of disallowed medications. (Section 4.51).
Atomoxetine has been removed from the list of disallowed medications. (Sections 4.52 and 4.53).

This information will be added to the next version of the protocol. Please contact the protocol team at actg.teamp1080@fstrf.org if you have any questions or concerns about the information provided in this letter. Please file with your protocol documents.
This is Clarification Memo #5 for IMPAACT P1080 "A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents” Version 1.0 dated June 17th, 2010.

This Clarification Memo can be obtained from the P1080 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1080] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to clarify the following regarding Appendix I-Schedule of Evaluations, Footnote 10:

   It is expected that those on the amphetamine/dextroamphetamine arm will test positive for amphetamines. Further testing for methamphetamine, if not already part of the standard drug screen, is not required prior to enrollment for these participants, and a positive urine test for amphetamines does not exclude them from participation.

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1080@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1080.
This is Clarification Memo #4 for IMPAACT P1080 "A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents” Version 1.0 dated June 17th, 2010.

This Clarification Memo can be obtained from the P1080 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1080] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to clarify the following:

1. The timing of the dextromethorphan dose and the 4-hour urine collection period has been clarified in Footnote 19 Appendix I – Schedule of Evaluations to include:

   The date and time of the dextromethorphan dose should be recorded, and this is the start time of the 4-hour urine collection period. The date and time of the first void and the final void within the 4-hour period after administration of the dextromethorphan dose should be recorded. See Section 3.23 for further details.

2. Additional detail has been provided for Section 3.23 of the protocol to better describe the timing of the dextromethorphan dose and the 4-hour urine collection period:

   The CYP 3A4 and 2D6 metabolic phenotype of each subject will be measured by the 3-hydroxy-morphinan/dextromethorphan and the dextromethorphan/dextrorphan (DM/DX) ratios. First, the subject will be asked to void any urine. This void is discarded and NOT included in the collection. Next, a single oral dose of cough syrup (dextromethorphan) will be administered at the FDA-approved dose for each subject. The study will provide the dextromethorphan cough syrup to the participating sites [15 mg per 5 mL] per Section 5.4. Specific dosing recommendations are described in Section 5.11. This will serve as a marker for 2D6 and 3A4 activity, and will allow us to predict the metabolism of psychiatric medications. The date and time of the dextromethorphan dose will be recorded, and this will be the start time of the 4-hour urine collection. All urine produced for the 4 hours after the dextromethorphan dose time will be collected. The date and time of the first void within the 4-hour time window should be recorded. The subject should be asked to empty their bladder at the 4-hour time point, and this final sample should be included in the urine collection. The date and time of the final void within the 4-hour time window should be recorded (even if it occurs earlier than exactly at the 4-hour urine collection time point) as the last collection date and time. All urine collected within the 4-hour window will be pooled as a single specimen. The total volume of that specimen will be measured and recorded, and a 15 mL aliquot will be stored for analysis of dextromethorphan, dextrorphan and 3-hydroxy-morphinan concentrations in the urine.

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1080@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1080.
TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in P1080
FROM: P1080 Protocol Team
DATE: February 16, 2011

DAIDS ES #: 10768

THE FOLLOWING INFORMATION IMPACTS THE P1080 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR REVIEW. THIS LETTER OF AMENDMENT MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

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This letter of amendment can be obtained from the P1080 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1080] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

This Letter of Amendment (LOA) serves to make the following changes in P1080, Version 1.0:

- Correction to Section 3.0, Study Design:
  - Page 35, Section 3.0, 1st sentence, 2nd paragraph has been updated to read as follows:
    
    HIV uninfected subjects will be recruited per the description in Section 4.6.

- Correction to Section 3.3, Week 24 Pharmacokinetic (PK) Visit:
  - Page 38, Section 3.3, 1st sentence, 1st paragraph has been updated to read as follows:
    
    The second PK visit will take place at approximately 24 weeks following the study subject’s entry visit.
• Correction to Appendix I, Schedule of Evaluations:
  
  o Footnote 1 has been updated to read as follows:

  Screening and entry may occur at the same visit or on separate days up to 4 weeks apart. **Follow-up visit dates should be calculated from the entry visit.**

• Corrections to Appendix III-A, DAIDS Sample Informed Consent for HIV-1 Infected Children and Adolescents:

  o Page 4, under the “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?” section, sub-section “Week 6 and Week 24 Pharmacokinetic (PK) Visits”, the first sentence has been updated to read as follows:

  Approximately 6 weeks and 24 weeks after your/your child’s **entry** visit, you/your child will return to the clinic before taking your/your child’s usual medicine.

  o Page 5, under the “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?” section, sub-section “Weeks 30, 42 and 52 Telephone Call”, the first sentence has been updated to read as follows:

  At approximately 30 weeks, 42 weeks and 52 weeks after your /your child’s **entry** visit, the study staff will call you by phone to see how you/your child is doing.

• Corrections to Appendix III-B, DAIDS Sample Informed Consent for HIV Un-Infected Children and Adolescents:

  o Page 2, under the “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?” section, the reference to ARV medications has been removed and should read as follows:

  If you/your child agree(s) to take part in this study, there will be three study visits described below. In addition, you/your child will be contacted by telephone every 3 months to collect any additional information about changes in ADHD medications.

  o Page 2, under the “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?” section, sub-section “Screening Visit”, the first sentence of the second bullet point has been updated to read as follows:

  If you are/your child is 13 years of age or older, and have not had an HIV test **in the past year**, 1 teaspoon of blood will be drawn to test your blood for the HIV virus.
o Page 3, under the “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?” section, sub-section “Week 6 and Week 24 Pharmacokinetic (PK) Visits”, the first sentence has been updated to read as follows:

Approximately 6 weeks and 24 weeks after your/your child’s entry visit, you/your child will return to the clinic before taking your/your child’s usual medicine.

o Page 4, “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?” sub-section “Weeks 30, 42 and 52 Telephone Call”, has been updated to read as follows (note: reference to antiretroviral medications has been removed):

At approximately 30 weeks, 42 weeks and 52 weeks after your /your child’s entry visit, the study staff will call you by phone to see how you/your child is doing. These calls will take approximately 30 minutes. Study staff will also ask about your/your child’s medication history, including all dose changes to ADHD medications. Study staff will ask you/your child about whether you/your child have stayed on the medication as prescribed since the last visit. If you have/your child has discontinued the ADHD medication since your last PK visit, you will be asked why. Study staff may also ask to briefly speak to your child about any symptoms they may be experiencing.

This information will be added to the next version of the protocol. Please contact the protocol team at actg.teamp1080@fstrf.org if you have any questions or concerns about the information provided in this letter. Please file with your protocol documents.
This is Clarification Memo #3 for IMPAACT P1080 “A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents” Version 1.0 dated June 17th, 2010.

This Clarification Memo can be obtained from the P1080 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1080] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to update the following:

1. The footnotes for Physical Exam (6), Hematology (9), Chemistries (11), and Lymphocyte (17) subsets have been updated and a footnote has been added for the Vanderbilt Scale Questionnaire in Appendix I – Schedule of Evaluations. These changes may be relevant for participants whose Screening Visit test results will not be available the same day and who cannot return to the clinic for a separate Entry Visit.
   a. The following information has been added to footnotes 6, 9, 11, and 17:

   For the Entry Visit, data may be abstracted from the patient’s medical chart if performed for clinical care within 12 weeks prior to the Entry Visit.

   b. Footnote 20 has been added for the Vanderbilt Scale Questionnaire and reads as follows:

   The Vanderbilt Scale Questionnaire can be administered via telephone at the Entry Visit.

   Sites should also note that a pregnancy test is required at the Entry Visit, but there is a 72 hour window, so it would not have to be repeated if the participant is enrolled within 72 hours of the Screening Visit.

2. The first sentence of Footnote 5 in Appendix I – Schedule of Evaluations has been updated to read as follows:

   Complete history including source documentation for lifetime exposure to antiretroviral medications; CDC diagnoses; most recent CD4 count and CD4%, nadir CD4 count and CD4%; most recent viral load, and total lymphocyte count (for HIV-1 infected subjects); Tanner stage, neuropsychiatric diagnoses; and lifetime exposure to psychiatric medications for all subjects.

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1080@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1080.
DATE: 25 August 2010

RE: CLARIFICATION MEMO #2 for P1080 “A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents”

TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in IMPAACT P1080

FROM: P1080 Protocol Team

This is Clarification Memo #2 for IMPAACT P1080 “A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents” Version 1.0 dated June 17th, 2010.

This Clarification Memo can be obtained from the P1080 protocol specific web page (http://www.impaactgroup.org). The username is impaact and the password is cure (all lower case). The document is located under the section titled “Current Protocol Related Documents”.

The purpose of this memo is to correct the following typographical error regarding the duration of the study:

1. The duration of the study should read: “the entire trial” instead of “the entire 144 week trial”. This clarification will affect the following sections of the protocol:
   - Section 4.18
   - Section 4.20
   - Appendix III-A (Sample Informed Consent for HIV-1 Infected Subjects) – Screening Visit section of “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?”
   - Appendix III-B (Sample Informed Consent for HIV-1 Uninfected Subjects) – Screening Visit section of “What Do I/Does My Child Have To Do If I Am / He / She Is In This Study?”

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1080@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1080.
This is Clarification Memo #1 for IMPAACT P1080 "A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents” Version 1.0 dated June 17, 2010.

This Clarification Memo can be obtained from the P1080 protocol specific web page (http://www.impaactgroup.org/). The username is impaact and the password is cure (all lower case). The document is located under the section titled “Current Protocol Related Documents”.

This memo serves to clarify the following:

1. Testing for propoxyphene at the screening visit is no longer required as part of the urine drug screening panel (Section 4.31 and Appendix I, footnote 10). However, if the assay is still currently part of the routine screening at the site, the result should be recorded on the appropriate CRF as part of the study.

2. Appendix I, footnote 9, first sentence should read, “Hematology for Entry Visit should include . . .”

3. Appendix I, footnote 13, first sentence should read, “… within 72 hours of the 6 week and 24 week PK visits.”

These clarifications will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1080@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1080.
A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents

A Multicenter, Domestic Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID) and The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Non-IND Protocol
DAIDS ES ID# 10768

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Version 1.0
FINAL
June 17, 2010
IMPAACT P1080 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to actg.teamp1080@fstrf.org. Remember to include the subject’s PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1080@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration materials can be sent electronically to epr@tech-res.com or sent via Fax (301) 897-1701 or 1-800-418-3544. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by email at sdac.random.desk@fstrf.org.

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# GLOSSARY OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>CD</td>
<td>Continuous Delivery</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
</tr>
<tr>
<td>CES1</td>
<td>Carboxylesterase 1</td>
</tr>
<tr>
<td>CHARTER</td>
<td>CNS HIV Anti-retroviral Therapy Effects Research</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>Cpre</td>
<td>Pre-dose Concentration</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DAERS</td>
<td>DAIDS Adverse Event Reporting System</td>
</tr>
<tr>
<td>DM/DX</td>
<td>Dextromethorphan/dextrorphan</td>
</tr>
<tr>
<td>EFV</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>ER</td>
<td>Extended Release</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HCG</td>
<td>Human Chorionic Gonadotropin</td>
</tr>
<tr>
<td>HIV-1</td>
<td>Human Immunodeficiency Virus Type I</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate Release</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>K_e</td>
<td>Elimination rate constant</td>
</tr>
<tr>
<td>LA</td>
<td>Long Acting</td>
</tr>
<tr>
<td>MDR1</td>
<td>Multidrug resistance transporter gene</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>OHRP</td>
<td>Office for Human Research Protections</td>
</tr>
<tr>
<td>PGP</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>PI</td>
<td>Protease Inhibitor</td>
</tr>
<tr>
<td>PIBA</td>
<td>Push in bottle adaptors</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>RCC</td>
<td>Regulatory Compliance Center</td>
</tr>
<tr>
<td>RTV</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Events</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SODAS</td>
<td>Spheroidal Oral Drug Absorption System</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>SR</td>
<td>Slow Release or Sustained Release</td>
</tr>
<tr>
<td>T½</td>
<td>Half-life</td>
</tr>
<tr>
<td>Tmax</td>
<td>Corresponding time of maximum concentration</td>
</tr>
<tr>
<td>US DHHS</td>
<td>United States Department of Health and Human Services</td>
</tr>
<tr>
<td>V_d / F</td>
<td>Apparent volume of distribution</td>
</tr>
<tr>
<td>XR</td>
<td>Extended Release</td>
</tr>
</tbody>
</table>
SCHEMA

A PILOT STUDY OF PSYCHIATRIC AND ANTIRETROVIRAL MEDICATION CONCENTRATIONS IN HIV-1 INFECTED AND UNINFECTED CHILDREN AND ADOLESCENTS

DESIGN: Pilot population pharmacokinetic study

SAMPLE SIZE: A maximum of 90 evaluable subjects; 45 evaluable subjects per study arm.

POPULATION: HIV-1 infected and uninfected children and adolescents ages ≥6 to <25 years who are currently receiving methylphenidate or amphetamine/dextroamphetamine for treatment of attention deficit hyperactivity disorder (ADHD).

STRATIFICATION: Subjects will be stratified by medication, HIV status and HIV antiretroviral therapy as follows:

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Arm 1 Methylphenidate</th>
<th>Arm 2 Amphetamine / dextroamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15 HIV uninfected subjects</td>
<td>15 HIV uninfected subjects</td>
</tr>
<tr>
<td>B</td>
<td>15 HIV-1 infected subjects who are taking concomitant (prescribed) efavirenz</td>
<td>15 HIV-1 infected subjects who are taking concomitant (prescribed) efavirenz</td>
</tr>
<tr>
<td>C</td>
<td>15 HIV-1 infected subjects who are taking a (prescribed) protease inhibitor (PI)* with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir.</td>
<td>15 HIV-1 infected subjects who are taking a (prescribed) protease inhibitor (PI)* with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir.</td>
</tr>
</tbody>
</table>

*PI may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir

REGIMEN: Subjects must already be taking methylphenidate or amphetamine/dextroamphetamine for clinical care of ADHD as prescribed by their care provider. Subjects must be on a stable dose of one of these ADHD psychiatric medications for ≥ 1 week prior to each of the PK visits. This study does not prescribe any therapy nor provide medications for study subjects.
STUDY DURATION: Subjects will be on study for up to 14 months.

PRIMARY OBJECTIVE:
To describe the pharmacokinetics of the selected psychiatric medications currently prescribed in HIV-1 infected and uninfected children and adolescents.

SECONDARY OBJECTIVES:
1. To compare psychiatric medication exposure in HIV-1 infected children and adolescents on selected antiretrovirals to that seen in uninfected children and adolescents.
2. To compare ARV (PI and NNRTI) exposure in subjects taking selected psychiatric medications with published ARV (PI and NNRTI) pharmacokinetic values in children and adolescents.
3. To compare psychiatric medication concentrations in HIV-1 infected subjects taking ritonavir versus HIV-1 infected subjects taking efavirenz versus HIV uninfected subjects (taking neither ritonavir nor efavirenz).
4. To compare the frequency of psychiatric medication dose changes, dose requirement in mg/kg and tolerance between HIV-1 infected and HIV uninfected subjects with routine use of psychiatric medications over one year.
1.0 INTRODUCTION

1.1 Background and Overview

Children infected with HIV-1 are twice as likely to use psychiatric medications as uninfected children\(^1\). The pharmacokinetics of psychotropics has never been studied in HIV-1 infected pediatric subjects, and pharmacokinetic studies for some psychotropics are also limited in HIV-uninfected pediatric subjects. One small observational study in HIV-1 infected adults found lower than expected concentrations of selective serotonin reuptake inhibitors, regardless of concomitant use of antiretroviral medications, raising the concern that HIV-1 infection itself may decrease exposure to these agents. Furthermore, most psychiatric medications are substrates of and may alter the activity of common metabolizing enzymes, as do many antiretroviral (ARV) medications, creating the potential for complex, unpredictable drug interactions in HIV-1 infected children on these combined therapies. While psychiatric medications are often titrated to patient response, the typical starting dose and typical titration ranges may need to be altered in different patient populations (such as HIV-1 infected subjects or subjects with interacting drug combinations) to yield exposures that have shown efficacy in patient populations without co-morbid conditions. The development of appropriate dosing regimens of psychiatric medications in pediatric subjects is critical to the health and development of these children. Underdosing may lead to inadequate psychiatric symptom control with implications detrimental for health, development and well-being of the child. Overdosing may lead to medication toxicities including central nervous system adverse effects, again with potential developmental implications. The pharmacokinetics of these agents needs to be described in this population to assess appropriateness of common dose regimens. Among various classes of psychiatric medications prescribed to children and adolescents, the stimulants used to treat ADHD seem to be particularly important, since ADHD is one of the most common pediatric neurobehavioral disorders, with an estimated prevalence of 6-9% among school-aged children\(^2\). Stimulant clinical efficacy in HIV uninfected children and adolescents is well established\(^3\).

1.11 HIV-1 and Antiretroviral Effects on the Central Nervous System

The effects of HIV-1 and ARV treatment on the central nervous system (CNS) in children and adolescents are poorly understood. Unchecked viral replication during brain development may lead to selective damage on specific areas of the brain. Understanding which ARVs penetrate into the CNS and to what extent are crucial pieces of information needed to adequately treat these patients. Conversely, ARV agents themselves may be neurotoxic, and specific drugs or drug classes may be associated
with particular psychiatric co-morbidities. Furthermore, the potential CNS adverse effects of ARVs could be more severe for less mature brains, and treatment risk may be greater for early versus later-onset treatment regimens.

1.12 Psychiatric Medication Use in HIV-1 Infected Children and Adolescents

As children live longer with HIV-1 infection, they may be at increased risk for psychiatric illnesses. Among 1808 HIV-1 infected children who were <15 years of age in the PACTG trial 219C, hospitalization for psychiatric manifestations occurred with an incidence of 6.17 cases per 1000 person-years. This is significantly higher than psychiatric hospitalizations in the general <15 year old pediatric population, which has an incidence of 1.70 cases per 1000 person-years, yielding an incidence ratio of 3.62 (95% confidence interval: 2.11-5.80)(4). Of the 32 children hospitalized for psychiatric manifestations, the majority were admitted for depression (n=16) or behavioral disorders (n=8), 3 of 32 children were hospitalized for major depression with psychosis, and 3 of 32 were hospitalized for bipolar disorder.

Many unanswered questions remain regarding appropriate use and correct doses of psychiatric medications in children and adolescents. These knowledge deficits may particularly impact children and adolescents infected with HIV-1, considering that HIV-1 infected children are twice as likely as uninfected children to receive psychiatric medications. P1055 was a prospective, two-year observational study of psychiatric symptoms in 323 HIV-1 infected youth and 259 control children from ≥6 to < 18 years of age(1). In P1055, 23% of the HIV-1 infected children took psychiatric medications verses 12% of control children. The most common psychiatric medications used by HIV-1 infected children were methylphenidate (11%), amphetamine/ dextroamphetamine (6%), sertraline (3%), fluoxetine (3%), risperidone (2%), and atomoxetine (2%). However, the children < 12 years old were most commonly taking the following medications: methylphenidate (8%), amphetamine/ dextroamphetamine (5%), risperidone (2%), and atomoxetine (1%). Fluoxetine and sertraline were prescribed for < 0.3% of children, <12 years of age. The rate of risperidone use is expected to increase following the August 2007 FDA approval of the use of risperidone in adolescents ≥12 years old for schizophrenia and in children and adolescents ages ≥10 to ≤17 for bipolar I disorder. This is the first FDA approval of an atypical antipsychotic drug to treat either disorder in these age groups (5;6).
1.13 Psychiatric Medication Use in HIV-1 Infected Adults

Psychiatric medication use is being observed in a cohort of HIV-1 infected adults in the CHARTER (CNS HIV Anti-retroviral Therapy Effects Research) study.\(^7\) Of about 650 subjects at baseline thus far, 30% report use of Selective Serotonin Reuptake Inhibitors (SSRIs), and this is increasing each year. The CHARTER group is measuring concentrations of various psychiatric agents prescribed for clinical care in this cohort. SSRI concentrations were widely variable for every SSRI, and for many drugs (notably paroxetine and sertraline), the plasma concentrations were well below those seen in HIV-uninfected populations. Even among subjects taking concomitant ritonavir, a known cytochrome P450 (CYP) 2D6 inhibitor, concentrations of SSRIs (substrates of CYP 2D6) were below expected, and similar to concentrations seen in those not on ritonavir, which was an unexpected finding. Furthermore, the unexpectedly low SSRI concentrations seen in subjects who were not taking ARVs suggests that HIV-1 infection itself may alter the pharmacokinetic profiles of these agents. The decreased exposure noted in HIV-1 infected adults might indicate that these medications will not work as well in this population due to poor adherence and/or to potential under dosing.

1.14 Psychiatric Medication Pharmacology

1.141 Current Use of Stimulants

RxList is an internet drug index (www.rxlist.com) owned and operated by WebMD, containing drug information on brand and generic drugs. Each year, it compiles lists of the Top 200 drugs prescribed in the previous year in the U.S. For the calendar year 2007, the following Attention Deficit Hyperactivity Disorder (ADHD) treatment medications were among the top 200 prescribed drugs in this country: Adderall\(^\text{®}\) XR (amphetamine/dextroamphetamine, #36), Concerta\(^\text{®}\) (methylphenidate, #44), Strattera\(^\text{®}\) (atomoxetine, #96), Focalin\(^\text{®}\) XR (dexamethasone, #140), and Methylin\(^\text{®}\) (methylphenidate, #170).

1.142 Methylphenidate

Description

Methylphenidate is a central nervous system (CNS) stimulant structurally similar to the amphetamines, but with milder peripheral pharmacologic actions. It blocks re-uptake of dopamine and norepinephrine in the CNS, resulting in an increase in sympathomimetic activity. It is used to treat ADHD. Many pharmaceutical products
contain a racemic (50/50) mixture of d- and l-methylphenidate. D-
methylphenidate is likely the pharmacologically active enantiomer. Only
the d-methylphenidate binds to the dopamine receptor in the basal
ganglia.\(^{(8)}\) Further, the bioavailability (F) of l-methylphenidate is very
low (5%) compared with d-methylphenidate (F=23\%).\(^{(9)}\) In some
studies, the l-methylphenidate is not detectable after oral administration
of the racemate. Both enantiomers are primarily metabolized by
carboxylesterase CES1A1 de-esterification to the inactive d- and l-
alpha-phenyl-piperidine acetic acid (ritalinic acid), which is excreted
in the urine. Methylphenidate is a schedule C-II controlled substance.
(Schedule C-II controlled substances are drugs that have a high abuse
potential with severe psychological or physical dependence liability, but
have accepted medical use in the U.S.)

Table 1: Summary of Methylphenidate Formulations in this Study

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient</th>
<th>Manufacturer</th>
<th>Dosage Form*</th>
<th>Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin(^1)</td>
<td>dl-Methylphenidate HCl</td>
<td>Novartis</td>
<td>Tablet</td>
<td>Yes</td>
</tr>
<tr>
<td>Ritalin SR(^2)</td>
<td>dl-Methylphenidate HCl</td>
<td>Novartis</td>
<td>Extended Release Tablet</td>
<td>Yes</td>
</tr>
<tr>
<td>Ritalin LA(^3)</td>
<td>dl-Methylphenidate HCl</td>
<td>Novartis</td>
<td>Extended Release Capsule</td>
<td>No</td>
</tr>
<tr>
<td>Concerta(^4)</td>
<td>dl-Methylphenidate HCl</td>
<td>Alza</td>
<td>Extended Release Tablet</td>
<td>No</td>
</tr>
<tr>
<td>Metadate ER(^2)</td>
<td>dl-Methylphenidate HCl</td>
<td>UCB, Inc</td>
<td>Extended Release Tablet</td>
<td>Yes</td>
</tr>
<tr>
<td>Metadate CD(^5)</td>
<td>dl-Methylphenidate HCl</td>
<td>UCB, Inc</td>
<td>Extended Release Capsule</td>
<td>No</td>
</tr>
<tr>
<td>Methylin(^1)</td>
<td>dl-Methylphenidate HCl</td>
<td>Mallinckrodt</td>
<td>Chewable Tablet, Solution</td>
<td>No</td>
</tr>
<tr>
<td>Methylin ER(^2)</td>
<td>dl-Methylphenidate HCl</td>
<td>Mallinckrodt</td>
<td>Extended Release Tablet</td>
<td>Yes</td>
</tr>
<tr>
<td>Focalin(^1)</td>
<td>d-methylphenidate HCl</td>
<td>Novartis</td>
<td>Tablet</td>
<td>Yes</td>
</tr>
<tr>
<td>Focalin XR(^3)</td>
<td>d-methylphenidate HCl</td>
<td>Novartis</td>
<td>Extended Release Capsule</td>
<td>No</td>
</tr>
</tbody>
</table>

Adapted with permission from "Methylphenidate Formulation Table" by Arthur B. Straughn, Pharm.D. Professor Emeritus, UT-Memphis
*as classified by the FDA
\(^1\) Immediate Release (IR)
\(^2\) Conventional Sustained Release (SR)
\(^3\) Biphasic pulse dose (50% IR and 50% IR at 4 hrs)
\(^4\) Biphasic ramp (22% IR and remainder controlled release)
\(^5\) Biphasic ramp (30% IR and remainder slow release)

While many formulations of methylphenidate are available, all of the
ones to be included in this study basically boil down to two types:
immediate release and sustained release. The biphasic formulations are
essentially like taking an immediate release and a sustained release dose
at the same time. The only difference between the immediate and
sustained release types is how fast they get absorbed. The remaining
pharmacokinetic parameters do not differ. Once the drug gets in the
body from either type of formulation, either quickly or slowly, clearance
and half-life can be estimated for the whole group. A summary of the
oral methylphenidate formulations is provided in Table 1.

Dosing and Formulations of Methylphenidate to be studied in P1080

For all formulations described below, both brand name drugs and generics (when available) will be included in this study.

Methylphenidate (Ritalin®) immediate release was first FDA-approved in 1955. The starting dose in children ≥6 years and adults is 5 mg orally twice daily before breakfast and lunch. The dose may be increased by 5 – 10 mg/day at weekly intervals up to a maximum dose of 60 mg/day. The usual dose is 0.3 – 2 mg/kg/day.

Sustained-release preparations were introduced in the mid-1990s (e.g. Ritalin® - Slow Release (SR) and Metadate® ER), but some of these first sustained release preparations were less efficacious than the twice or three times daily dosing of the immediate release product. Second-generation sustained release products have been formulated to try to mimic the pharmacokinetic profiles of multiple daily doses of the immediate release formulation.

Concerta® was FDA-approved in July 2000. In children, adolescents and adults, the starting dose is 18 mg orally once daily. The dose may be adjusted in 9 to 18 mg increments at weekly intervals to a maximum of 54 mg/day in children ≥6 to ≤12 years, and a maximum of 72 mg/day (not to exceed 2 mg/kg/day) in adolescents and adults. It is a multi-layer tablet designed to mimic 5 mg three times daily of immediate-release methylphenidate. The tablet is coated with approximately 22% of the dose in immediate-release methylphenidate on the outer layer, which dissolves quickly in the gastrointestinal tract. The inner layers of the tablet contain an osmotic controlled release delivery system (OROS) that delivers the remainder of the dose at a controlled rate between 4 and 12 hours after administration. This formulation yields a consistent profile, with a quick increase in methylphenidate concentrations, and then a second increase to a peak around 6 – 8 hours, as shown in Figure 1 from the Concerta® package insert.
Figure 1: Mean methylphenidate plasma concentrations in 36 adults, following a single dose of Concerta® 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours(10).

Metadate® CD was approved by the FDA in April 2001. Children ≥6 years, adolescents and adults start with 20 mg orally once daily in the morning. The dose may be adjusted at weekly intervals by 20 mg/day to a maximum of 60 mg/day. This system contains individual beads prepared with specific rate-controlling membranes. Each capsule contains a mixture of 30% rapid-release beads and 70% extended-release beads. The resulting pharmacokinetic profiles are compared to two doses of immediate release methylphenidate in Figure 2 below from the package insert.
Figure 2: Comparison of immediate release (IR) and METADATE® CD formulations after repeated doses of methylphenidate HCl in children with ADHD(11).

Ritalin®-LA was FDA-approved in May 2002. The starting dose for children (≥ 6 years), adolescents and adults is 20 mg orally once daily in the morning. The dose may be adjusted by 10 mg/day at weekly intervals up to a maximum of 60 mg/day. This formulation uses SODAS (Spheroidal Oral Drug Absorption System) technology. Each capsule contains 50% immediate-release beads and 50% enteric-coated, delayed-release beads, which yields an initial peak concentration 1 – 3 hours post dose, and a second peak concentration at 6 hours after dose administration as shown below in Figure 3 from the package insert.
Figure 3: Mean plasma concentration time-profile of methylphenidate after a single
dose of Ritalin® LA 40 mg once daily and Ritalin® 20 mg given in two doses four
hours apart.(12)

Methylin® is a chewable tablet and an oral solution formulation
(immediate-release) that was re-introduced to the US market in June
2006, after it was voluntarily withdrawn in February 2005 due to
manufacturing issues that have been resolved. These products are
bioequivalent to, and have the same plasma concentration-time profile
as, Ritalin® immediate release tablets. Methylin ER® tablets are
bioequivalent to and have the same plasma concentration-time profile as
Ritalin SR® sustained release tablets. These Methylin® and Methylin
ER® products have identical dosing and age ranges as the Ritalin® and
Ritalin SR® products.

Immediate-release dexmethylphenidate (Focalin®) was approved by the
FDA in November, 2001. This product contains only the d-
d-methylphenidate stereoisomer. The starting dose in patients ≥6 years old
is 2.5 mg orally twice daily. The dose may be adjusted at weekly
intervals in 2.5 – 5 mg increments to a maximum of 20 mg/day. A once-
daily, extended release capsule of dexmethylphenidate (Focalin® XR)
was FDA-approved in May 2005. Children (≥6 years) and adolescents
start with 5 mg orally once daily in the morning, adjusting the dose by 5
mg/day in weekly intervals up to a maximum of 20 mg/day. Adults start
with 10 mg orally once daily in the morning, and adjust doses by 10 mg
increments at weekly intervals up to a maximum of 20 mg/day. The Focalin® XR formulation produces two peak concentrations, the first at about 1.5 hours post-dose, and the second about 4 hours later, as shown in Figure 4 below from the package insert.

![Graph of Mean dexmethylphenidate plasma concentration-time profiles after administration of 1 x 20 mg Focalin® XR (n=24) capsules and 2 x 10 mg Focalin® immediate-release tablets (n=25).](image)

**Figure 4**: Mean dexmethylphenidate plasma concentration-time profiles after administration of 1 x 20 mg Focalin® XR (n=24) capsules and 2 x 10 mg Focalin® immediate-release tablets (n=25)(13).

**Additional Methylphenidate Formulations Not Included in this Study**

Daytrana™, a methylphenidate transdermal patch, was FDA-approved in April 2006 in children ≥6 to ≤12 years, but is not FDA-approved in adolescents and adults. This formulation will not be included in this study because the absorption profile and other pharmacokinetic parameters are significantly different from the other formulations, and could not be included in the combined analysis.
Pharmacokinetics of Methylphenidate in HIV Uninfected Children and Adolescents

Several pharmacokinetic studies of various dosage forms of methylphenidate have been performed in children. Older studies published up through the 1990s typically used less precise laboratory techniques (gas-liquid chromatography-GLC for example) to measure the d- and l-methylphenidate. A population pharmacokinetic study of immediate-release methylphenidate evaluated 273 children and adolescents aged 5 – 18 years. The estimated half life and oral clearance were 4.5 hours and 90.7 mL/min/kg, respectively.(14) More recent studies of newer formulations in healthy adults have used the currently accepted standard assay techniques of high performance liquid chromatography/ mass spectrometry or tandem mass spectrometry (LC/MS or HPLC-MS/MS).

Multiple studies have been published describing Concerta® pharmacokinetics; however, all but one study were conducted in healthy adult subjects. The single report of Concerta® pharmacokinetics in 15 children only provides a concentration-time figure, but does not report the pharmacokinetic parameters of this formulation in children (pharmacokinetics were not the primary endpoint of this study)(15). Likewise, three studies have been published describing Focalin® and/or Focalin® XR pharmacokinetics, but all three studies were conducted in healthy adult subjects. Further, the FDA-approved package inserts describe the efficacy and safety findings of these products used in children, but only provide pharmacokinetic data from healthy adult studies. Pediatric pharmacokinetic data for the two most commonly used methylphenidate preparations (Concerta® and Focalin® XR) are not publicly available in either the biomedical literature or in the product information.

Pharmacokinetics in HIV-1 Infected Children and Adolescents

No pharmacokinetics of any formulation of methylphenidate has been published for HIV-1 infected adults, adolescents or children.

1.143 Amphetamine/dextroamphetamine

Description

Amphetamines are non-catecholamine sympathomimetics with several possible therapeutic actions in the treatment of ADHD. They stimulate the release of norepinephrine and other biologic amines from central adrenergic receptors, and block re-uptake of norepinephrine and
dopamine. Amphetamine prescription products combine 4 salts in equal parts: dextroamphetamine sulfate, dextroamphetamine saccharate, racemic amphetamine sulfate (equal parts dextro (d)- and levo (l)-amphetamine sulfate), and racemic amphetamine aspartate (equal parts dextro (d)- and levo (l)-amphetamine aspartate). This results in a ratio of d-amphetamine to l-amphetamine of 3:1. Both d- and l-amphetamine are active. They are metabolized in the liver via aromatic hydroxylation (via cytochrome P450 2D6), N-dealkylation and deamination. Prescription amphetamine medications are Schedule C-II controlled substances.

Dosing and Formulations of Amphetamine/ Dextroamphetamine to be Studied in P1080

The two basic categories of formulations of amphetamine/ dextroamphetamine to be included in this study are fast or slow absorption (immediate or sustained release). A population modeling approach can account for two different absorption rates, and the remaining pharmacokinetic parameters (clearance and half-life, for example) can be estimated from the entire combined group of subjects. For all formulations described below, both brand name drugs and generics (when available) will be included in this study.

The brand name of mixed amphetamine salts is Adderall®. The original immediate release Adderall® tablets and their generic equivalents are usually dosed once or twice daily. For twice daily dosing, the doses are typically taken at breakfast and again at lunch (a 4-6 hour dosing interval). Children ≥6 years, adolescents and adults begin with 5 mg orally once or twice daily, and increase by 5 mg/day at weekly intervals to the minimum effective dose. The maximum dose for children ≥6-12 years old is 40 mg/day, while the maximum dose for adults and adolescents is 60 mg/day.

Adderall® XR, a once-daily capsule formulation was FDA-approved for use in children ≥6-12 years old in October 2001. The indication was extended to adults in August 2004 and to adolescents (13-17 years) in July 2005. This formulation contains two types of drug-containing beads, immediate release and extended release, in a 1:1 ratio distributed uniformly throughout the capsule. The immediate release beads release the first half of the dose upon ingestion, while the delayed release beads begin to release the second half of the dose 4 hours later. The recommended starting dose of this formulation for patients ≥6 years old is 10 mg orally once daily in the morning. The daily dosage may be titrated by 5 mg or 10 mg/day at weekly intervals, and the maximum dose is 30 mg/day.
Dexedrine® (dextroamphetamine sulfate) is the dextro isomer of amphetamine sulfate, and is twice as potent on a weight basis as racemic amphetamine. It was approved for use in the U.S. in 1958. A sustained release formulation (Dexedrine Spansule®) is a hard gelatin capsule filled with a blend of drug-coated pellets. Forty percent of the pellets are immediate release, and 60% are sustained release. Liquadd™ is an immediate release oral solution of dextroamphetamine sulfate approved by the FDA in January 2008. The starting dose is 5 mg immediate release once or twice daily in children ≥6 years, adolescents and adults. The dose may be titrated by no more than 5 mg/day at weekly intervals. The maximum daily dose is 40 mg of immediate-release or 45 mg for sustained release formulations in children 6-12 years. The maximum daily dose of both formulations in adolescents and adults is 60 mg. The sustained release formulation dose for children, adolescents and adults is simply the immediate release total daily dose given as a single dose in the morning.

Additional Amphetamine Formulations Not Included in this Study
Lisdexamfetamine dimesylate (Vyvanse™) is an inactive pro-drug that gets gradually converted into l-lysine and d-amphetamine (the latter being responsible for drug’s activity) after ingestion. It was developed to provide an extended duration of effect that is consistent throughout the day, and with a reduced potential for abuse, overdose and drug tampering. It was approved by the FDA in February 2007 for the treatment of ADHD in children ≥6-12 years old, and was approved for use in adults (≥18 years of age) in April 2008. It is not currently approved for use in adolescents (13 – 17 years old). This formulation will be excluded from this study because the pharmacokinetics of this pro-drug is significantly different from the other formulations, and subjects taking this drug could not be combined with the other subjects for pharmacokinetic analysis.

Pharmacokinetics of Amphetamine/ Dextroamphetamine in HIV Uninfected Children and Adolescents
Several studies have described immediate release amphetamine/ dextroamphetamine pharmacokinetics in children and adolescents. Typical area under the concentration versus time curve (AUC) values with a 10 mg dose were 340-430 ng/mL/hr for the d-isomer, and 125-140 ng/mL/hr for the l-isomer,\( ^{(16-18)}\) with 20 – 40% intersubject variability. Time to maximum concentration is about 3 hours for the immediate release formulation, and is delayed to approximately 5-7 hours with the extended release product, as shown in Figure 5 below from the Adderall® XR package insert.
Figure 5: Mean d-amphetamine and l-amphetamine plasma concentrations following administration of Adderall® XR 20 mg (8 am) and Adderall® (immediate release) 10 mg twice daily (8 am and 12 noon) in the fed state.¹⁹

For Adderall® XR, three published studies describe the pharmacokinetics of this formulation in healthy adult volunteers (>18 years old).²⁰⁻²² Only a single published study has described the pharmacokinetics of Adderall® XR in children (≥6 to ≤12 years old).¹⁷ After a 20 mg Adderall XR dose, the dextroamphetamine Tₘ₉ₐₓ=6.8 hours, Cₘ₉ₐₓ=49 ng/mL, and AUC₀₋₂₄=704 ng/mL/hr. The levoamphetamine results were Tₘ₉ₐₓ=6.9 hours, Cₘ₉ₐₓ=15 ng/mL, and AUC₀₋₂₄=216 ng/mL/hr. The coefficients of variation ranged from 27-47%. No published studies have described the pharmacokinetics of Adderall® XR in adolescents.

Published studies of pharmacokinetics of Dexedrine® and Dexedrine Spansules® have only included healthy adult subjects (n=12 and n=24).²³,²⁴ Pharmacokinetics of dextroamphetamine after administration of Vyvanse™ (lisdexamfetamine dimesylate) have only
been published to date in two studies of healthy adults (n=12 and n=18).\(^{(25,26)}\)

Pharmacokinetics of Amphetamine/ Dextroamphetamine in HIV-1 Infected Children and Adolescents

No pharmacokinetic studies of any formulation of amphetamine/ dextroamphetamine have been published for HIV-1 infected adults, adolescents or children.

1.15 Potential for Antiretroviral and Psychiatric Drug Interactions

In addition to the lack of PK data noted above, drug interactions between ARV and psychiatric medications in HIV-1 infected children and adolescents have not been described. Some of the differences in severity of psychiatric symptoms in these patients as compared to non-HIV-1 infected patients could potentially be due to inadequate or toxic exposure to the psychiatric agents stemming from drug interactions between the psychiatrics and the ARVs or the psychiatrics and the HIV-1 disease itself.

The majority of psychiatric drugs are metabolized by the cytochrome P450 enzymes, primarily CYP 2D6. The importance of CYP 2D6 in amphetamine metabolism is unclear. Several older studies report hydroxylation by CYP 2D6 as a minor pathway (~ 4%),\(^{(27,28)}\) while more recent studies report hydroxylation accounting for up to half of the metabolism.\(^{(19)}\) Ritonavir has demonstrated potent inhibition of CYP 2D6 when used in high doses of 500 mg twice daily.\(^{(29)}\) The AUC of desipramine, used as a probe for CYP 2D6 activity, increased 2.5 fold in these subjects. Since ritonavir is rarely used at full doses currently, a more recent study evaluated 100 mg twice daily of ritonavir in combination with desipramine.\(^{(30)}\) This study found that low-dose ritonavir inhibited CYP 2D6 activity, resulting in a 26% increase in desipramine AUC.

The most commonly used psychiatric in children, methylphenidate, is hepatically metabolized, but not by oxidation (the method of the cytochrome P450 enzymes). Methylphenidate is metabolized by de-esterification by carboxylesterase 1 (CES1). While methylphenidate is not metabolized by CYP 2D6, it does increase desipramine concentrations. Since desipramine is a probe substrate to determine CYP 2D6 activity, this finding suggests a potential for drug interactions between methylphenidate and other CYP 2D6 substrates as well. Methylphenidate has also been noted to inhibit the metabolism of phenytoin, phenobarbital, primidone, warfarin and tricyclic
antidepressants, and may also decrease the metabolism of SSRIs. These agents are metabolized by a variety of CYP enzymes, including 1A2, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, and 3A4. Since ARVs are also metabolized by a variety of CYP enzymes, including 1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5, the impact of concomitant methylphenidate and ARVs needs to be studied. Carbamazepine is a well-known inhibitor of CYP 3A4, similar to ritonavir. Carbamazepine reduces methylphenidate concentrations through an unknown mechanism.

Psychiatric medication interactions with efavirenz are also possible, as efavirenz also inhibits CYP 2D6 in vitro, although at concentrations much higher than those achieved clinically. Efavirenz is a potent inducer of CYP 3A4 in vivo, and could potentially decrease exposure to psychiatric agents that are also metabolized by this enzyme, such as sertraline and risperidone.

The two antiretrovirals that are most likely to demonstrate significant drug interactions with psychiatric medications are ritonavir and efavirenz. For this reason, our pilot study will enroll equal numbers of HIV-1 infected subjects on standard dose efavirenz OR ritonavir at boosting doses. HIV-1 infected subjects taking both efavirenz AND ritonavir at boosting doses as part of their regimen will be excluded.

1.16 Pharmacogenetics of Antiretrovirals and Psychiatrics

Pharmacogenetic differences between individuals may be able to explain some of the inter-individual variability observed in medication concentrations. The pharmacogenetic information obtained by a single blood sample can complement the pharmacokinetic information being obtained. Specific genetic patterns (for example, CYP 2D6 poor, intermediate or fast metabolizers) can be incorporated into population pharmacokinetic models to determine their influence on the pharmacokinetics of the medications, leading to more precise and less variable pharmacokinetic parameter estimates. Further, this information may be useful to assess whether the cause of unexpectedly high or low drug concentrations are a result of primarily genetic influences or of a potential drug-drug interaction.
1.161 CYP 2B6

Efavirenz is metabolized mainly by CYP 2B6. Concentrations of efavirenz are associated with the CYP 2B6 516G→T genetic polymorphism,\(^{(31-35)}\) and are also associated with frequent CNS-related adverse effects.\(^{(36;37)}\) Patients with the 516TT genotype typically have very high efavirenz concentrations. In a pharmacokinetic analysis, this genetic polymorphism can account for some of the variability observed in efavirenz pharmacokinetics and be incorporated into the models to provide more precise pharmacokinetic estimates. If high concentrations of efavirenz are observed in subjects in this study, the CYP 2B6 genotype information will be important to know in order to assess if the high efavirenz concentrations could be due to a drug interaction with the psychiatric medication or due purely to genotypic susceptibility.

1.162 CYP 3A4/5 and MDR1

The protease inhibitors are substrates for P-glycoprotein (PGP), the multidrug efflux pump encoded by the multi-drug resistance transporter (MDR1) gene. Polymorphic expression of PGP has been correlated with non-nucleoside reverse transcriptase inhibitor hepatotoxicity.\(^{(38;39)}\) Associations between polymorphisms in the MDR1 gene and plasma concentrations of both efavirenz and nelfinavir have been demonstrated. These polymorphisms were also correlated with immune recovery.\(^{(40)}\) An \textit{in vitro} study by Woodahl and colleagues examined the permeability of protease inhibitors across PGP-expressing cells.\(^{(41)}\) A mutation in MDR1 (G→A transition at nucleotide 1199; G1199A) significantly decreased the transport of protease inhibitors (amprenavir, indinavir, lopinavir, ritonavir and saquinavir) across the cell membrane, suggesting that subjects with this MDR1 mutation will have decreased protease inhibitor absorption from the intestine and decreased penetration across the blood-brain barrier. In addition, PGP may modulate the expression of CYP3A4, as well as impact certain immune components. Polymorphisms in MDR1 (the gene coding for PGP) may impact protease inhibitor exposure, immune recovery, or both.

Protease inhibitors are also commonly substrates for CYP 3A enzymes. Several genetic variants of CYP 3A5 lead to nonexpression or functionally defective enzymes and decreased activity.\(^{(42;43)}\) While many alleles for CYP 3A4 have been identified, consistent correlations with antiretroviral concentrations have not been reported.\(^{(40)}\) The relevance of MDR1 and CYP 3A polymorphisms for antiretrovirals remains uncertain.
1.163 CYP 2D6

CYP 2D6 is a highly polymorphic gene that metabolizes numerous commonly used drugs. Over 60 allelic variants and subvariants have been defined, including fully functional alleles, reduced function alleles and non-functional alleles. The various combinations of these alleles result in a wide range of enzyme activity from no to ultra rapid metabolism. Metabolic phenotyping using the dextromethorphan/dextrorphan (DM/DX) ratio is a simple, readily available, non-invasive method to get a crude estimate of CYP 2D6 activity. For a better estimation of CYP 2D6 activity, genotypic information can be combined and interpreted via an algorithm to produce an “activity score” which can be used on its own with 6 classifications, or converted into the more common 4 classifications of poor, intermediate, extensive and ultra rapid metabolism. Further, the activity score provides population-specific (more precise) estimates of enzyme activity for Caucasians and African Americans. With smaller gradations between enzyme activity categories, relationships with concentration data will be easier to detect. The metabolic phenotype can provide an initial estimate of CYP 2D6 activity. If CYP 2D6 appears to be important in amphetamine metabolism, a genotypic analysis can be explored in this pilot study setting.

1.164 Carboxylesterase 1 (CES1)

Methylphenidate is metabolized by CES1. Recently, a patient was identified with gene mutations that led to dysfunctional CES1A1 and extremely high methylphenidate concentrations. If any subjects in this study have similarly high methylphenidate concentrations that cannot be explained by other mechanisms, this genetic mutation can be assessed. Again, this will be important to determine if unusual concentrations are a result of genetics or of a significant drug interaction with an antiretroviral.

1.165 Metabolic Phenotyping

A commonly used method to assess CYP 2D6 activity is measuring the dextromethorphan/dextrorphan (DM/DX) urinary metabolic ratio (known as metabolic phenotyping). Dextromethorphan is converted to the active metabolite dextrorphan primarily by CYP 2D6, with some metabolism also by CYP 3A4. As such, drugs which alter CYP 2D6 activity will alter the concentrations and thus the ratio of DM/DX correspondingly. Formation of another metabolite, 3-hydroxymorphinan, is dependent on CYP 3A activity. Quantification of both metabolites provides a non-invasive assessment of both CYP 3A and 2D6 activity. These results can be incorporated into a pharmacokinetic
analysis to help understand sources of variability in observed pharmacokinetic parameters, which can help discriminate between likely genetic effects versus possible drug interactions. Dextromethorphan, 3-hydroxy-morphinan and dextrorphan have no known inhibiting or inducing effects on any metabolic pathways. Thus, giving a dose of dextromethorphan in order to measure CYP 3A and 2D6 activity will not alter the concentrations of either antiretrovirals or psychiatric medications.

1.17 Self-medicating with Psychiatric Drugs

The impact of illicit substance use and drug abuse treatment must also be considered in these patients. Use of methamphetamine and derivatives may further complicate the picture, as these are also stimulants and CYP 2D6 substrates, and 2D6 poor metabolizers may be at higher risk for toxicity from illicit amphetamine-like drug use. Many of the prescribed medications used to treat substance abuse are also metabolized by CYP enzymes, and may be involved in drug interactions with antiretrovirals and other psychiatric agents. For example, bupropion, methadone, and buprenorphine are CYP enzyme substrates, and are significantly increased by concomitant use of ritonavir.

1.18 Importance of Pharmacokinetic Studies of Psychiatric Agents

Even though psychiatric medications are often titrated to effectiveness within a patient, the typical starting dose and typical titration range may need to be altered in different patient populations (such as HIV-1 infected and/or pediatric subjects) to yield the exposures that have shown efficacy in standard patient populations without co-morbid conditions and interacting drugs. Without any knowledge of the pharmacokinetics of these agents in pediatric, HIV-1 infected subjects, clinicians will use the same starting doses, maximum doses and titration schedules that they use in other populations. If HIV-1 infected subjects have significantly lower or higher exposure to these psychiatrics than uninfected children, then the HIV-1 infected patients will potentially be either under dosed or exposed to toxic concentrations by using the standard titration range. Further, the high likelihood of drug interactions between psychiatrics and antiretroviral drugs will increase the risk that the systemic exposure following standard starting and titration doses of psychiatrics may be very different in HIV-1 infected pediatric subjects taking antiretrovirals as compared to HIV uninfected populations.
1.19 Non-invasive Longitudinal Drug Exposure Measures

In this pilot study, retrospective data on psychiatric dose medication titration will be collected, and the frequency of dose changes with routine clinical use of psychiatric medications will be observed over one year, and compared between the HIV uninfected and HIV-1 infected groups. The frequency of antiretroviral regimen switches in HIV-1 infected subjects taking psychiatric medications will also be observed over one year. The need for psychiatric medication dose titration in HIV-1 infected subjects will potentially be impacted by the HIV-1 disease itself, interacting antiretrovirals, changes in antiretrovirals, and pharmacogenetics. In addition to the frequency of psychiatric medication dose changes, the dose requirement in mg/kg will be collected over one year and compared between HIV uninfected and HIV-1 infected subjects. This provides a non-invasive method to collect longitudinal psychiatric drug exposure data over the course of a year. This will enhance the interpretation and understanding of the cross-sectional pharmacokinetic data collected at the PK visits. The reasons for any dose titrations or medication changes (tolerance) will be collected whenever possible over this year. In addition to assessing differences in dose titration frequency and dose requirements between HIV uninfected and HIV-1 infected subjects, this will also provide some information on any potential differences in the clinical management of subjects who have lower psychiatric drug concentrations versus those who have higher drug concentrations.

1.20 Psychiatric Medication Concentrations Correlate with Clinical Outcomes

Toxic effects of psychiatrics are often closely related to systemic exposure of psychiatrics. For example, drug-induced prolongation of the Q-Tc interval is associated with increasing concentrations of tricyclic antidepressants and antipsychotics. Of particular relevance at this time is the possibly increased risk of cardiovascular effects with stimulant use. Stimulants have effects on chronotropic (heart rate) and ionotropic (contractility) activity of the heart. A thorough heart work-up including electrocardiogram before starting stimulant therapy is now recommended by the American Heart Association. Cardiovascular injury has been associated with HIV-1 infection itself as well as with protease inhibitor therapy. A clear understanding of the stimulant and antiretroviral pharmacokinetics is warranted in these “triple-threat” patients (HIV-1 infected, on a protease inhibitor, and on a stimulant) from a cardiovascular safety perspective.
The two psychiatric agents being studied in this protocol have demonstrated exposure (pharmacokinetic)/response (pharmacodynamic) relationships.\(^{(16)}\) For example, increasing concentrations of amphetamine in children have been associated with increasing numbers of math problems solved and improvements in attention and deportment measures.\(^{(16;50)}\) In a functional magnetic resonance imaging study in adults, greater area under the plasma concentration-time curve for methylphenidate was positively correlated with the strength of activation in motor and premotor cortex, temporoparietal cortex and caudate nucleus during a four choice motor reaction task.\(^{(50)}\) Additional studies have demonstrated that increasing doses of stimulants (and thereby increased blood concentrations of stimulants) correlates with increasing symptom control and improved therapeutic responses.\(^{(51)}\) For example, initial studies of stimulant use in adults with ADHD used doses of approximately 0.6 mg/kg/day and found a 50\% response rate to treatment.\(^{(52)}\) When increased doses were studied in adults (1 mg/kg/day, which is closer to typical pediatric doses), the response rates for methylphenidate increased to 78\% and the response rates for amphetamine salts increased to 70\%\(^{(53;54)}\). Response rates were defined as a 30\% or greater improvement in clinical symptoms. Likewise, in children, ascending blood concentrations throughout the day are necessary to overcome tolerance and optimize symptom control.\(^{(55)}\) A dose-response study in children with ADHD combined type or ADHD inattentive type found a clear linear dose-response (increasing doses increased response) relationship in patients with ADHD-combined type\(^{(56)}\). Greater numbers of subjects had significant reductions in symptoms with the higher doses. Interestingly, children with inattentive type ADHD responded optimally to lower doses and had less benefit from higher doses. In all subjects, the side effects of insomnia, decreased appetite and increased pulse rate worsened with increasing doses. These studies further stress the importance of understanding pharmacokinetics of these agents for optimal use.

Additional psychiatric medications commonly used in HIV-1 infected children and adolescents for which adequate pharmacokinetic data are lacking may be studied in future protocol versions by using the protocol amendment mechanism.
1.2 Study Rationale

1.21 Rationale for Psychiatric Medication Study Arms

The psychiatric medications selected for this study, methylphenidate, and amphetamine/dextroamphetamine, were identified in P1055 as the agents most commonly used by HIV-1 infected children and adolescents for ADHD and related disorders, and those most likely to be used in the near future; however, pharmacokinetic data in HIV-1 infected pediatric subjects is not available. Further, no data exist regarding potentially significant drug interactions between these agents and antiretrovirals.

The formulations selected for this study include immediate-release, sustained release, and the commonly-used biphasic release (combinations of immediate and sustained-release in a single product). While the newer biphasic formulations have been studied in healthy adult volunteers, pharmacokinetic studies have not been reported for HIV-1 infected or HIV uninfected children and adolescents.

1.22 Rationale for Study Strata

The HIV uninfected subjects are important to include in this study to ensure that pharmacokinetic data for currently used formulations and dosing practices will be available from subjects with similar ages, genders and races to the HIV-1 infected subjects. This will allow comparisons to see if pharmacokinetic and dosing differences exist between typical children taking psychiatric medications that are either HIV uninfected or HIV-1 infected. For the HIV-1 infected subjects, the concomitant antiretroviral medications of efavirenz or ritonavir will be studied, as those are commonly used agents that are most likely to demonstrate significant drug-drug interactions due to their metabolic inducing and inhibiting effects.

1.23 Rationale for Study Design

The proposed approach of measuring population pharmacokinetics in subjects taking psychiatric medications with and without antiretrovirals in combinations and doses used in routine care will provide a reasonable estimate of pharmacokinetics for the most commonly-used psychiatric drugs in the context of typical doses and combinations with antiretrovirals. The pharmacokinetic estimates generated by this study will be generalizable to subjects who tolerate the psychiatric/antiretroviral medication combinations after the start of therapy. Subjects may be enrolled if they have already been receiving a
psychiatric medication of interest for ≥ 1 week prior to the pharmacokinetic study assessment. If the psychiatric medication is prescribed on school days (Monday through Friday) the subject will need to have taken all doses for at least two consecutive days prior to the pharmacokinetic assessment to ensure steady-state. This study will not be limited only to subjects newly starting a psychiatric medication of interest because the medication use estimates from P1055 and P219C suggest that timely enrollment with this limitation would not be feasible.

A key benefit of the proposed population pharmacokinetic analysis (as compared to intensive pharmacokinetic studies of many samples in only a few subjects) is that the subjects do not need to be sub-divided by different demographics, doses or formulations. Even though multiple formulations of stimulant medications will be used in this study, they all boil down to only two essential types of formulations: immediate-release and extended-release. All of the biphasic formulations can be modeled with just these two absorption profiles in different ratios. The only significant PK parameter difference between the formulations that will be included in this study is the absorption rate. Several formulations that have more significant pharmacokinetic parameter differences will be excluded (e.g., the patch). The clearance of the drug (the primary or gold-standard PK parameter), along with other PK parameters of interest can be estimated from the combined cohort regardless of the included formulations by using population modeling and the two absorption rates.

The powerful computational power of population analysis essentially accounts or corrects for different subject size and age, doses, and absorption rates (formulations) to estimate pharmacokinetic parameters in the entire cohort taking the drug of interest. There are 2 different sampling strategies (6 hours and 12 hours), depending on the formulation used. The specific sampling times were selected to ensure that the appropriate information will be collected in order to develop the population models.

1.24 Summary Rationale

Many knowledge gaps exist for the appropriate use of psychiatric medications in children and adolescents. In HIV uninfected children, pharmacokinetic data available for the stimulant drugs are limited mainly to immediate release and older, less commonly used, preparations.

Limited observational studies in HIV-1 infected adults who were not taking ARVs noted decreased psychiatric medication exposure as compared to that seen in uninfected adults; one potential explanation is
that infection with HIV-1 itself may alter the pharmacokinetic profiles of these drugs. Furthermore, for HIV-1 infected subjects who are taking ARVs, notably ritonavir and efavirenz, the potential for drug interactions with psychiatric medications is high, but the effects of the interactions are unpredictable. For example, high-dose and low-dose ritonavir have both exhibited inhibitory effects on CYP 2D6, but the HIV-1 infected adult subjects taking ritonavir in the CHARTER observational cohort did not display increased SSRI concentrations as expected. In fact, the opposite effect was noted. Decreased adherence is one possible explanation, as are unpredictable drug interactions and/or genetic modifications to metabolic activity. Given the current state of knowledge (or lack thereof), predicting psychiatric medication exposure in HIV-1 infected children on and off ARVs is fraught with uncertainty.

Prescribing various psychiatric medications in combination with antiretroviral regimens is a standard clinical practice occurring without adequate evidence regarding benefits and risks. The goals of this study are to determine plasma concentrations of psychiatric and antiretroviral medications in children and adolescents. Psychiatric medication dose requirement and exposure in HIV-1 infected subjects will be compared to that seen in uninfected children and adolescents, and antiretroviral exposure will be compared to published studies in children and adolescents. Amendments to the protocol will be considered to add arms for psychiatric medications whose prevalence of use increases in HIV-1 infected pediatric subjects. The premise is that describing the pharmacokinetics of psychiatric and antiretroviral medications will help improve dosing guidelines and appropriate use for these medications alone and in combination in children and adolescents.

2.0 STUDY OBJECTIVES

2.1 Primary

2.11 To describe the pharmacokinetics of the selected psychiatric medications currently prescribed in HIV-1 infected and uninfected children and adolescents.

2.2 Secondary

2.21 To compare psychiatric medication exposure in HIV-1 infected children and adolescents on selected antiretrovirals to that seen in uninfected children and adolescents.
2.22 To compare ARV (PI and NNRTI) exposure in subjects taking selected psychiatric medications with published ARV (PI and NNRTI) pharmacokinetic values in children and adolescents.

2.23 To compare psychiatric medication concentrations in HIV-1 infected subjects taking ritonavir versus HIV-1 infected subjects taking efavirenz versus HIV-uninfected subjects (taking neither ritonavir nor efavirenz).

2.24 To compare the frequency of psychiatric medication dose changes, dose requirement in mg/kg and tolerance between HIV-1 infected and HIV-uninfected subjects with routine use of psychiatric medications over one year.

3.0 STUDY DESIGN

P1080 is a pilot population pharmacokinetic study of HIV-1 infected and uninfected children and adolescents who are taking methylphenidate or amphetamine/dextroamphetamine for the treatment of ADHD. The study subjects will be accrued over a one year period. Subjects will be on study for up to fourteen months. Enrollment progress will be followed by tracking accrual at sites monthly, with a regular review of accrual targets to ensure that enrollment remains on track.

HIV uninfected subjects will be recruited from the siblings/household members of HIV-1 infected subjects at IMPAACT sites, in a similar fashion to the successful recruitment strategy of P1055 (described in Section 4.6). The group of uninfected subjects will be matched to the group of HIV-1 infected subjects by age, gender and race within each arm. All subjects will have a screening/entry visit, two PK visits and three follow-up telephone calls. These three visits and three follow-up calls are described in Sections 3.1, 3.2, 3.3 and 3.4. On the basis of subjects’ HIV status and medications, they will be divided into 3 strata as indicated in Table 2 below.

Table 2: Protocol Stratification

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Arm 1 Methylphenidate</th>
<th>Arm 2 Amphetamine / dextroamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15 HIV uninfected subjects</td>
<td>15 HIV uninfected subjects</td>
</tr>
<tr>
<td>B</td>
<td>15 HIV-1 infected subjects who are taking (prescribed) concomitant efavirenz</td>
<td>15 HIV-1 infected subjects who are taking (prescribed) concomitant efavirenz</td>
</tr>
<tr>
<td>C</td>
<td>15 HIV-1 infected subjects who are taking a (prescribed) protease inhibitor (PI)* with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir</td>
<td>15 HIV-1 infected subjects who are taking a (prescribed) protease inhibitor (PI)* with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir</td>
</tr>
</tbody>
</table>

*PI may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir
3.1 Screening / Entry Visit (s)

Screening and entry visit(s) should preferably be performed at the same time, but may be performed up to 4 weeks apart. Subjects must have agreed to, and signed, an informed consent form before any screening tests are undertaken.

At screening, the subject will provide a urine sample to test for illicit drug use. Results of the urine toxicology screen will be discussed with the subject. The decision about whether to share these results with parents will follow local, institutional and IRB guidelines. Subjects with a positive urine toxicology screen for drugs that have the potential to interact with psychiatric and/or antiretroviral medications (see section 4.5 for specific drugs) will be excluded.

Female subjects of child bearing potential will be required to take a pregnancy test, which must be negative for the subject to continue on the study. Per the inclusion criteria (section 4.1), the subject must have been taking the psychiatric medication for at least one week in order to be eligible for this study.

3.2 Week 6 Pharmacokinetic (PK) Visit

Approximately two days prior to the PK visit, the sites will contact subjects/caregivers by phone to verify and encourage adherence for all medications (ARV and psychiatric) and to confirm that the PK visit can proceed as scheduled (see section 9.2). The PK visit will include a pharmacokinetic assessment (see Section 3.21) with medication history, an adherence survey, a Vanderbilt Scale questionnaire, an electrocardiogram if the subject has not had one for routine clinical care within the past 6 months and a genotypic (see Section 3.22) and phenotypic (see Section 3.23) assessment. Chart review will be performed to document demographics, psychiatric diagnosis, and HIV-1 infection risk category. HIV-1 infected subjects must be taking their antiretroviral medications consistently for at least 4 weeks prior to pharmacokinetic sampling. Similarly, all subjects must be taking their psychiatric medications consistently for at least 1 week prior to PK sampling.

Subjects who are prescribed either methylphenidate or amphetamine/dextroamphetamine for symptomatic control of ADHD will be eligible for this study. Subjects may be taking prescribed methylphenidate or amphetamine/dextroamphetamine either daily or only on certain days of the week. For example, a pediatric subject who takes a stimulant medication as prescribed once daily on Monday through Friday (school days) every week will qualify for the study. If the psychiatric medication is prescribed on school days (Monday through Friday), the subject should have taken doses for at least two consecutive days before they are eligible for the PK visit. In the example above, of the subject
taking a stimulant on Monday through Friday, the subject would be able to schedule a PK visit on Wednesday, Thursday or Friday. Additionally, female subjects of child bearing potential will be required to take a pregnancy test, which must be negative for the subject to continue on the study.

3.21 PK Sampling
Each PK visit should be scheduled so that a witnessed dose of psychiatric and antiretroviral medications will occur on time (according to that subject’s dosing regimen). The study visit may be around a morning or an evening dose. If dose times are switched to facilitate PK sampling, the subject should have been on the new schedule for at least 2 consecutive days prior to sampling. The subject’s own dose(s) of the psychiatric drug, with or without the subject’s antiretroviral drug(s), should be administered on site after the pre-dose sample is drawn. Either 4 or 5 pharmacokinetic blood samples will be collected according to the schedule in Appendix II, depending on the psychiatric drug formulation that the subject is taking. Sample times are pre-dose, 2, 4 and 6 hours post-dose, plus an additional 12 hour post-dose sample for some formulations, e.g. extended release formulations.

3.22 Genotypic Assessment
An additional blood sample will be collected and processed to obtain DNA from every subject at the week 6 PK visit only, in order to perform relevant pharmacogenetic studies of drug metabolizing or transporter enzymes. DNA collected from cells will be analyzed for polymorphic expression of known alleles in CYP 2B6 that may impact efavirenz drug exposure for those subjects taking efavirenz. For the subjects taking ritonavir or no antiretrovirals, cells may be analyzed for known alleles in CYP 2D6, CYP 3A4/5, CES1 and MDR1 if the metabolic phenotyping and/or observed concentrations warrant these genotypic studies to contribute to the understanding of the secondary objectives of the study.

3.23 Phenotypic Assessment
The CYP 3A4 and 2D6 metabolic phenotype of each subject will be measured by the 3-hydroxy-morphinan/dextromethorphan and the dextromethorphan/dextrorphan (DM/DX) ratios. First, the subject will be asked to void any urine. Next, a single oral dose of cough syrup (dextromethorphan) will be administered at the FDA-approved dose for each subject. The study will provide the dextromethorphan cough syrup to the participating sites [15 mg per 5 mL] per Section 5.4. Specific dosing recommendations are described in Section 5.11. This will serve as a marker for 2D6 and 3A4 activity, and will allow us to predict the metabolism of psychiatric medications. All urine produced for the 4 hours after the dextromethorphan dose will be collected. The volume
will be measured and recorded, and a 15 mL aliquot will be stored for analysis of dextromethorphan, dextrorphan and 3-hydroxy-morphinan concentrations in the urine.

3.3 Week 24 Pharmacokinetic (PK) Visit

The second PK visit will take place at approximately 24 weeks following the study subject’s screening visit. The procedures for the second PK visit will be identical to the first PK visit with two exceptions. First, an additional blood sample for the genotypic assessment is not necessary at the second PK visit. Second, an electrocardiogram is not necessary at the second PK visit.

Additionally, female subjects of child bearing potential will be required to take a pregnancy test, which must be negative for the subject to continue on the study. All other procedures will occur as outlined above (in section 3.2).

3.4 Weeks 30, 42 and 52 Telephone Calls

At weeks 30, 42 and 52, the study subjects/caregivers will be contacted by telephone to collect information regarding any dose, drug, or regimen changes, reasons for regimen changes, symptom control using the Vanderbilt Scale, and tolerance for both psychiatric and antiretroviral medications. The time frame of one year of follow-up was selected for two reasons. First, the final follow-up call will occur at approximately the same time of the year as the first PK visit, so there is a similar level of symptom control (with presumably similar psychiatric medication doses). Second, the final follow-up call will be able to capture a full year’s worth of psychiatric medication use in all subjects, which will provide a control for the seasonal variation in dose requirements.

3.5 Replacement of Subjects

Subjects will be replaced if pharmacokinetic results from the Week 6 PK visit only are deemed un-evaluable by the study team (for example, mislabeled specimens, insufficient quantity, contaminated, mistimed samples, discontinued study medication), or if subject tests positive for disallowed medications or illicit drugs, or if subject becomes otherwise ineligible before the first PK visit takes place.

3.6 Early Discontinuation

Subjects who withdraw from the study before the Week 52 call will be requested to return to the clinic for a final visit (See Appendix I).

Refer to Appendix I, Schedule of Evaluations for specific study requirements.
4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria for HIV-1 Infected Subjects

4.11 Children and adolescents age ≥6 to <25 years at entry.

4.12 Documented HIV-1 infection defined as positive test results obtained from 2 different samples. Tests may include two of the same type OR two different types of tests listed below, as long as they are positive test results obtained from the 2 different samples:

- HIV-1 DNA PCR
- HIV-1 culture
- HIV-1 RNA PCR > 5,000 copies/mL
- HIV-1 p24 antigen detection
- HIV-1 antibody test (any licensed ELISA test kit, and confirmation by either serum HIV-1 antigen test, HIV-1 antibody test done by a method that is not an ELISA, Western blot, or plasma HIV-1 RNA)

4.13 Subject must be taking antiretroviral medications for clinical care for at least 4 weeks prior to pharmacokinetic sampling, with no changes in drugs, doses or formulations.

4.14 Subject must be taking either efavirenz (EFV) OR a PI with ritonavir (RTV) OR lopinavir/ritonavir as part of combination antiretroviral therapy. Note that RTV dosing must be as a “booster” for the protease inhibitor. Protease inhibitors may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir. Subjects may not be taking more than one full-dose PI. Subjects may not be taking EFV in addition to lopinavir/ritonavir or other PI.

4.15 Subject must be taking methylphenidate or amphetamine/ dextroamphetamine for treatment of ADHD for at least 1 week prior to enrollment.

4.151 Allowable methylphenidate formulations include: immediate-release (Methylin®, Ritalin® or other generic, Focalin®), sustained-release (Ritalin® SR, Metadate® ER or generic), or biphasic (Ritalin® LA, Metadate® CD, Concerta®, Focalin® XR).

4.152 Allowable formulations for amphetamine/ dextroamphetamine include: Adderall®, Adderall® XR, Dexedrine®, Liquadd™, and Dexedrine Spansules® (and any generic equivalents).
4.153 For both study arms, any dose up to the maximum FDA-approved dose by age (see Section 5.3) will be allowed.

4.16 Subjects must be able to come in for PK sampling after at least 2 days of consecutive, uninterrupted psychiatric and antiretroviral medication delivery.

4.17 Parent/primary caregiver, subjects >18 years or emancipated minors must be able and willing to provide signed informed consent. Assent of the minor subject should be obtained where required per site procedures and IRB recommendations.

4.18 Female subjects of reproductive potential (having reached menses, or not having reached menopause or not having undergone hysterectomy, bilateral oophorectomy, or tubal ligation) who engage in sexual activity that could lead to pregnancy must agree to avoid pregnancy during the entire 144 week trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception. A list of acceptable methods can be found at the FDA Birth Control Guide (http://www.fda.gov/fdac/features/1997/babyguide.pdf).

Note: “Female subjects of reproductive potential” is defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (e.g. who have had menses within the preceding 24 months), or have not undergone a sterilization procedure (hysterectomy, bilateral oophorectomy or salpingotomy). If the female subject is not of reproductive potential, she is eligible without requiring contraception.

4.2 Inclusion Criteria for HIV Uninfected Subjects

4.21 Children and adolescents age ≥6 to <25 years at entry.

4.22 Subject is not known to be HIV-1 infected. 
Note: For perinatally-exposed subjects, definitive exclusion of HIV-1 infection in a non-breastfed infant is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at ≥4 months, or two negative HIV-1 antibody tests from separate specimens obtained at age ≥6 months. Per current CDC guidelines, uninfected subjects ≥13 years will be screened for HIV-1. A documented negative HIV-1 antibody screening test or negative HIV-1 RNA or DNA PCR within the past year will be accepted to fulfill this criterion.

4.23 Subject must be taking methylphenidate or amphetamine/dextroamphetamine for treatment of ADHD for at least one week prior to enrollment.
4.231 Allowable methylphenidate formulations include: immediate-release (Methylin®, Ritalin® or other generic, Focalin®), sustained-release (Methylin® ER, Ritalin® SR, Metadate® ER or generic), or biphasic (Ritalin® LA, Metadate® CD, Concerta® and Focalin® XR).

4.232 Allowable formulations for amphetamine/ dextroamphetamine include: Adderall®, Adderall® XR, Dexedrine®, Liquadd™, and Dexedrine Spansules® (and any generic equivalents).

4.233 For both arms, any dose up to the maximum FDA-approved dose by age (see Section 5.3) will be allowed.

4.24 Subjects must be able to come in for PK sampling after at least 2 days of consecutive, uninterrupted psychiatric medication delivery.

4.19 Parent/primary caregiver, subjects >18 years or emancipated minors must be able and willing to provide signed informed consent. Assent of the minor subject should be obtained where required per site procedures and IRB recommendations.

4.20 Female subjects of child bearing potential (having reached menses, or not having reached menopause or not having undergone hysterectomy, bilateral oophorectomy, or tubal ligation) who engage in sexual activity that could lead to pregnancy must agree to avoid pregnancy during the entire 144 week trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception. A list of acceptable methods can be found at the FDA Birth Control Guide (http://www.fda.gov/fdac/features/1997/babyguide.pdf).

Note: “Female subjects of child bearing potential” is defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (e.g. who have had menses within the preceding 24 months), or have not undergone a sterilization procedure (hysterectomy, bilateral oophorectomy or salpingotomy). If the female subject is not of child bearing potential, she is eligible without requiring contraception.

4.3 Exclusion Criteria for All Study Subjects

4.31 A positive urine test at screening for use of the following disallowed drugs: methamphetamine; methadone, barbiturates; benzodiazepines; opiates; phencyclidine; or propoxyphene.
4.32 Treatment with other routine (medications prescribed for daily and/or consistent use) psychiatric medications concurrently (due to the high likelihood of increasingly complicated and unpredictable drug interactions). Psychiatric medications prescribed for occasional use (such as as-needed anti-anxiety or anti-insomnia medications) will be allowed for study entry, but should not be used in the week prior to the PK Visit (see Disallowed Medications, Section 4.5).

4.33 Chemotherapy for malignancy within three months prior to study screening.

4.34 Pregnancy or breastfeeding an infant.

4.35 Any clinically significant diseases (other than HIV-1 infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator’s opinion, would compromise the outcome of this study.

4.37 Study drugs prescribed above the FDA-recommended maximum dose by age (see Section 5.3).

4.38 Known or demonstrated hypersensitivity or intolerance to Dextromethorphan.

4.39 Subjects taking a disallowed medication (see Section 4.5).

4.310 For HIV-1 Infected Subjects Only:
Presence of an active CDC Stage C (per 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age, or 1993 Revised Classification System for HIV Infection Among Adolescents and Adults) opportunistic infection or serious bacterial infection requiring therapy within two weeks prior to screening.

4.4 Deferral of Pharmacokinetic (PK) Visits

The Week 6 and Week 24 pharmacokinetic visits may be deferred if needed within the visit window for any of the following reasons, described below. If the deferral falls outside of the visit window, the site should contact the P1080 team for approval before proceeding with the PK visit.
4.41 If required, the week 6 and/or week 24 PK visits may be deferred as needed until the subject is 100% adherent with psychiatric medications and (if HIV-1 infected) with antiretroviral medications in the 48 hours prior to the visit.

4.42 The week 6 and/or week 24 PK visit may be deferred as needed if the subject has an intercurrent acute illness that may affect the study outcome.

4.5 Disallowed Drugs

The drugs listed below are disallowed for 1 week prior to the first or second PK visit and the day of the first and second PK visit.

4.51 For all study subjects, the following drugs are disallowed:

- Acamprosate
- Barbiturates: amobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, thiopental
- Benzodiazepines: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, midazolam, quazepam, temazepam, triazolam
- Bupropion
- Buprenorphine
- Daytrana™ (methylphenidate patch)
- Disulfiram
- Methadone
- Methamphetamine
- Naltrexone
- Opiates and opioid agonists: alfentanil, codeine, fentanyl, heroin, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, propoxyphene, sufentanil
- Phencyclidine (PCP)
- Propoxyphene
- Varenicline
- Vyvanse® (lisdexamfetamine)

4.52 For methylphenidate, the following drugs are disallowed:

- Atomoxetine
- Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
- Psychostimulants: amphetamine/dextroamphetamine, dexamphetamine, modafinil, sodium oxybate
• Sympathomimetics: phenylephrine, pseudoephedrine

4.53 For amphetamine/dextroamphetamine, the following drugs are disallowed:
• Atomoxetine
• Meperidine
• Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
• Psychostimulants: methylphenidate, dexamfetamine, modafinil, sodium oxybate
• Sympathomimetics: phenylephrine, pseudoephedrine

4.54 For efavirenz, the following drugs are disallowed:
• Anticonvulsants: carbamazepine, phenobarbital, phenytoin
• Antifungal: voriconazole
• Antihistamines: astemizole, cisapride
• Calcium channel blocker: bepridil
• Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine
• Neuroleptic: pimozide
• Protease Inhibitors: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, saquinavir, tipranavir

4.55 For ritonavir, the following drugs are disallowed:
• Antiarrhythmics: amiodarone, flecanide, propafenone, quinidine
• Anticonvulsants: carbamazepine, phenobarbital, phenytoin
• Antihistamines: astemizole, cisapride, terfenadine
• Antimycobacterial: rifampin
• Calcium channel blocker: bepridil
• Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine
• HMG-CoA reductase inhibitors: lovastatin, simvastatin
• Neuroleptic: pimozide
• Non-nucleosides: delavirdine, efavirenz, nevirapine
• SSRI: St. John’s Wort (hypericum perforatum)
• Antialcoholics: disulfiram, metronidazole
• Synthetic corticosteroid: fluticasone
• Grapefruit juice
4.6 Enrollment Procedures

Prior to implementation of this study, each site must have the protocol document and the consent form approved by the local Institutional Review Board (IRB). Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Compliance Center (RCC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL NOT be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RCC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

If necessary to obtain urine toxicology screening results, the screening visit and study entry may occur on different days, within 4 weeks of each other.

Subjects for the HIV-1 infected strata will be recruited from the patients who are routinely evaluated at each domestic IMPAACT site. Subjects for the HIV uninfected strata will be recruited from members of households with a parent, sibling or other family member who has been infected with HIV-1. HIV
uninfected household members of subjects who are participating in the HIV-1 infected stratum of this study and who meet inclusion/exclusion criteria for the uninfected cohort may be recruited. Uninfected subjects may be recruited from other sources at the site as well (enrollment is not limited only to household members and siblings of HIV-1 infected subjects).

4.7 Co-Enrollment Procedures

Co-enrollment is permitted except for protocols that would violate the exclusion criteria and where permitted by local regulations. All co-enrollments in protocols require the assent of the protocol chairs of this protocol as well as the co-enrollment protocols.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

P1080 will enroll subjects who are receiving specific antiretroviral and/or psychiatric medications that are prescribed by their physician (psychiatric medications are described in sections 5.11 and 5.12). Subjects must have been on the same dose and formulation of these psychiatric study medications for at least 1 week prior to each of the PK visits. HIV-1 infected subjects will have been taking their antiretroviral regimen at the same dose and formulation for at least 4 weeks prior to the two PK visits in this study.

5.11 Arm 1: Methylphenidate

5.111 HIV-1 Infected Pharmacokinetic Sampling Day Dosing Schedule

Single oral dose of dextromethorphan cough syrup will be administered (15 mg for subjects ≥6 to <12 years old, 30 mg for subjects ≥12 to < 25 years old).

Observed dose of methylphenidate or dexamethylphenidate orally up to the maximum FDA-approved dose using formulations listed in 5.2.

Observed dose of either one of the following regimens:
- Efavirenz orally at an FDA approved dose;
- Atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir at an FDA-approved dose and ritonavir boost at a recommended dose to a maximum of 200 mg twice daily;
- Lopinavir/ritonavir at an FDA-approved dose. Other doses of the protease inhibitor will be considered subject to pre-approval by the protocol chair.\(^{(57)}\)

5.112 HIV Uninfected Pharmacokinetic Sampling Day Dosing Schedule

Single oral dose of dextromethorphan cough syrup will be administered (15 mg for subjects ≥6 to <12 years old, 30 mg for subjects ≥12 to < 25 years old).

Observed dose of methylphenidate or dextmethylphenidate orally up to the maximum FDA-approved dose using formulations listed in 5.2.

5.12 Arm 2: Amphetamine/dextroamphetamine

5.121 HIV-1 Infected Pharmacokinetic Sampling Day Dosing Schedule

Single oral dose of dextromethorphan cough syrup will be administered (15 mg for subjects ≥6 to <12 years old, 30 mg for subjects ≥12 to < 25 years old).

Observed dose of mixed amphetamine salts (amphetamine/dextroamphetamine) or dextroamphetamine sulfate up to the maximum FDA-approved dose using a formulation listed in 5.2.

Observed dose of one of the following regimens:

- Efavirenz orally at an FDA-approved dose;
- Atazanavir, darunavir, fosamprenavir, indinavir; saquinavir or tipranavir at FDA-approved dose and boosting ritonavir to a maximum of 200 mg twice daily;
- Lopinavir/ritonavir at an FDA-approved dose. Other doses of the protease inhibitor will be considered subject to pre-approval by the protocol chair.\(^{(57)}\)

5.122 HIV Uninfected Cohort Pharmacokinetic Sampling Day Dosing Schedule

Single oral dose of dextromethorphan cough syrup will be administered (15 mg for subjects ≥6 to <12 years old, 30 mg for subjects ≥12 to < 25 years old).

Observed dose of mixed amphetamine salts (amphetamine/dextroamphetamine) or dextroamphetamine sulfate orally up to the maximum FDA-approved dose using a formulation listed in Section 5.2.
5.2 Drug Formulation

For the methylphenidate arm, the following formulations are allowed in this study:
- Methylin® (methylphenidate) Immediate-Release chewable tablets or oral solution
- Ritalin® (methylphenidate) Immediate-Release tablets (or generic equivalent Immediate-Release tablets)
- Ritalin® SR (methylphenidate) Extended-Release tablets (or generic equivalent Sustained-Release tablets)
- Metadate® ER (methylphenidate) Extended-Release tablets (or generic equivalent Sustained-Release tablets)
- Ritalin® LA (methylphenidate) Extended-Release capsules
- Metadate® CD (methylphenidate) Extended-Release capsules
- Concerta® (methylphenidate) Extended-Release tablets
- Focalin® (dextymethylphenidate) Immediate-Release tablets
- Focalin® XR (dexamethylphenidate) Extended-Release capsules

For the amphetamine/dextroamphetamine arm, the following formulations are allowed in this study:
- Adderall® (amphetamine/dextroamphethamine) Immediate-Release tablets (or generic equivalent Immediate-Release tablets)
- Adderall® XR (amphetamine/dextroamphethamine) Extended-Release capsules
- Dexedrine® (dextroamphetamine sulfate) Immediate-Release tablets or Liquadd™ oral solution (or generic equivalent Immediate-Release tablets or oral solution)
- Dexedrine Spansule® (dextroamphetamine sulfate) Sustained-Release capsules
5.3 FDA-Approved Maximum Daily Doses

Table 3: FDA Approved Maximum Daily Doses

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<thead>
<tr>
<th>Drug Formulation</th>
<th>FDA-approved Maximum Daily Dose</th>
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| Methylin® Ritalin® (or generic equivalent), Ritalin® SR, Metadate® ER (or generic equivalent), Ritalin® LA, Metadate® CD | ≥6 to 12 years: 60 mg daily  
| | >12 years: 60 mg daily |
| Concerta® | ≥6 to 12 years: 54 mg daily  
| | 13 to 17 years: 72 mg daily (not to exceed 2 mg/kg/day)  
| | >17 years: 72 mg daily |
| Focalin® and Focalin® XR | ≥6 to 12 years: 20 mg daily  
| | >12 years: 20 mg daily |
| Adderall® Dexamphetamine® Liquadd™ (or generic equivalent), Dexamphetamine Spansule® CD® (or generic equivalent) | ≥6 to 12 years: 40 mg daily  
| | >12 years: 60 mg daily |
| Adderall® XR | ≥6 to 12 years: 30 mg daily  
| | >12 years: 30 mg daily |

5.4 Drug Supply, Distribution and Pharmacy

Dextromethorphan syrup 15 mg/5 mL will be purchased by the IMPAACT Network and will be made available through the NIAID Clinical Research Products Management Center. Dextromethorphan syrup is to be stored at 20-25°C (68-77°F). Push in bottle adaptors (PIBAs) for the bottles of dextromethorphan syrup will be available through the CRPMC. To use the PIBAs, open the lid and push in the adaptor with the end with the small opening facing up. Use an oral dispenser to withdraw the correct dose. Cap and label the oral dispenser. Replace the lid of the bottle leaving the PIBA in the bottle.

This study will not supply or distribute any ARVs or psychiatric medications to study subjects.

The IMPAACT pharmacist can obtain the study products for this protocol by following the instructions in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section Study Product Management Responsibilities.

5.5 Study Product Accountability

The IMPAACT pharmacist is required to maintain complete records of the dextromethorphan syrup received from the NIAID Clinical Research Products Management Center and subsequently dispensed.
All unused study products must be returned to the NIAID Clinical Research Products Management Center after the study is completed or terminated. The procedures to be followed are provided in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section Study Product Management Responsibilities.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

Protocol participation requires but does not prescribe therapy with methylphenidate or amphetamine salts (“study drugs”). Therefore, monitoring and management of possible toxicity while on study is the responsibility of the treating clinician and should follow standard management practice at the site. The study team will collect and monitor possible toxicities while the subject is on study.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, Clarification August 2009, will be used to report adverse events for participating children and adolescents, and is available on the RCC web site (http://rcc.tech-res.com/safetyandpharmacovigilance/).

6.2 Subject Management

This protocol does not dictate clinical management of the study subjects.

6.21 Handling Positive Pregnancy Tests and Drug Screens

Female subjects should agree to plan not to become pregnant while on study. If a subject becomes pregnant while on study, they will be discontinued from the study. Emancipated minors and subjects who are 18 years or older will be informed of any positive pregnancy test; this information will NOT be shared with parents / caregivers unless requested by the subject or if local guidelines require it. Subjects who are under 18 years of age are considered minors; the disclosure of positive pregnancy tests will follow local, institutional and IRB guidelines.

Similarly, subjects who are 18 years or older, or who are emancipated minors, and who provide positive drug screens, will be informed without the information being shared with their parents / caregivers. Subjects, who are under 18 years old, will be informed of positive drug tests and
the information will be shared with their parents / caregivers, unless local guidelines prevent this. Subjects of all ages will be referred for counseling for positive drug tests.

Ultimately, guidelines for handling pregnancy or positive drug screens will be made locally and based on local regulations and standard of practice.

6.22 Vomiting During a PK Visit
If during the PK visit, the subject vomits within 15 minutes of the dose, the subject may be re-dosed once, with time zero re-set to the time of the repeat dose. If the subject vomits after being re-dosed, the PK visit must be cancelled and may be rescheduled. If the subject vomits >15 minutes and < 2 hours after dosing, the PK visit must be cancelled and may be rescheduled. If subject vomits 2 or more hours after the dose, and the medication is not visualized in the emesis, proceed with and complete the PK visit. Blood samples will be drawn over 6 to 12 hours depending on psychiatric drug formulation (see Appendix II).

6.3 Criteria for Treatment Discontinuation
This protocol will not involve making decisions about treatment discontinuation. Treatment decisions are the responsibility of the care providers.

6.4 Criteria for Study Discontinuation
Subjects must be discontinued from the study if:

6.41 The site investigator, NIAID, IMPAACT, the Office for Human Research Protection (OHRP), other governmental agencies or the site’s Institutional Review Board (IRB) discontinues this study;

6.42 The subject/legal guardian refuses further participation in the study;

6.43 The subject/legal guardian refuses further treatment with the prescribed ARVs and ADHD medications;

6.44 The investigator determines further participation would be detrimental to the subject’s health or well-being;

6.45 The subject fails to comply with the study requirements, so as to cause harm to self or seriously interfere with the validity of the study results;

6.46 The study drug was discontinued or the dose changed by the prescribing clinician such that the subject is no longer eligible for the study before completion of the first PK visit.
7.0 SERIOUS ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RCC website at http://rcc.tech-res.com/safetyandpharmacovigilance/.

The DAERS internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RCC website: http://rcc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RCC (RCCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

- The study agents for which expedited reporting are required are methylphenidate formulations, amphetamine/dextroamphetamine formulations and dextromethorphan cough syrup.

7.3 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is used and is available on the RCC website at http://rcc.tech-res.com/safetyandpharmacovigilance/.

7.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study 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).

- After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to
DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is an opportunistic study that will include HIV-1 infected and uninfected subjects who are taking selected common psychiatric medications for symptomatic relief of ADHD. The objective is to determine the population pharmacokinetics of these drugs in HIV-1 infected and uninfected children and adolescents, and to compare exposure in various subgroups of the subjects enrolled. The study will enroll subjects who are already taking the study drugs of interest (methylphenidate – arm 1; and amphetamine/ dextroamphetamine – arm 2). The group of uninfected subjects will be matched to the group of HIV-1 infected subjects by age, gender and race. Subjects will be replaced if Week 6 pharmacokinetic results are deemed un-evaluable by the study team (for example, mislabeled specimens, insufficient quantity, contaminated, mistimed samples, discontinued study medication, etc.).

8.2 Outcome Measures

8.21 Primary Outcome Measure

Estimation of steady-state oral clearance (Cl/F) for each psychiatric study medication is the primary outcome.

Additional pharmacokinetic parameters [area under the concentration-time curve (AUC), apparent volume of distribution (Vd/F), half-life (t½), pre-dose concentration (Cpre), maximum concentration (Cmax), corresponding time of maximum concentration (Tmax), elimination rate constant (ke), and between and within-subject variability] for the selected psychiatric medications in HIV-1 infected and uninfected children and adolescents will also be determined.

8.22 Secondary Outcome Measures

8.221 Comparison of oral clearance and additional pharmacokinetic parameters between HIV-1 infected and uninfected groups.

8.222 Estimation of pharmacokinetic parameters for the most commonly-used protease inhibitor and/or non-nucleoside reverse transcriptase inhibitor medications in HIV-1 infected children and adolescents.
8.223 Comparison of oral clearance (and additional pharmacokinetic parameters) of psychiatric medications between HIV-1 infected subjects on ritonavir versus HIV-1 infected subjects on efavirenz versus HIV-uninfected subjects (on neither ritonavir nor efavirenz).

8.224 To compare the frequency of psychiatric medication dose changes, dose requirement in mg/kg and tolerance between HIV-1 infected and HIV uninfected subjects who routinely used psychiatric medications over one year.

8.3 Randomization and Stratification

There will be no randomization. Subjects will be stratified by HIV-1 status and ARV group with concomitant ritonavir or efavirenz use in each arm as follows:

- Stratum A: 15 HIV uninfected subjects
- Stratum B: 15 HIV-1 infected subjects who are taking concomitant efavirenz
- Stratum C: 15 HIV-1 infected subjects who are taking a protease inhibitor (PI may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir) with concomitant ritonavir (at boosting doses) or lopinavir/ritonavir.

8.4 Sample Size and Accrual

Forty-five subjects will be enrolled in each of the two arms (Arms 1 and 2), for a total of 90 subjects. The primary objective is to estimate the mean oral clearance in pediatric subjects for each psychiatric medication. Fifteen subjects with evaluable PK data will be enrolled into each HIV-1 status/psychiatric medication/ARV cell for Arms 1 and 2, and secondary objectives are to estimate mean oral clearance for each psychiatric medication for HIV-1 infected versus uninfected and in each cell.

HIV-1 infected subjects will be enrolled first to determine the proportion of HIV-1 infected subjects according to three demographic characteristics: age group (≥6 to < 12; ≥12 to < 25), gender (male; female) and race/ethnicity (white, non-Hispanic; black, non-Hispanic; Hispanic; other). HIV uninfected subjects will then be enrolled in similar proportions to ensure that the groups are comparable. Specifically, individuals in each age category will be counted by gender and by race/ethnicity table for the HIV-1 infected subjects, and will be enrolled in parallel proportion of HIV uninfected subjects (allowing at most a 10% discrepancy per cell). The planned population pharmacokinetic analysis will compare groups of subjects; therefore groups with similar overall
demographics would need to be enrolled. Individual paired comparisons are not performed in a population pharmacokinetic analysis, so the protocol will not match specifically on an individual-to-individual basis. Weight information will be collected and incorporated into the pharmacokinetic parameter estimates to account for size.

For the primary objective, shown below are published estimates of the mean and coefficient of variation (CV) for each psychiatric medication. The last three columns show the width of a 95% confidence interval that would be estimable with 5, 10 and 15 subjects per cell. For example for methylphenidate, where the CV=30% and if the variability in the study sample was similar, with 15 subjects, the mean would be estimable with 95% certainty to within ± 0.07 L/h/kg. The precision with which the mean can be estimated increases with the sample size.

Table 4: Published Estimates of the Mean and Coefficient of Variation (CV) for Each Psychiatric Medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Clearance (mean)</th>
<th>CV</th>
<th>SD</th>
<th>Estimated width of 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>0.4 (L/h/kg)</td>
<td>30%</td>
<td>0.12</td>
<td>±0.15 ± 0.09 ± 0.07</td>
</tr>
<tr>
<td>Amphetamine/dextroamphetamine</td>
<td>30 (L/h)</td>
<td>30%</td>
<td>9.00</td>
<td>±11.17 ± 6.44 ± 4.98</td>
</tr>
</tbody>
</table>

Two of the secondary objectives of the study focus on comparing mean clearance between selected cells. Shown below are the required sample sizes in each cell to detect the specified fold difference in mean clearance with 80% power and a Type I error of 5% for a range of CVs. For example, with 15 subjects per cell, there would be more than 80% power to detect a 50% difference in means between cells if the CV in each cell was similar to published studies at ≤30%. This pilot study will provide necessary baseline pharmacokinetic parameter data in HIV-1 infected pediatric subjects, and will be able to identify moderate-to-large clearance differences between groups to identify priority areas for further study.
Table 5: Sample Size Required in Each Cell to Detect Specified Fold Difference in Mean Clearance With 80% Power and a Type I Error of 5% for a Range of CVs.

<table>
<thead>
<tr>
<th>CV</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>13</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>29</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>40</td>
<td>&gt;30</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>&gt;30</td>
<td>26</td>
<td>15</td>
</tr>
</tbody>
</table>

For the fourth secondary objective, a sample size of 30 HIV uninfected and 60 HIV-1 infected subjects will provide well over 90% power to detect a mean difference of one additional dose change in one group compared to the other. Within an arm, a sample size of 15 HIV uninfected and 30 HIV-1 infected subjects provides over 85% power to detect a mean difference of one additional dose change in one group versus the other. Therefore, even with potential loss to follow-up, the study will have power to detect a difference between groups in the mean number of dose titrations collected retrospectively at study entry and prospectively over one year.

8.5 Monitoring

A monitoring plan will be developed for this study to ensure that the data collected are clean, complete, and of high quality, and to make the team aware of the study’s progress in an ongoing manner. Monthly conference calls will be held by the study team to assess accrual of both HIV-1 infected and HIV uninfected subjects, and follow-up statistics will be reported to the team by the data management group on a monthly basis. Rate of enrollment will be closely monitored, with input provided from team members and participating sites on methods to speed enrollment if needed. Protocol violations and adverse events, if any, will be enumerated in the same reports. Section 7 provides detailed information on adverse event reporting to DAIDS. Monthly team calls will be conducted at study initiation, with frequency to be adjusted as needed as the study progresses.

8.6 Analyses

The primary analysis of the population pharmacokinetic modeling, as described in section 9.3, will be performed in each arm once all subjects in that arm have completed the PK visits. Analysis for the primary objective consists of computation of confidence intervals for key PK parameters for psychiatric
medications in HIV-1 infected and uninfected children and adolescents. Exploratory tests for heterogeneities associated with other variables, such as age, race or gender, will be conducted, and if such are identified, appropriate adjustments will be carried out.

Analysis for secondary objective one consists of comparing pharmacokinetic parameter distributions between HIV-1 infected children and adolescents and their uninfected counterparts in the study. Appropriate two-sample tests will be used; for example, if parameters are found to have skewed distributions within strata, log transformations will be conducted before t-test or Analysis of Variance (ANOVA) are carried out; if log transformations do not induce symmetry, rank-based tests will be used.

Analysis for secondary objective two consists of computation of confidence intervals for PI and NNRTI exposures among children receiving psychiatric medications, and comparing these to published values in children not receiving psychiatric medications. Analysis for secondary objective three involves comparing PK parameters for psychiatric medications among the uninfected, infected receiving ritonavir, and infected receiving efavirenz. Tukey’s honest significant differences procedure will be adopted to test the null hypotheses that mean psychiatric medicine PK parameters are equivalent across ARV treatment classes (untreated, ritonavir, efavirenz).

The analysis to address the fourth secondary objective will be performed for each arm after all subjects in that arm have completed the Week 52 Follow-Up visit. Appropriate categorical data analysis tools will be employed in order to assess differences in psychiatric medication dose changes between HIV uninfected and HIV-1 infected subjects by arm and across both arms. In addition, average dose requirements over the year in mg/kg will be compared by arm between HIV uninfected and HIV-1 infected subjects using appropriate two-sample tests.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

9.11 The primary clinical pharmacology objective of this study is:

9.111 To assess the steady-state pharmacokinetics of methylphenidate and amphetamine/ dextroamphetamine in HIV-1 infected and uninfected pediatric subjects.
9.12 The secondary pharmacology objectives are:

9.121 To compare psychiatric medication pharmacokinetics in HIV-1 infected to uninfected subjects;

9.122 To compare antiretroviral pharmacokinetics (PIs and NNRTIs) in HIV-1 infected subjects to historical control data;

9.123 To compare psychiatric medication pharmacokinetics between HIV-1 infected pediatric subjects who are taking ritonavir to HIV-1 infected pediatric subjects who are taking efavirenz to HIV uninfected pediatric subjects; and

9.124 To compare the frequency of dose changes, dose requirement in mg/kg and tolerance of psychiatric medications in HIV-1 infected versus HIV uninfected subjects with routine use of psychiatric medications over one year.

9.2 PK Study Eligibility Criteria / Re-Schedule / Exclusion Criteria

9.21 Deferral of Pharmacokinetic (PK) Visits
The Week 6 and Week 24 pharmacokinetic visits may be deferred if needed within the visit window for any of the following reasons, described below. If the deferral falls outside of the visit window, the site should contact the P1080 team for approval before proceeding with the PK visit.

- If required, the week 6 and/or week 24 PK visits may be deferred as needed until the subject is 100% adherent with psychiatric medications and (if HIV-1 infected) with antiretroviral medications in the 48 hours prior to the visit.

- The week 6 and/or week 24 PK visit may be deferred as needed if the subject has an intercurrent acute illness that may affect the study outcome.

9.22 Exclusion Criteria for Pharmacokinetic (PK) Visits
Subjects, who are ineligible for the PK visits based on the following reasons, will be discontinued from study:

- Pregnancy

- Week 6 PK specimens are deemed un-evaluable by the study team (e.g. mislabeled specimens, insufficient quantity, contaminated, mistimed samples, discontinued study medication)

- Positive urine drug test (see section 4.5 for the list of disallowed drugs)
9.3 Study Design, Modeling and Data Analysis

The primary population pharmacokinetic model for each study arm will be developed and the results disseminated once the PK visits are complete for all subjects in that arm. The primary or key pharmacokinetic endpoint for all analyses will be the oral clearance of the medication. Clearance is the gold-standard parameter to assess as it provides the best estimate of overall exposure and is independent of dose. In other words, subjects taking different doses of the same medication can be included together in a population pharmacokinetic study to estimate oral clearance of a drug. Likewise, the formulations of psychiatric drugs included in this study all fall into two categories of absorption rate (immediate or sustained release). The population model will be able to correct for the two absorption profiles, so that all subjects will be included in the combined analysis of pharmacokinetic parameters.

Secondary pharmacokinetic endpoints for each psychiatric medication include the area under the concentration-time curve (AUC), apparent volume of distribution ($V_d/F$), half-life ($t_{1/2}$), pre-dose concentration ($C_{pre}$), maximum concentration ($C_{max}$), corresponding time of maximum concentration ($T_{max}$), elimination rate constant ($k_e$), and estimates of between and within-subject variability. The specific formulation of each psychiatric medication used by study subjects will be collected.

Secondary drug exposure endpoints include the number of times that a psychiatric medication dose was changed in the retrospective medication history collected at baseline, the number of times the dose is changed over one year from enrollment to the one year telephone follow-up call, and the average dose requirement in mg/kg at study entry and over that year for the psychiatric medication.

Forty-five subjects will be enrolled in each Arm for a total of 90 subjects. We will be using a population pharmacokinetic modeling approach in order to provide pharmacokinetic parameter estimates and estimates of variability for these psychiatric medications in HIV-1 infected populations where no data currently exist (this is the primary objective). The population model will also include random effects, if found to be appropriate through assessment of components of variance, in order to accommodate for correlations among responses taken on family members, household members, or otherwise closely linked participants (59). A sample size of 45 pediatric subjects completing two pharmacokinetic visits should provide an accurate estimate of the population oral clearance and its variability both between and within subjects for the agents.
in study arms 1 and 2. Within-subject variability is typically much less than between-subject variability but might still be clinically relevant. The second PK visit will allow us to estimate this within-subject variability, which is currently unknown.

For commonly used ARVs, the same approaches as described for the psychiatric medications can be taken for analysis of protease-inhibitor and non-nucleoside reverse transcriptase inhibitor pharmacokinetics in the setting of psychiatric use. For less common medications (those that do not have enough subjects or samples to make a population pharmacokinetic analysis feasible), the concentrations will be compared to reported literature values and expressed as a percent of predicted concentration. For all medications, by using a percent of predicted value, we may pool the various drug concentration results to explore associations with genetic polymorphisms, non-invasive drug exposure variables and plasma viral loads.

The key benefits of using a population pharmacokinetic approach include only needing a limited number of samples per patient, and the ability to not only estimate pharmacokinetic parameters of interest, but also to estimate realistically the variability seen in a larger population. An additional benefit of the population pharmacokinetic approach is that we can begin to assess the influence of variables, including potential drug interactions, genotype/phenotype correlations and clinical management differences, while describing the pharmacokinetics of these agents. In other words, we can attempt to define some of the causes of or factors associated with the variability noted in the pharmacokinetic parameters.

Variables that may explain differences in the group will be explored. If we have at least 10 subjects with a target characteristic that we would like to explore (for example, taking ritonavir, or taking efavirenz), then we can assess in the population modeling approach whether that characteristic can help explain some portion of the variability seen between subjects (and we can define what percent of the variation is accounted for by that characteristic). Other variables usually explored in population pharmacokinetic analyses include demographics, organ function (chemistry & hematology assays), and disease severity (estimated by viral loads and CD4 counts for HIV and by Vanderbilt Scale scores for ADHD). Using this approach, we can test the impact of different variables in the population model to begin to identify reasons for observed variability in pharmacokinetics. If the data gathered in this study suggest a potentially significant, specific drug-drug interaction may be occurring, then a follow-up, formal Phase 1 drug interaction study of that specific combination will be considered for development. Formal drug interaction studies are typically performed after the pharmacokinetics of an agent have already been described in the target population. As noted in the
In addition to modeling the typical variables described above, this study will perform exploratory analyses to see if any relationships, correlations or cut-off values exist between pharmacokinetic parameters and the clinical management of subjects, such as the number of dose titrations or regimen changes over one year or between pharmacokinetic parameters and symptom control as documented by the Vanderbilt Scale scores. The population pharmacokinetic modeling process will also assess the impact of phenotypic categories (such as slow, intermediate and fast metabolizers) and genotypic profiles (such as the presence of single nucleotide polymorphisms) on the pharmacokinetics of the study medications. For example, the population pharmacokinetic model could estimate oral clearance values for three different groups of subjects, slow, intermediate and fast metabolizers. Then, for each of these categories, the pharmacokinetic parameters specific for that category can be used to simulate the doses that would be needed to achieve expected drug concentrations in that phenotype category.

9.4 **Anticipated Outcomes**

The data from this study will describe psychiatric medication pharmacokinetics in HIV-1 infected and uninfected pediatric subjects. By doing so, we will assess whether or not HIV-1 infected pediatric subjects are using comparable doses and more importantly, achieving comparable systemic psychiatric medication exposures as HIV uninfected pediatric subjects in this study. We will also compare the systemic exposures to those reported in the literature for HIV uninfected adult populations. This information will provide guidance as to whether or not typical psychiatric doses used in HIV-1 infected youth appear appropriate.
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 re-signs the consent. The plan should follow all IRB, local, state and national guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

10.2 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 of the subject, except as necessary for monitoring by the Office for Human Research Protections (OHRP), the NIAID and the local IRB.

10.3 Study Discontinuation

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

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

12.0 BIOHAZARD CONTAINMENT

Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory viruses are transmitted by droplet aerosolization and fomites. Appropriate blood and secretion precautions will
be employed by all personnel in the collection of samples and the shipping and handling of all specimens for this study, as currently recommended by the CDC.

All infectious specimens will be transported in compliance with Federal Regulations and 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 and to the ACTN Guidelines for Shipment and Receipt of Category B Biological Substance Shipment and ACTN Instruction for Overnight Shipments documents at https://actgnetwork.org/lab_resources/shipping_guidelines.aspx.
13.0 REFERENCES


(11) UCB I. Metadate CD package insert. 2007. Smyra, GA.


## APPENDIX I - SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th></th>
<th>Screening¹</th>
<th>Entry²</th>
<th>Week 6 PK visit²</th>
<th>Week 24 PK visit</th>
<th>Week 30³</th>
<th>Week 42³</th>
<th>Week 52³</th>
<th>Early Discont. Visit⁴</th>
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<tr>
<td></td>
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### CLINICAL EVALUATIONS

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<th>Week 6 PK visit²</th>
<th>Week 24 PK visit</th>
<th>Week 30³</th>
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<th>Early Discont. Visit⁴</th>
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<td>Vanderbilt Scale Questionnaire</td>
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<td>Instructions and planning for PK Visit</td>
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### LABORATORY EVALUATIONS

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<th>Week 6 PK visit²</th>
<th>Week 24 PK visit</th>
<th>Week 30³</th>
<th>Week 42³</th>
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<td>Dextromethorphan Dose and 4-Hour Urine Collection</td>
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<td>TOTAL BLOOD VOLUMES</td>
<td>5mL</td>
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<td>37-43mL</td>
<td>27-33mL</td>
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</tbody>
</table>
Footnotes

1. Screening and entry may occur at the same visit or on separate days up to 4 weeks apart.
2. The PK visit should be scheduled as soon as the inclusion/exclusion criteria are confirmed, but may extend to any time within 8 weeks after the entry visit so long as eligibility status does not change.
3. Study subjects/caregivers will be contacted by telephone to collect information regarding any dose, drug, or regimen changes and tolerance for both psychiatric and antiretroviral medications.
4. If subject withdraws from study prior to the 52 week follow-up call, a study discontinuation visit will be done. This should include a physical exam, a detailed medication history and tolerability report from subject/parent.
5. Complete history including source documentation for lifetime exposure to antiretroviral medications; CDC diagnoses; most recent CD4 count and CD4%, nadir CD4 count and CD4%; viral load and total lymphocyte count (for HIV-1 infected subjects); Tanner stage, neuropsychiatric diagnoses; and lifetime exposure to psychiatric medications for all subjects. A targeted history is sufficient at subsequent visits; includes changes in history from previous visit. The medication history should retrospectively capture the original dose titration and dose modification history of the psychiatric medication to the best extent possible.
6. Physical exam should include height, weight, and vital signs
7. Adherence Questionnaire is to be completed by a member of the site staff in a face-to-face interview at the PK visits and over the telephone for the telephone follow-up visits with study subjects (if they are responsible for administering their own medications) or with their parents/primary caregivers (if they are responsible for administering medications). It asks about medications missed over the past three days. The subject (or parent/primary caregiver) will be asked to identify medications taken, frequency of administration, and number of doses missed within the three days prior to the clinic visit.
8. Approximately two days prior to the week 6 and week 24 PK visits, sites should contact subjects/caregivers to review and encourage medication adherence (both to ARV meds and to psychiatric meds), and to determine if the PK visit needs to be rescheduled due to section 9.2.
9. Hematology for Screening Visit should include CBC with differential and platelet count. For HIV-1 positive subjects at the PK visits, WBC and % lymphocytes should be included if needed for dual platform flow cytometer lymphocyte subsets results.
10. Urine toxicology screen is for disallowed drugs. These include barbiturates, benzodiazepines, opiates, phencyclidine, and propoxyphene for all study subjects. For methylphenidate arm subjects, amphetamines are also disallowed.
11. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase, albumin.
12. An electrocardiogram will be performed only in study subjects who have not had an EKG in the past 6 months. Abnormal EKG findings should be referred to the subject’s physician for treatment if indicated. Study management of the toxicity should proceed as per section 6.1 of the protocol.
13. Pregnancy test may be either HCG urine or HCG blood serum test and must be performed on all females of childbearing potential within 72 hours of enrollment as well as within 72 hours of the 6 week and 18 week PK visits. If the screening and entry visits are completed within 72 hours, a pregnancy test does not have to be repeated at the entry visit.
14. Non-viable PBMC pellets for DNA genotypic analysis should be collected at the first PK visit (Week 6 visit) for all subjects.
15. For HIV-uninfected subjects only: Subjects’ age ≥13 years will have an HIV-1 antibody test at the screening visit to document negative status. A negative HIV-1 test documented in the subject's medical chart within the past year can be used instead of an HIV-1 screening test at the screening visit to satisfy this inclusion criterion.
16. This is for HIV-1 infected cohort only, and must be performed at DAIDS VQA-certified laboratory.
17. This is for HIV-1 infected cohort only. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at DAIDS IQA-certified laboratory.

18. PK sampling time points are listed by study drug formulation in Appendix II (*Pharmacokinetic Sampling Schedule for Selected Psychiatric Medications/Formulations*). Sites should contact subjects by telephone for the two days prior to the PK visits (Weeks 6 and 24) to encourage adherence. If the subject reports missing doses in the two days prior to the PK visit day, reschedule the PK visit.

19. 4-Hour urine collection for CYP 2D6 and 3A4 metabolic phenotyping; to include measurement of dextromethorphan, 3-hydroxy-morphinan and dextrorphan.
# APPENDIX II

**PHARMACOKINETIC SAMPLING SCHEDULE FOR SELECTED PSYCHIATRIC MEDICATIONS / FORMULATIONS**

<table>
<thead>
<tr>
<th>ALLOWED STUDY DRUG FORMULATIONS</th>
<th>PK SAMPLING SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METHYLPHENIDATE</strong></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate Immediate-Release chewable tablets or oral solution</td>
<td>6 hours</td>
</tr>
<tr>
<td>Methylphenidate Immediate-Release tablets (or generic equivalent Immediate-Release tablets)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Methylphenidate Extended-Release tablets (or generic equivalent Sustained-Release tablets)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Methylphenidate Extended-Release tablets (or generic equivalent Sustained-Release tablets)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Methylphenidate Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Methylphenidate Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Methylphenidate XR (dextromethorphan/nortriptyline) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Methylphenidate XR (dextromethorphan/nortriptyline) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td><strong>AMPHETAMINE/DEXTROAMPHETAMINE</strong></td>
<td></td>
</tr>
<tr>
<td>Adderall® (amphetamine/dextroamphetamine) Immediate-Release tablets (or generic equivalent Immediate-Release tablets)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Adderall® XR (amphetamine/dextroamphetamine) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Adderall® XR (amphetamine/dextroamphetamine) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Adderall® XR (amphetamine/dextroamphetamine) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td><strong>6 Hour Sampling Schedule:</strong> Pre-dose, and at 2, 4, and 6 hours post-dose. Note: the 6 hour sample should be obtained prior to the next (midday) dose.</td>
<td></td>
</tr>
<tr>
<td><strong>12 Hour Sampling Schedule:</strong> Pre-dose, and at 2, 4, 6 and 12 hours post-dose.</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX III-A

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

DAIDS SAMPLE INFORMED CONSENT for HIV-1 INFECTED CHILDREN and ADOLESCENTS

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 1.0, Dated June 17, 2010

SHORT TITLE FOR THE STUDY: ARV & Psychiatric Medication Concentrations in HIV Infected & Uninfected Children

INTRODUCTION

You are/your child is being asked to take part in this research study because you are/your child is infected with HIV-1 and is taking certain antiretroviral (ARV) medications (medication for the treatment of HIV), as well as a stimulant medication (methylphenidate or amphetamine/ dextroamphetamine) for treatment of attention deficit hyperactivity disorder (ADHD). The main purpose of this study is to find out how these stimulant medications are broken down in HIV-1 infected and HIV uninfected children and adolescents. The study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator).

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

WHY IS THIS STUDY BEING DONE?

Children and adolescents who are infected with HIV-1 are twice as likely to use stimulant medications as uninfected children and adolescents. However, there has never been a study to look at the way in which these medicines interact with antiretroviral drugs. This study will look at the way stimulant medicines (methylphenidate and amphetamine / dextroamphetamine) are broken down by children and adolescents who are not HIV-1 infected, and compare the results to the way the same stimulant medicines are broken down in HIV-1 infected children and adolescents.
down by HIV-1 infected children and adolescents who are also taking certain ARVs, such as Ritonavir or Efavirenz. We will look at how your body / your child’s body breaks down both the ADHD drugs and the ARVs when both are being taken, by drawing some of your /your child’s blood at specific times.

Management of your / your child’s ARV and ADHD medications will continue to be performed by your regular doctor; this study will not look at whether these medications are right for you / your child or whether they need to be adjusted.

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

If you/your child agree(s) to take part in this study, there will be three study visits described below. In addition, you/your child will be contacted by telephone every 3 months to collect any additional information about any change in either your/your child’s ADHD or ARV medications.

Screening Visit (this will take approximately 1 hour)
• Once you agree/allow your child to participate in this study, you/your child will be asked some questions about your/your child’s history of exposure to antiretroviral and ADHD medications to be sure you/your child can participate in this study.
• A urine sample will also be collected to screen for illegal use of drugs, including the following:
  • Methamphetamine (also known as ‘speed’, ‘meth’, ‘crank’, ‘ice’)
  • Barbiturates (also known as ‘downers’, and include Amytal, Nembutal and Seconal)
  • Benzodiazepines (also known as ‘benzos’ and include Valium)
  • Opiates (including morphine, heroin, codeine, hydrocodone, oxycodone)
  • Phencyclidine (also known as ‘PCP’)
  • Propoxyphene (including Darvon and Darvocet).

If the results of the urine test are positive for any of these drugs, you/your child will not be allowed to participate in the study. [Sites: please clarify procedures in regard to parental notification]. Positive results will NOT be shared with law enforcement.

• If you are/your child is female, of child bearing potential and are/is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].
• If you are/your child is female, of child bearing potential and are/is sexually active, you /your child must also agree to avoid pregnancy during the entire 144 week trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception.

• The study staff will explain to you/your child the details of what will take place during the next study visit. The screening visit and the entry visit may occur on the same day if the results of the urine and blood tests are available.

Entry Visit (this will take approximately 30 minutes)
• Approximately 1 teaspoon of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection) and chemistry levels (tests which help us see how well your liver and kidneys are working). The results of these tests will be shared with you as soon as they are available.

• You/your child will also have a physical exam, a medical history and will be asked some questions about your/his/her behavior.

• If you are/your child is female, of child bearing potential and are/is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification]. Also at this visit, the study staff will explain to you/your child the details of what will take place during the next study visit.

• Depending on which medications you are /your child is taking, you/your child will be entered into one of the 4 groups described in the table below.

<table>
<thead>
<tr>
<th>HIV-1 Infected Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARM 1</strong></td>
</tr>
<tr>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Efavirenz</td>
</tr>
<tr>
<td>Protease Inhibitor and ritonavir or lopinavir/ritonavir</td>
</tr>
<tr>
<td><strong>ARM 2</strong></td>
</tr>
<tr>
<td>Amphetamine/ dextroamphetamine</td>
</tr>
<tr>
<td>Efavirenz</td>
</tr>
<tr>
<td>Protease Inhibitor and ritonavir or lopinavir/ritonavir</td>
</tr>
</tbody>
</table>

Week 6 and Week 24 Pharmacokinetic (PK) Visits (each visit will take about $6\frac{1}{2}$ or $12\frac{1}{2}$ hours, depending on which medication(s) you are/your child is taking.)
Approximately 6 weeks and 24 weeks after your/your child’s screening visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visits, sites will contact subjects/caregivers by phone to ask about missed doses and to encourage medication adherence. At these clinic visits, the following will take place:

- Approximately 1 teaspoon of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection) and chemistry levels (tests which help us see how well your liver and kidneys are working). The results of these tests will be shared with you as soon as they are available.

- You/your child will also have a physical exam, a medical history and will be asked some questions about your/his/her behavior. Study staff will ask you/your child some questions about medications you have/your child has taken within the three days before the visit.

- An electrocardiogram will be performed at the Week 6 visit if you have /your child has not had an electrocardiogram in the past 6 months. This is to monitor your/your child’s safety. An electrocardiogram is a special test that measures the movements of the heart, and it is not painful. The results of these tests will be shared with you as soon as they are available.

- Approximately 1 teaspoon of blood will be collected at the Week 6 visit in order to look at your /your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. You may choose not to have this blood collected if you prefer not to.

- If you are/your child is female, of child bearing potential and are/is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

- You/your child will be given a single oral dose of cough syrup (dextromethorphan) at the Food and Drug Administration’s (FDA) approved dose. For the 4 hours following the dose of cough medicine, you/your child will be asked to collect your/your child’s urine, so that the urine can be measured, recorded, and analyzed. Analyzing your/your child’s urine after taking the cough syrup will allow the study investigators to predict how you/your child will process different doses of stimulant medication.

- A total of 5-6 teaspoons of blood will be collected to look at how your body breaks down both your ADHD medications and your antiretroviral medications. This blood will be collected over 6 hours - 3 teaspoons will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours and 6 hours after you/your child takes the medication. If you
are/your child is taking an extended release medication, about one teaspoon will also be collected 12 hours after you/your child takes your medication. These results will be made available to your healthcare provider upon request.

Weeks 30, 42 and 52 Telephone Call
At approximately 30 weeks, 42 weeks and 52 weeks after your /your child’s screening visit, the study staff will call you by phone to see how you/your child is doing. These calls will take approximately 30 minutes. Study staff will also ask about your/your child’s medication history, including all dose changes to ADHD medications, and to antiretroviral medications. Study staff will ask you/your child about whether you have /your child has stayed on the medications as prescribed since the last visit. If you have/your child has discontinued the ADHD medication since your last PK visit, you/your child will be asked why. Study staff may also ask to briefly speak to your child about any symptoms they may be experiencing.

If You/Your Child Stop(s) the Study Early
If you/your child stop(s) the study before you have /your child has completed the Week 52 follow-up visit, you/your child will be asked to return to the clinic for a final visit where you/your child will be given a physical exam and asked about your/your child’s medication history and reactions to the medication(s). This visit will last about 30 minutes.

OTHER INFORMATION
Sometimes a heparin lock (small plastic tube) is used when collecting more than one blood sample over a period of time, such as during a pharmacokinetic visit. It is left in the vein until all of the blood draws are completed, and then it is removed. This allows blood to be taken repeatedly without having to stick you/your child with a needle many times. Any blood samples that remain after tests are run for this study will be destroyed.

GENETIC TESTING
At the pharmacokinetic visit at Week 6, about 1 teaspoon of blood will be drawn and used for genetic testing, which is a study of your/your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. The researchers do not plan to contact you, your child, or the study doctor with the results of these studies. This is because research studies are often done with experimental procedures, and these results should not be used to make decisions about your/your child’s HIV or ADHD care.

However, in case researchers learn new information that makes them believe that a certain study result is important for your/your child’s HIV or ADHD care, then your/your child’s study doctor will be informed. If you would like the researchers to also tell you this information in a case like this, then, you/your child will need to tell the study staff if
your/your child’s address or phone number change. You/your child may decide that you/your child do not want blood used for genetic testing. You/your child can still be in this study even if you/your child make this decision. Please read the statement below, and mark your initials in the spaces to indicate whether you agree to allow your /your child’s blood to be used for genetic testing.

I agree to have my blood used for genetic testing as part of this study.

___________ Yes  ____________ No  ____________ Date

I agree to have my child’s blood used for genetic testing as part of this study.

___________ Yes  ____________ No  ____________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 90 subjects will take part in this study; 60 HIV-1 infected and 30 HIV-uninfected children and adolescents.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
You/your child will be in this study for up to fourteen months.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THIS STUDY EARLY?
The study doctor may need to take you/your child off the study early without your permission if:

- The study is stopped or cancelled
- You/your child refuse further participation in the study;
- You/your child refuse further treatment with ARVs or ADHD medications
- The investigator determines further participation would be harmful to your/your child’s health or well-being;
- You/your child fails to meet study requirements, in a way that would harm you/your child or seriously interfere with the study results;
- The ARVs or ADHD medications were discontinued or the dose changed such that eligibility status is changed by the prescribing clinician before completion of the study
WHAT ARE THE RISKS OF THE STUDY?
Since you are/your child is already taking the ADHD and ARV medicines before joining this study, any risks associated with these medicines should be discussed with the doctor who prescribed them.

Cough Syrup Risks
Side effects of a single dose of cough syrup are uncommon, and may include mild sleepiness or dizziness.

Blood Drawing Risks
Blood drawing from a vein may cause some discomfort, bleeding, or bruising where the needle goes into the skin. A small blood clot may form at the site of injection, or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. A feeling of lightheadedness may also occur.

WILL I RECEIVE ANY COMPENSATION?
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
Since no study drugs will be given, there will not be any direct benefit from taking part in this study. Information learned from this study may help others who take stimulant medications.

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

People who may review your / your child’s records include the site IRB (insert name of site IRB), the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), the National Institutes of Allergies and Infectious Disease (NIAID), study staff, and study monitors and their designees.

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

WHAT ARE THE COSTS TO ME?
Taking part in this study will not lead to added costs to you and your insurance company.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your/your child’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are/your child is otherwise entitled.

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

WHAT DO I 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/your child’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
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>
</tr>
</thead>
<tbody>
<tr>
<td>Participant’s Legal Guardian (print)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>(As appropriate)</td>
<td></td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Witness’ Name (print)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>(As appropriate)</td>
<td></td>
</tr>
<tr>
<td>Father’s Name</td>
<td>Father’s Signature and Date</td>
</tr>
<tr>
<td>(If father’s consent is required)</td>
<td>(If father’s consent is required)</td>
</tr>
</tbody>
</table>
APPENDIX III-B

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIALS GROUP (IMPAACT)

DAIDS SAMPLE INFORMED CONSENT for HIV UN-INFECTED CHILDREN and ADOLESCENTS

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 1.0, Dated June 17, 2010

SHORT TITLE FOR THE STUDY: ARV & Psychiatric Medication Concentrations in HIV-1 Infected & Uninfected Children

INTRODUCTION
You are/your child is being asked to take part in this research study because you are/your child is taking a stimulant medication (methylphenidate or amphetamine/dextroamphetamine) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The main purpose of this study is to find out how these stimulant medications are processed in HIV-1 infected and HIV-uninfected children and adolescents. You are/your child is being asked to take part in this study to allow us see how stimulant medicines are processed in different people. The 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/your child decide(s) if you want to be/want your child to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?
Children and adolescents who are infected with HIV are twice as likely to use stimulant medications as uninfected children and adolescents. However, there has never been a study to look at the way in which these medicines interact with antiretroviral drugs. This study will look at the way stimulant medicines (methylphenidate and amphetamine/dextroamphetamine) are processed by children and adolescents who are not HIV-1 infected, and compare the results to the way the same stimulant medicines are processed by HIV-1 infected children and adolescents who are also taking other medications.
Management of your/your child’s ADHD medications will continue to be performed by your regular doctor; this study will not look at whether these medications are right for you / your child or whether they need to be adjusted.

WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/HE/SHE IS IN THIS STUDY?
If you/your child agree(s) to take part in this study, there will be three study visits described below. In addition, you/your child will be contacted by telephone every 3 months to collect any additional information about changes in either ADHD or ARV medications.

Screening Visit (this will take approximately 1½ hours)
- Once you agree/allow your child to participate in this study, you/your child will be asked some questions about your/your child’s history of exposure to antiretroviral and stimulant medications to be sure you/your child can participate in this study.

- If you are / your child is 13 years of age or older, and have not had an HIV test before, 1 teaspoon of blood will be drawn to test your blood for the HIV virus. You / your child will be informed of the results of this test as soon as it is available.

- A urine sample will also be collected to screen for illegal use of drugs, including the following:
  - Methamphetamine (also known as ‘speed’, ‘meth’, ‘crank, ‘ice’)
  - Barbiturates (also known as ‘downers’ and include Amytal, Nembutal and Seconal)
  - Benzodiazepines (also known as ‘benzos’ and include Valium)
  - Opiates (including morphine, heroin, codeine, hydrocodone, oxycodone)
  - Phencyclidine (also known as ‘PCP’)
  - Propoxyphene (including Darvon and Darvocet).

If the results of the urine test are positive for any of these drugs, you/your child will not be allowed to participate in the study. [Sites: please clarify procedures in regard to parental notification]. Positive results will NOT be shared with law enforcement.

- If you are/your child is female, of child bearing potential and you are / your child is sexually active, you/your child will be asked to take a pregnancy test. If you are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

- If you are/your child is female, of child bearing potential and are/is sexually active, you /your child must also agree to avoid pregnancy during the entire 144
week trial and to consistently and appropriately use at least two of the following contraception methods: condoms, diaphragm or cervical cap with spermicide, IUD, hormonal-based contraception.

**Entry Visit** (this will take approximately 30 minutes)

- Approximately 1 teaspoon of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection) and chemistry levels (tests which help us see how well your liver and kidneys are working). The results of these tests will be shared with you as soon as they are available.

- You/your child will also have a physical exam, a medical history and will be asked some questions about your/his/her behavior.

- If you are / your child is female and of reproductive age, you/your child will be asked to take a pregnancy test. If you are / your child is found to be pregnant, you/your child will not be able to participate in this study. Also at this visit, the study staff will explain to you/your child the details of what will take place during the next study visit.

- Depending on what medications you are/your child is taking, you/your child will be placed into one of the groups listed below:

<table>
<thead>
<tr>
<th>HIV Uninfected Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1</td>
</tr>
<tr>
<td>ARM 2</td>
</tr>
</tbody>
</table>

**Week 6 and Week 24 Pharmacokinetic (PK) Visits** (each visit will take about 6½ or 12½ hours, depending on which medication(s) you are/your child is taking.)

Approximately 6 weeks and 24 weeks after your/your child’s screening visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visits, sites will contact subjects/caregivers to encourage medication adherence. At these visits, the following will take place:

- Approximately 1 teaspoon of blood will be drawn to check your/your child’s blood count and chemistry levels. The results of these tests will be shared with you as soon as they are available.

- You/your child will also have a physical exam, a medical history and will be asked some questions about your/his/her behavior. Study staff will also ask you/your child some questions about medications you have/your child has taken within the three days before the visit.

- If you are / your child is female, of child bearing potential and you are / your child is sexually active, you/your child will be asked to take a pregnancy test. If you
are/your child is found to be pregnant, you/your child will not be able to participate in this study. [Sites: please clarify procedures in regard to parental notification].

- An electrocardiogram will be performed at the Week 6 visit if you have /your child has not had an electrocardiogram in the past 6 months. This is to monitor your/your child’s safety. An electrocardiogram is a special test that measures the movements of the heart, and it is not painful. The results of these tests will be shared with you as soon as they are available.

- Approximately 1 teaspoon of blood will be collected at the Week 6 visit in order to look at your /your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. You may choose not to have this blood collected if you prefer not to.

- You/your child will be given a single oral dose of cough syrup (dextromethorphan) at the Food and Drug Administration’s (FDA) approved dose. For the 4 hours following the dose of cough medicine, you/your child will be asked to collect your/your child’s urine, so that the urine can be measured, recorded, and analyzed. Analyzing your/your child’s urine after taking the cough syrup will allow the study investigators to predict how you/your child will process different doses of ADHD medication.

- A total of 5-6 teaspoons of blood will be collected to look at how your body breaks down your medication. This blood will be collected over 6 hours - 3 teaspoons will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours and 6 hours after you/your child takes the medication. If you are/your child is taking an extended release medication, about one teaspoon will also be collected 12 hours after you/your child takes your medication. These results will be made available to your healthcare provider upon request.

**Weeks 30, 42 and 52 Telephone Call**
At approximately 30 weeks, 42 weeks and 52 weeks after your /your child’s screening visit, the study staff will call you by phone to see how you/your child is doing. These calls will take approximately 30 minutes. Study staff will also ask about your/your child’s medication history, including all dose changes to ADHD medications, and to antiretroviral medications. Study staff will ask you/your child will be asked about whether you/your child have stayed on the medication as prescribed since the last visit. If you have/your child has discontinued the ADHD medication since your last PK visit, you will be asked why. Study staff may also ask to briefly speak to your child about any symptoms they may be experiencing.
If You/Your Child Stop(s) the Study Early
If you/your child stop(s) the study before you have /your child has completed the Week 52 follow-up visit, you/your child will be asked to return to the clinic for a final visit where you/your child will be given a physical exam and asked about your/your child’s medication history and reactions to the medication(s). This visit will last about 30 minutes.

OTHER INFORMATION
Sometimes a heparin lock (small plastic tube) is used when collecting more than one blood sample over a period of time. It is left in the vein until all of the blood draws are completed, and then it is removed. This allows blood to be taken repeatedly without having to stick you/your child with a needle many times. Any blood samples that remain after tests are run for this study will be destroyed.

GENETIC TESTING
At the PK visit at Week 6, about 1 teaspoon of blood will be drawn and used for genetic testing, which is a study of your/your child’s genes (DNA). This will help researchers understand how the genetic differences between people may explain how their body processes and responds differently to combinations of drugs. The researchers do not plan to contact you, your child, or the study doctor with the results of these studies. This is because research studies are often done with experimental procedures, and these results should not be used to make decisions about your/your child’s ADHD care. However, in case researchers learn new information that makes them believe that a certain study result is important for your/your child’s ADHD care, then your/your child’s study doctor will be informed.

If you would like the researchers to also tell you this information in a case like this, then, you/your child will need to tell the study staff if your/your child’s address or phone number change. You/your child may decide that you/your child do not want blood used for genetic testing. You/your child can still be in this study even if you/your child make this decision. Please read the statement below, and mark your initials in the spaces to indicate whether you agree to allow your/your child’s blood to be used for genetic testing.

I agree to have my blood used for genetic testing as part of this study.

___________ Yes  ____________ No  ____________ Date

I agree to have my child’s blood used for genetic testing as part of this study.

___________ Yes  ____________ No  ____________ Date
HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 90 subjects will take part in this study; 60 HIV-1 infected and 30 HIV-uninfected children and adolescents.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
You/your child will be in this study for up to fourteen months.

WHY WOULD THE DOCTOR TAKE ME / MY CHILD OFF THIS STUDY EARLY?
The study doctor may need to take you/your child off the study early without your permission if:

- The study is stopped or cancelled
- You/your child refuse further participation in the study;
- You/your child refuse further treatment with ADHD medications
- The investigator determines further participation would be harmful to your/your child’s health or well-being;
- You/your child fails to meet study requirements, in a way that would harm you/your child or seriously interfere with the study results;
- The ADHD medications were discontinued or the dose changed such that eligibility status is changed by the prescribing clinician before completion of the study;

WHAT ARE THE RISKS OF THE STUDY?
Since you are/your child is already taking the ADHD medicines before joining this study, any risks associated with these medicines should be discussed with the doctor who prescribed them.

Cough Syrup Risks
Side effects of a single dose of cough syrup are uncommon, and may include mild sleepiness or dizziness.

Blood Drawing Risks
Blood drawing from a vein may cause some discomfort, bleeding, or bruising where the needle goes into the skin. A small blood clot may form at the site of injection, or there may be swelling in the area. There is a small risk of a minor infection at the blood draw site. A feeling of lightheadedness may also occur.

WILL I RECEIVE ANY COMPENSATION?
You will receive $XX for each study visit you attend. If you attend all study visits, you may receive up to $XX.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?
Since no study drugs will be given, there will not be any direct benefit from taking part in this study. Information learned from this study may help others who take stimulant medications.

**WHAT ABOUT CONFIDENTIALITY?**
To help us protect your /your child’s privacy we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

People who may review your /your child’s records include the site IRB (insert name of site IRB), the Office of Human Research Protection (OHRP), the National Institutes of Health (NIH), the National Institute of Allergy and Infectious Disease (NIAID), study staff, study monitors, and their designees.

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

**WHAT ARE THE COSTS TO ME?**
Taking part in this study will not lead to added costs to you and your insurance company or your child’s insurance company.

**WHAT HAPPENS IF I AM / MY CHILD IS INJURED?**
If you are/your child is injured as a result of being in this study, you / your child will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. You will not be giving up any of your legal rights by signing this consent form.

**WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?**
Taking part in this study is completely voluntary. You may choose not to take part/not to allow your child to take part in this study or leave this study/take your child out of the study at any time. Your decision will not have any impact on your/your child’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are/your child is otherwise entitled.
We will tell you about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I 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/your child’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
SIGNATURE PAGE

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

__________________________________  ____________________________________
Participant’s Name (print)  Participant’s Signature and Date

__________________________________  ________________________________
Participant’s Legal Guardian (print)  Legal Guardian’s Signature and Date
(As appropriate)

__________________________________  ____________________________________
Study Staff Conducting  Study Staff Signature and Date
Consent Discussion (print)

__________________________________  ____________________________________
Witness’ Name (print)  Witness’s Signature and Date
(As appropriate)

__________________________________  ____________________________________
Father’s Name  Father’s Signature and Date
(If father’s consent is required)
(If father’s consent is required)