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 2.0 of IMPAACT P1080, which is comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #1, dated 15 August, 2014
- Protocol Version 1.0, dated 22 April, 2014
Letter of Amendment #1 for:

IMPAACT P1080
A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 2.0, dated 22 April 2014

Non-IND Protocol
DAIDS ES ID# 10768

Letter of Amendment Date: 15 August 2014

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT P1080 study, including the study informed consent forms (ICFs), and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval with revised site specific ICFs. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA, including use of revised site-specific informed consent forms for newly enrolled participants. Unless directed by site IRBs/ECs, re-consenting is not required for current study participants.

Upon receiving IRB/EC approval and approval of any other applicable regulatory entities, this LoA is to be implemented 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 after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1080.

If the IMPAACT P1080 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

Summary of Modifications and Rationale

This LoA clarifies the data collection expectations with respect to the medications history (Appendix I-B) and the study population that are required to have 24-hour PK sampling (Appendices I-B, III-C and III-D).
Implementation

Detailed modifications of the protocol text are shown below. Deletions in the protocol text are indicated by strikethrough, and additions are indicated in bold.

1.) Appendix I-B (SCHEDULE OF EVALUATIONS FOR SUBJECTS ENROLLED UNDER VERSION 2); footnote 3

Footnote 3: 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 neuropsychiatric signs and symptoms that are not related to these diagnoses; and lifetime exposure to psychiatric medications for all subjects. A targeted history is sufficient at the PK visit; includes changes in history from previous visit. The medication history should retrospectively capture the original dose titration and dose modification history; start date and the current dose of the psychiatric medication of interest; all medications (including OTC and herbal preparations) used on a regular basis (i.e., not simply on a PRN basis) in the 90 days prior to the study visit; and all drug exposure (i.e., inclusive of those taken PRN) in the 7 days prior to the study visit. To the best extent possible.

2.) Appendix I-B (SCHEDULE OF EVALUATIONS FOR SUBJECTS ENROLLED UNDER VERSION 2); footnote 15

Footnote 15: PK sampling time points are pre-dose, and 2, 4, 6, and 12 hours post-dose. A 24 hours post-dose sample is required if any of the study drugs of interest (i.e., the psychiatric drug of interest and/or ARVs) are taken on a once daily basis. Depending on date of enrollment in relation to the PK visit, sites should contact subjects by telephone for the two days prior to the PK visit to encourage adherence. If the subject reports missing doses in the two days prior to the PK visit day, reschedule the PK visit.

3.) Appendix III-C (DAIDS SAMPLE INFORMED CONSENT for HIV-1 INFECTED CHILDREN and ADOLESCENTS WHO ENROLL UNDER VERSION 2.0).

Pharmacokinetic (PK) Visit (this visit will take about between 12 and 24 hours). Within 8 weeks after your/your child’s Entry Visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visit, the staff will contact you/your child by phone to ask about missed doses and to encourage medication adherence. At this clinic visit, the following will take place: […]

- A total of about 3 tablespoons of Blood will be collected to look at how your child’s body breaks down both the psychiatric medications and the antiretroviral medications. If any of these psychiatric or ARV medications are taken once a day, then blood will be collected at different time points through 24 hours. If the psychiatric or ARV medications are taken twice a day, then blood will be collected at different time points through 12 hours only. This blood will be collected over 24 hours. For this testing, about 1 teaspoon will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours, 6 hours, and 12 hours, and 24 hours, after you/your child takes the medication for a total of 5 teaspoons (about 2 tablespoons). An additional 1 teaspoon will be collected if the 24 hour collection is needed. To obtain the 24 hour specimen, study staff will discuss with
you whether the option of staying overnight is available or you should return the next day. These results will be made available to your healthcare provider upon request.

4.) Appendix III-D (DAIDS SAMPLE INFORMED CONSENT for HIV UN-INFECTED CHILDREN and ADOLESCENTS).

Pharmacokinetic (PK) Visit (this visit will take about between 12 and 24 hours.)
Within 8 weeks after your/your child’s entry visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visit, the staff will contact you/your child to encourage medication adherence. At this visit, the following will take place: […]

- A total of about 3 tablespoons of blood will be collected to look at how your body breaks down your medication. If your medication is taken once a day, then blood will be collected at different time points through 24 hours. If your medication is taken twice a day, then blood will be collected at different time points through 12 hours only. This blood will be collected over 24 hours. For this testing, about 1 teaspoon will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours, 6 hours, and 12 hours, and 24 hours, after you/your child takes the medication for a total of 5 teaspoons (about 2 tablespoons). An additional 1 teaspoon will be collected if the 24 hour collection is needed. To obtain the 24 hour specimen, study staff will discuss with you whether the option of staying overnight is available or you should return the next day. These results will be made available to your healthcare provider upon request.
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) and The National Institute of Mental Health (NIMH)

Non-IND Protocol DAIDS ES ID# 10768

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Version 2.0
22 April 2014
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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APPENDICES:

Appendix I-A: Schedule of Evaluations for subjects enrolled under Version 1.0
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Appendix II: Pharmacokinetic Sampling Schedule for Selected Psychiatric Medications / Formulations for subjects enrolled under Version 1.0
Appendix III-A: DAIDS Sample Informed Consent for HIV-1 Infected Children and Adolescents who enrolled under Version 1.0
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Appendix III-C: DAIDS Sample Informed Consent for HIV-1 Infected Children and Adolescents who enroll under Version 2.0
Appendix III-D: DAIDS Sample Informed Consent for HIV Uninfected Children and Adolescents who enroll under Version 2.0
GLOSSARY OF TERMS

ADHD  Attention deficit hyperactivity disorder
AE    Adverse Event
ANOVA Analysis of Variance
ARV   Antiretroviral
AUC   Area under the curve
CD    Continuous Delivery
CDC   Centers for Disease Control
CES1  Carboxylesterase 1
CHARTER CNS HIV Anti-retroviral Therapy Effects Research
CNS   Central nervous system
Cpre  Pre-dose Concentration
CV    Coefficient of Variation
CYP   Cytochrome P450
DAERS DAIDS Adverse Event Reporting System
DM/DX Dextromethorphan/dextrorphan
EFV   Efavirenz
ER    Extended Release
FDA   Food and Drug Administration
HCG   Human Chorionic Gonadotropin
HIV-1 Human Immunodeficiency Virus Type I
ICH   International Conference on Harmonization
IR    Immediate Release
IRB   Institutional Review Board
K_e   Elimination rate constant
LA    Long Acting
MDR1  Multidrug resistance transporter gene
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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>RSC</td>
<td>Regulatory Support 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>T_{1/2}</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>
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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:** Under Version 1.0, planned accrual was forty-five subjects in each of two arms (Arms 1 and 2) for a total of 90 subjects. Under Version 2.0, forty-five subjects will be enrolled in each of 4 arms, for a total of 180 subjects; total planned accrual in both versions: 270 subjects.

**POPULATION:** Under Version 2.0, enrolling arms will have HIV-1 infected and uninfected children and adolescents < 25 years who are currently receiving citalopram, escitalopram, risperidone, sertraline, fluoxetine or paroxetine.

Upon receipt of required local IRB approvals of Version 2.0, study sites will cease enrollment into the Version 1.0 study arms (methylphenidate or amphetamine/dextroamphetamine), but subjects in follow up under that version will continue on study to completion as per Appendix I-A.

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

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Arm: Psychiatric Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</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>
</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>
</tr>
</tbody>
</table>

*PI may be any of the following: atazanavir, darunavir, fosamprenavir, indinavir, saquinavir or tipranavir
Under Version 1.0, the Study Arms were:
Arm 1: Methylphenidate
Arm 2: Amphetamine/Dextroamphetamine

Under Version 2.0, the Study Arms Open to Enrollment are:
Arm 3: Citalopram or Escitalopram
Arm 4: Risperidone
Arm 5: Sertraline
Arm 6: Fluoxetine or Paroxetine

REGIMEN: Subjects must already be taking the listed study psychiatric medication for clinical care as prescribed by their care provider. Subjects must be on a stable dose of one of these psychiatric medications for ≥ 2 weeks prior to the PK visit (≥ 5 weeks for fluoxetine). This study does not prescribe any therapy or provide medications for study subjects.

STUDY DURATION: Subjects enrolled under Version 1.0 will be on study for up to 14 months. Subjects enrolled under Version 2.0 will be on study for up to 2 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. (Applies only to subjects enrolled under Version 1.0.)
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 have 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 (SSRIs), 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. Under dosing 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] Among various classes of psychiatric medications prescribed to adolescents, risperidone and SSRIs were the most commonly used in a survey of P1080 study sites in fall 2011.

1.1.1 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 versus 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 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 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.)
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.

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. [10] 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) [11]. 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 [12, 13]. 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.

1.142 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.

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 [14-16], 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 1 below from the Adderall® XR package insert.
Figure 1: 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. [17]

For Adderall® XR, three published studies describe the pharmacokinetics of this formulation in healthy adult volunteers (>18 years old). [18-20] Only a single published study has described the pharmacokinetics of Adderall® XR in children (≥6 to ≤12 years old). [15] After a 20 mg Adderall XR dose, the dextroamphetamine T\text{max} = 6.8 hours, C\text{max} = 49 ng/mL, and AUC\text{0-24} = 704 ng/mL/hr. The levoamphetamine results were T\text{max} = 6.9 hours, C\text{max} = 15 ng/mL, and AUC\text{0-24} = 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) [21, 22]. 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). [23, 24]
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.

1.143 Citalopram/Escitalopram

Description

Citalopram is an SSRI approved to treat depression in adults. It is also commonly used off-label for these disorders in children and adolescents, as well as for anxiety disorders, hot flashes and premenstrual dysphoric disorder. When administered orally, the absolute bioavailability is about 80% and is not affected by food. It is about 80% protein bound, and reaches steady-state within about one week with daily dosing. Citalopram is metabolized primarily by CYP 3A4 and 2C19. In patients who are 2C19 poor metabolizers or who are taking 2C19 inhibitors, lower doses are recommended in order to prevent dose-dependent QT-prolongation which can occur with citalopram. The metabolites are much less potent than citalopram. The elimination half-life is about 35 hours, and it is supplied as oral tablets and oral solutions.

Citalopram is a racemic mixture of S and R enantiomers. The S enantiomer is the active moiety, while the R enantiomer is inactive. The active enantiomer is marketed as escitalopram. Escitalopram is approved for depression and generalized anxiety disorder in adults, and for depression in 12 to 17 year olds. A meta-analysis in adults suggested that escitalopram was more effective than citalopram [25] (the postulated mechanism was that the R enantiomer in the racemate antagonized/interfered with the binding of the active S enantiomer), but these findings were not confirmed in subsequent studies. [26] The pharmacokinetic parameters of escitalopram are similar to those of citalopram. Prior pharmacokinetic studies (not efficacy studies) suggest that 20 mg of escitalopram is bioequivalent to 40 mg of citalopram. The elimination half-life is 27 – 32 hours, and it is available in oral solution and oral tablet formulations.

Interestingly, a placebo controlled, randomized efficacy study of escitalopram in 102 HIV-infected adults showed no difference between placebo and escitalopram efficacy in the treatment of depression. The response rate was 62% for escitalopram and 59% for placebo. The authors attributed the lack of difference with placebo to an unusually
high placebo response rate. No drug concentrations were reported in this study [27].

Pharmacokinetics of Citalopram/Escitalopram in HIV-uninfected children and adolescents.

For citalopram, a combined report of a prospective and a retrospective study in a total of 44 adolescent subjects under 21 years of age evaluated only trough concentrations [28]. This study found that females had higher trough concentrations than males, and strong serum concentration-dose relationships were found in non-smokers, girls not taking oral contraceptives and girls in the last 14 days of their menstrual cycle.

No pharmacokinetic studies of escitalopram (one of the two enantiomers of citalopram) in HIV-uninfected children or adolescents have been published.

Pharmacokinetics of Citalopram/Escitalopram in HIV-infected children and adolescents.

No pharmacokinetic studies of either citalopram or escitalopram have been published for HIV-1 infected adults, adolescents or children.

1.144 Risperidone

Description

Risperidone is an atypical antipsychotic that is considered a first-line treatment for schizophrenia and related disorders. It is also approved in adults for bipolar disorder. In October 2006, it was approved to treat irritability (for example, aggression towards others, deliberate self-injury, temper tantrums, and labile mood) associated with autism in children and adolescents. In 2007, it was approved for schizophrenia in adolescents and bipolar disorder in children ≥ 10 years.

Risperidone is administered orally or as a long-acting depot intramuscular injection. It is completely absorbed after oral administration, and both risperidone and its metabolites are highly protein bound in the plasma. Risperidone is metabolized by CYP 2D6 to its primary active metabolite, 9-hydroxyrisperidone, which has equal activity to risperidone. It is subject to drug-drug interactions with medications that alter CYP 2D6 activity. The half-life of oral risperidone is 3 hours in extensive metabolizers and 20 hours in poor metabolizers. The half-life of 9-hydroxyrisperidone is 21 hours in extensive metabolizers and 30 hours in poor metabolizers. For oral administration,
risperidone is formulated in oral solutions, oral tablets, and orally-disintegrating tablets, all of which are bioequivalent.

**Pharmacokinetics of Risperidone in HIV-uninfected children and adolescents.**

In a study of 20 children (ages 3 – 10 years) with autistic disorder, a single trough sample was drawn at week 12 to determine risperidone and 9-OH-risperidone concentrations [29]. The authors reported concentrations of these two moieties added together, ranging from 8 – 55 ng/mL. No other pharmacokinetic data are available in the literature on the use of risperidone in children and adolescents.

**Pharmacokinetics of Risperidone in HIV-infected children and adolescents.**

Pharmacokinetics of risperidone have not been studied in HIV-infected adults, adolescents or children.

1.145 Sertraline

**Description**

Sertraline is a selective serotonin reuptake inhibitor commonly used to treat major depression, anxiety disorders and premenstrual dysphoric disorder, along with various off-label uses. Sertraline is FDA-approved for obsessive-compulsive disorder in children ≥ 6 years old. Sertraline is administered orally, is highly protein bound (98%), and reaches steady-state in about one week with daily dosing. It undergoes extensive first-pass metabolism by multiple CYP enzymes (2B6, 2C9, 2D6, 3A4, and 2C19). Sertraline weakly inhibits 2D6, but does not affect other enzymes. The primary metabolite, N-desmethylsertraline, is much less active than sertraline. The elimination half-life of sertraline is about 26 hours, and the elimination half-life of N-desmethylsertraline is about 60 – 100 hours. Sertraline is formulated as immediate release oral tablets or solutions.

**Pharmacokinetics of Sertraline in HIV-uninfected children and adolescents.**

Two pharmacokinetic studies of sertraline have been performed in children and adolescents [30, 31]. Average sertraline and N-desmethylsertraline concentrations were approximately 70 – 85 ng/mL and 110 – 160 ng/mL in 40 patients [31]. A more comprehensive pharmacokinetic assessment was performed in 61 children and
adolescents (51 were white, six were black, and 4 were other ethnic origins)[30]. Weight-adjusted sertraline and N-desmethylsertraline AUCs were similar between children and adolescents, and were also similar to adults using doses of 50 – 200 mg daily.

*Pharmacokinetics of Sertraline in HIV-infected children and adolescents.*

Pharmacokinetics of sertraline have not been studied in HIV-infected adults, adolescents or children.

1.146 Fluoxetine

*Description*

Fluoxetine was the first selective serotonin reuptake inhibitor marketed in the U.S. It is approved to treat depression, obsessive-compulsive disorder, bulimia nervosa, panic disorder and premenstrual dysphoric disorder. Fluoxetine is also approved for pediatric depression and obsessive-compulsive disorder. Fluoxetine is well absorbed after oral administration. It is widely distributed and about 95% bound to alpha-1 acid glycoprotein. Fluoxetine is metabolized to an equipotent active metabolite, norfluoxetine by CYP 2D6 and 2C9. Fluoxetine significantly inhibits multiple CYP enzymes (2D6, 2C19, 3A4, 2C9 and 2C10), and has the potential to alter the pharmacokinetics of many concomitant medications. Both fluoxetine and norfluoxetine have the longest half-lives of all the SSRIs, and steady-state is reached after 3 to 4 weeks of daily dosing. Half-lives are highly variable between patients. After chronic administration, fluoxetine half-life is 4 – 6 days, while norfluoxetine half-life is 8 – 10 days.

Fluoxetine is formulated as oral capsules for daily (immediate release) or weekly (gastro-resistant pellets in capsules) administration. It also comes as immediate release oral solution for daily administration and immediate release oral tablets for daily administration. The once-weekly administration is recommended in adults only.

One population pharmacokinetic study has evaluated HIV-infected adults taking nevirapine and either fluoxetine or fluvoxamine. In seven subjects taking fluoxetine, fluoxetine had no effect on nevirapine exposure, but nevirapine significantly decreased both fluoxetine and norfluoxetine concentrations [32].
Pharmacokinetics of Fluoxetine in HIV-uninfected children and adolescents.

A single population pharmacokinetic study of 11 boys and 10 girls taking 20 mg fluoxetine daily for a depressive disorder or obsessive compulsive disorder reported an oral clearance and apparent volume of distribution of 0.181 L/kg/hr and 37.4 L/kg, respectively [33]. Ten subjects were children (6 – 11 years), and 11 were adolescents (12 – 17 years). Large variability was noted in oral clearance that was not attributable to age or body size measures.

Pharmacokinetics of Fluoxetine in HIV-infected children and adolescents.

Pharmacokinetics of fluoxetine have not been studied in HIV-infected adolescents or children.

1.147 Paroxetine

Description

Paroxetine is a selective serotonin reuptake inhibitor commonly used to treat depression, anxiety disorders, premenstrual dysphoric disorder, and menopause symptoms. Along with the immediate-release tablets and oral suspension, an extended-release tablet formulation is available (although both immediate and extended-release formulations are administered once daily). A bioequivalent salt form, paroxetine mesylate, is also approved.

Paroxetine is completely absorbed after oral administration. It is widely distributed and 93 – 95% protein-bound. Paroxetine is a substrate and potent inhibitor of CYP 2D6. Within the first week or two of dosing, paroxetine saturates the 2D6 pathway, and the steady-state AUC is several fold higher than that predicted from the single-dose due to excess accumulation from this saturation. At steady-state when 2D6 is saturated, paroxetine clearance becomes governed by alternative CYP enzymes such as CYP 3A4, which does not become saturated. The elimination half-life of the immediate-release product is 21 hours, while the elimination half-life of the controlled-release product is 15 – 20 hours.
Pharmacokinetics of Paroxetine in HIV-uninfected children and adolescents.

Paroxetine has been studied in 27 children and 35 adolescents in doses of 10, 20 and 30 mg daily [34]. Oral clearance and volume of distribution were highly dependent on paroxetine dose, CYP 2D6 genotype and weight, but not age or sex. At each dose level, paroxetine systemic exposure was higher in children than in adolescents, but the differences were greatest with the lowest doses. The differences lessened with increasing doses, and disappeared when corrected for weight between the age groups.

Pharmacokinetics of Paroxetine in HIV-infected children and adolescents.

Pharmacokinetics of paroxetine have not been studied in HIV-infected adults, adolescents or children.

1.15 Potential for Antiretroviral and Psychiatric Drug Interactions

In addition to a paucity 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 psychotropics and the ARVs or the psychotropics 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%),[35, 36] while more recent studies report hydroxylation accounting for up to half of the metabolism.[17] Ritonavir has demonstrated potent inhibition of CYP 2D6 when used in high doses of 500 mg twice daily.[37] 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.[38, 39] This study found that low-dose ritonavir inhibited CYP 2D6 activity, resulting in a 26% increase in desipramine AUC.
The most commonly used psychiatric medication 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 Psychotropics

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,[40-44] and are also associated with frequent CNS-related adverse effects.[45, 46] 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.[47, 48] 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.[49] An in vitro study by Woodahl and colleagues examined the permeability of protease inhibitors across PGP-expressing cells.[50] 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.[51, 52] While many alleles for CYP 3A4 have been identified, consistent correlations with antiretroviral concentrations have not been reported.[49] 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.[53] 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 psychotropic 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.[54] 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 dextrophan 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-hydroxy-
morphinan, is dependent on CYP 3A activity.[55] 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 dextrophan 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 psychiatric medications 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 psychiatric and antiretroviral drugs will increase the risk that the systemic exposure following standard starting and titration doses of psychiatric medications 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 (applicable only to subjects enrolled under Version 1.0)

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 visit. 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 psychiatric medications are often closely related to systemic exposure of psychiatric medications. For example, drug-induced prolongation of the Q-Tc interval is associated with increasing concentrations of tricyclic antidepressants and antipsychotics.[56] 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.[57] Cardiovascular injury has been associated with HIV-1 infection itself as well as with protease inhibitor therapy.[58] 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.
Psychotropic agents being studied in this protocol have demonstrated exposure (pharmacokinetic)/response (pharmacodynamic) relationships.[14] 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.[14, 59] 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. [59] 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.[60] 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 [61]. 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% [62, 63]. 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.[64] 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 [65]. 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**

1.2.1 Rationale for Psychiatric Medication Study Arms

The psychiatric medications selected for Version 1.0 of this protocol, 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 psychiatric medications selected for Version 2 of this protocol are those identified in Site Surveys as the top agents commonly used by HIV-infected adolescents for psychiatric disorders. These include citalopram/escitalopram, risperidone, sertraline, fluoxetine, and paroxetine used for depression and other psychiatric disorders. Specifically, in the fall of 2011, the P1080 team conducted a site survey to assess how many patients ages $\geq 6$ to $< 12$ and $\geq 12$ to $< 25$ years at study sites were taking other psychiatric medications. We queried all sites for use of the following medications: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, atomoxetine, guanfacine, clonidine, risperidone, quetiapine, lamotrigine, oxcarbazepine and valproate. We also asked open-ended questions to collect any additional psychiatric medications currently being used.

For the 6 – 12 year old age group, the use of these medications was not high. In general, anywhere from 0 to 4 sites (usually 1 or 2 sites) reported having between 1 and 5 patients on each of these individual medications. In subjects from $\geq 12$ to $< 25$ years of age, several drugs were fairly commonly used. In descending order, 22 out of 28 sites reported that they had between 1 and 5 patients taking sertraline. For risperidone, 17 of 27 sites had 1 to 5 subjects taking this medication. For citalopram and escitalopram, 14 of 26 sites, had 1 to 5 patients taking citalopram and 14 of 27 sites had 1 to 5 patients taking escitalopram. For fluoxetine, 13 of 27 sites had 1 to 5 patients taking this drug. For paroxetine, 5 of 24 sites had 1 to 5 patients, and 1 site had 6 to 10 patients taking this drug. No sites reported fluvoxamine use.

Approximately 90% of sites reported that at least some of the subjects taking these various psychiatric medications were concomitantly taking a ritonavir-boosted PI-based ARV regimen. Approximately 60% reported some of the subjects concurrently taking an efavirenz-based ARV regimen.

We would like to collect information on both fluoxetine and paroxetine, as our site survey indicates that these medications are being used in our patient populations, and we have no PK data in HIV-infected youth. Because the numbers of subjects may not be high enough to enroll a full cohort for each of these drugs, we propose enrolling subjects on either drug into a fourth study arm. The anticipated sample size would remain
15 subjects per stratum, and 45 subjects total for that arm, with a maximum of 10 subjects per drug in each stratum. Because fluoxetine and paroxetine have not been studied in HIV-infected adolescents, PK data from 15 to 30 subjects on each of these medications would still be an extremely valuable contribution to the biomedical literature, even if a full 45 subjects on each drug will not be enrolled.

Lifetime prevalence rates of major depressive disorder by age 19 are estimated to be 28% [66]. SSRIs are commonly used to treat symptoms of depression and related psychiatric disorders in adolescent patients. Therefore, children and adolescents < 25 years of age who are taking these psychiatric medications will be included. Again, no pharmacokinetic data are available for the use of these agents in HIV-infected populations. Additionally, limited pharmacokinetic data are available in uninfected children and adolescents, particularly for risperidone.

1.2.2 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 be included in the antiretroviral medication regimen.

In Version 1.0 of the protocol, we staggered enrollment of HIV-infected subjects, followed by selection of appropriate age/sex/race HIV-uninfected subjects, in order to roughly match the demographic characteristics of the two groups. We found that the HIV-uninfected subjects that were submitted for potential enrollment from the study sites did, in fact, fairly closely match the demographics of the HIV-infected group (even if we had not used the selection process), so the complicated screening and staggered enrollment should not be necessary in Version 2.0 of the protocol. Instead, enrollment of both HIV-infected and HIV-uninfected adolescents will occur simultaneously.
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 ≥ 2 weeks (≥ 5 weeks for fluoxetine) prior to the pharmacokinetic study assessment. 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). For the arms in Version 2.0, fewer formulations are available, with the vast majority being immediate release oral dosage forms with similar absorption profiles. 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 corresponding 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.
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 psychiatric 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 and adolescents 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.
1.25 Summary of Protocol Version 1.0

As of January 2014, 82 of 90 subjects in Arms 1 and 2 have been enrolled. 78 subjects have completed the one-year study, and 4 subjects are still on study. Methylphenidate concentrations have been measured in 30 subjects at the first pharmacokinetic (PK) visit (Visit A), and in 24 of those subjects at the final PK visit (Visit B). The mean (range) age was 12.1 (6 – 21) years; weight was 46 (18.6 – 73.5) kg; 18 were male; 24 were Black, 5 White, and 1 mixed race. Nine were HIV-. HIV+ were on efavirenz (EFV; n=6) and ritonavir boosted protease inhibitors (RTV-PI; n=15). Demographics were similar between strata. Subjects took Concerta® (n=22), Metadate CD® (n=3), RitalinLA® or FocalinXR® (n=4), and immediate-release methylphenidate (n=2). The mean (range) daily dose was 32 (10 – 66) mg. Geometric means (coefficients of variation) of selected parameters are summarized in Table 1.

Table 1. Methylphenidate Preliminary Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Uninfected</th>
<th>Infected</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=9, Visit A</td>
<td>n=21, Visit A</td>
<td></td>
</tr>
<tr>
<td>Daily Dose at Visit A</td>
<td>23 (19%)</td>
<td>31 (14%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Average Concentration (ng/mL) Normalized to 36 mg Dose, Visit A</td>
<td>3.8 (95%)</td>
<td>2.4 (90%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Daily Dose at Visit B</td>
<td>25 (17%)</td>
<td>31 (14%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Average Concentration (ng/mL) Normalized to 36 mg Dose, Visit B</td>
<td>4.7 (27%)</td>
<td>2.9 (84%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Overall Average Concentration (ng/mL) per Subject Normalized to 36 mg Dose</td>
<td>5.3 (39%)</td>
<td>2.7 (63%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Overall dose-normalized average concentrations were also significantly different between the strata; 5.3 (39%) in HIV-, 3.0 (65%) in RTV-PI, and 2.3 (47%) ng/mL in EFV subjects (p=0.047). A repeated measures comparison of the average dose-normalized concentration only in subjects who completed both visits was not significantly different by HIV status (p=0.26); Visit A and B geometric mean (%CV) concentrations in HIV- (n=8) were 3.3 (107%) and 4.7 (27%) ng/mL; and in HIV+ (n=16) were 2.6 (84%) and 2.9 (84%) ng/mL.

Our preliminary conclusion is that HIV+ children and adolescents have lower methylphenidate exposure at a given dose than uninfected children. EFV and possibly RTV-PI can induce methylphenidate metabolism; additional study is justified to develop dosing guidance for this population who may require higher doses of methylphenidate to achieve therapeutic systemic exposures. These preliminary results were
presented at the Conference on Retroviruses and Opportunistic Infections in Atlanta, GA from March 3-7, 2013.

As of January 2014, the team has been assaying the amphetamine/dextroamphetamine samples to begin to analyze the pharmacokinetic findings of that study arm. Once the amphetamine assays are completed, the remainder of the methylphenidate samples will be assayed so the findings for both arms can be finalized and published.

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. (Applies only to subjects enrolled under Version 1.0)

3.0 STUDY DESIGN

P1080 is a pilot population pharmacokinetic study of HIV-1 infected and uninfected children and adolescents who are taking selected psychiatric medications. The study subjects in Version 2.0 will be accrued within a one year period. Subjects will be on study for up to two 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. Note: subjects enrolled under Version 1.0 will complete follow up as
per Appendix I-A; subjects enrolled under Version 2.0 will complete evaluations and follow up as per Appendix I-B.

HIV uninfected subjects will be recruited per the description in Section 4.6. All subjects enrolled in Version 2.0 will have a screening/entry visit and one PK visit. These two visits are described in Sections 3.1 and 3.2. On the basis of subjects’ HIV status and medications, in each arm, 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 Psychiatric Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</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>
</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>
</tr>
</tbody>
</table>

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

Under Version 1.0, the Study Arms were:
- Arm 1: Methylphenidate
- Arm 2: Amphetamine/Dextroamphetamine

Under Version 2.0, the Study Arms Open to Enrollment are:
- Arm 3: Citalopram or Escitalopram
- Arm 4: Risperidone
- Arm 5: Sertraline
- Arm 6: Fluoxetine or Paroxetine

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 4.15), the subject must be taking citalopram, escitalopram, risperidone, sertraline, or paroxetine for at least 2 weeks or fluoxetine for at least 5 weeks prior to enrollment to be eligible for this study.

3.2 Pharmacokinetic (PK) Visit

Approximately two days prior to the PK visit, the sites will contact subjects/caregivers to verify and reinforce 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, 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 2 weeks (at least 5 weeks for fluoxetine) prior to enrollment. Note that subjects must be 100% adherent with psychiatric and (if HIV-1 infected) with antiretroviral medications in the 48 hours prior to the PK visit.

Subjects who are prescribed one of the psychiatric medications under study will be eligible for this study. 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

The 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. Six pharmacokinetic blood samples will be collected. Sample times are pre-dose, 2, 4, 6, 12 and 24 hours post-dose.
3.22 Genotypic Assessment

An additional blood sample will be collected and processed to obtain DNA at the PK visit only from every subject who consents to genetic testing, 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. 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 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.
3.3 Replacement of Subjects

Subjects will be replaced if pharmacokinetic results from the PK visit 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 PK visit takes place.

Refer to Appendix I-B, Schedule of Evaluations for specific study requirements for subjects enrolled under version 2.0.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria for HIV-1 Infected Subjects (Version 2.0)

4.11 Children and adolescents age <25 years at entry.

4.12 Documentation of HIV-1 infection is defined as positive results from two samples collected at different time points. All samples tested must be whole blood, serum or plasma. Results abstracted from medical records can be used to satisfy this criterion.

Sample #1 may be tested by non-study public program. However, both the result and the assay date must be recorded in subject’s charts. Source documentation {patient’s medical record/chart, Ministry of Health (MOH) registers, laboratory results, etc.} must be available if requested.

Sample #2 must be performed in a CAP/CLIA-approved laboratory (for US sites).

Acceptable Tests
Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test
Sample #2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR Western Blot OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection)
- One qualitative HIV RNA PCR
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid test

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 citalopram, escitalopram, risperidone, sertraline, or paroxetine for at least 2 weeks or fluoxetine for at least 5 weeks prior to enrollment.

4.151 Allowable citalopram or escitalopram formulations include: immediate-release oral solution or tablets (Celexa®, Lexapro® or other generic.)

4.152 Allowable risperidone formulations include: immediate-release oral solution or tablets (Risperdal®, Risperdal M-Tab® or other generic).

4.153 Allowable sertraline formulations include: immediate-release oral solution or tablets (Zoloft® or other generic).

4.154 Allowable fluoxetine formulations include: immediate-release oral solution, capsules or tablets (Prozac® or other generic).

4.155 Allowable paroxetine formulations include: immediate-release oral suspension, capsules or tablets (Paxil®, Pexeva®, Brisdelle® or other generic) or controlled-release tablets (Paxil CR® or other generic).
4.156 For all study arms, any dose up to the maximum recommended 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 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 <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 born to an HIV-infected mother will be considered when two separate peripheral blood specimens are drawn on different days and both are negative for HIV DNA or HIV-1 RNA. These tests must be performed in a CLIA-certified laboratory that is approved to perform the assay for protocol testing. Specimens must be drawn at least 4 weeks apart and must be drawn when the infant is four weeks of age or older and has been off antiretroviral drugs for at least two weeks. At least one specimen should be drawn when the infant is greater than 8 weeks of age. 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 citalopram, escitalopram, risperidone, sertraline, or paroxetine for at least 2 weeks or fluoxetine for at least 5 weeks prior to enrollment.

4.231 Allowable citalopram or escitalopram formulations include: immediate-release oral solution or tablets (Celexa®, Lexapro® or other generic).

4.232 Allowable risperidone formulations include: immediate-release oral solution or tablets (Risperdal®, Risperdal M-Tab® or other generic).

4.233 Allowable sertraline formulations include: immediate-release oral solution or tablets (Zoloft® or other generic).

4.234 Allowable fluoxetine formulations include: immediate-release oral solution, capsules or tablets (Prozac® or other generic).

4.235 Allowable paroxetine formulations include: immediate-release oral suspension, capsules or tablets (Paxil®, Pexeva®, Brisdelle® or other generic) or controlled-release tablets (Paxil CR® or other generic).

4.236 For all study arms, any dose up to the maximum recommended 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.

4.25 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.

4.26 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 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; or phencyclidine.

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

4.33 Pregnancy or breastfeeding an infant.

4.34 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.

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

4.36 Known or demonstrated hypersensitivity or intolerance to Dextromethorphan.

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

4.38 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) Visit

The pharmacokinetic visit 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 PK visit 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 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 PK visit and the day of the 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
- 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:

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

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

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
- St. John’s Wort (hypericum perforatum)
- Antialcoholics: disulfiram, metronidazole
- Synthetic corticosteroid: fluticasone
- Grapefruit juice
4.56 For citalopram/escitalopram, the following drugs are disallowed:
- Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
- Neuroleptic: pimozide

4.57 For risperidone, the following drugs are disallowed:
- Carbamazepine
- Fluoxetine
- Paroxetine

4.58 For sertraline, the following drugs are disallowed:
- Disulfiram (for the oral concentrate solution)
- Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
- Neuroleptic: pimozide

4.59 For fluoxetine, the following drugs are disallowed:
- Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
- Neuroleptic: pimozide
- Thioridazine

4.510 For paroxetine, the following drugs are disallowed:
- Monoamine oxidase inhibitors: isocarboxazid, moclobemide, phenelzine, tranylcypromine, linezolid, selegiline, procarbazine, furazolidone
- Neuroleptic: pimozide
- Thioridazine

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 Support Center (RSC). 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 RSC. 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 can 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). Sites are encouraged to enroll uninfected subjects with similar demographic characteristics (race, sex, age) as the HIV-infected subjects enrolled by that site to the study.
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 2 weeks prior (at least 5 weeks for fluoxetine) to enrollment. 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 PK visit in this study.

5.11 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 psychiatric study medication orally up to the maximum recommended 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.[67]

5.12 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 psychiatric study medication orally up to the maximum recommended dose using formulations listed in 5.2.
5.2 Drug Formulation

For the methylphenidate arm (closed to enrollment in Version 2), 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® (dexamethesphenidate) Immediate-Release tablets
- Focalin® XR (dexamethesphenidate) Extended-Release capsules

For the amphetamine/dextroamphetamine arm (closed to enrollment in Version 2), the following formulations are allowed in this study:
- Adderall® (amphetamine/dextroamphetamine) Immediate-Release tablets (or generic equivalent Immediate-Release tablets)
- Adderall® XR (amphetamine/dextroamphetamine) 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

For the citalopram/escitalopram arm, the following formulations are allowed in this study:
- Citalopram Hydrobromide Oral Solution
- Celexa® (citalopram hydrobromide) Tablets (or generic equivalent tablets)
- Lexapro® (escitalopram oxalate) Solution (or generic equivalent solution)
- Lexapro® (escitalopram) Tablets (or generic equivalent tablets)

For the risperidone arm, the following formulations are allowed in this study:
- Risperdal M-Tab® (risperidone) Orally Disintegrating Tablets (or generic equivalent orally disintegrating tablets)
- Risperdal® (risperidone) Oral Solution (or generic equivalent oral solution)
- Risperdal® (risperidone) Tablets (or generic equivalent tablets)
For the sertraline arm, the following formulations are allowed in this study:
- Zoloft® (sertraline hydrochloride) Concentrate Solution (or generic equivalent concentration solution)
- Zoloft® (sertraline hydrochloride) Tablets (or generic equivalent tablets)

For the fluoxetine arm, the following formulations are allowed in this study:
- Prozac® (fluoxetine hydrochloride) Pulvule (or generic equivalent capsules administered once daily)
- Fluoxetine Hydrochloride Solution
- Prozac® or Sarafem® (fluoxetine hydrochloride) Tablets (or generic equivalent tablets)

For the paroxetine arm, the following formulations are allowed in this study:
- Paxil® (paroxetine hydrochloride) Suspension (or generic equivalent suspension)
- Paxil® (paroxetine hydrochloride) Tablets (or generic equivalent tablets)
- Paxil CR® (paroxetine hydrochloride) Controlled-Release Tablets (or generic equivalent controlled-release or extended-release tablets)
- Pexeva® (paroxetine mesylate) Tablets (or generic equivalent tablets)
- Brisdelle® (paroxetine mesylate) Capsules (or generic equivalent capsules)
5.3 **Recommended Maximum Daily Doses**

Table 3: FDA Approved (or Recommended) Maximum Daily Doses

<table>
<thead>
<tr>
<th>Drug Formulation</th>
<th>FDA-approved (or Recommended) Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylin® Ritalin® (or generic equivalent), Ritalin® SR, Metadate® ER (or generic equivalent), Ritalin® LA, Metadate® CD</td>
<td>≥6 to 12 years: 60 mg daily &gt;12 years: 60 mg daily</td>
</tr>
<tr>
<td>Concerta®</td>
<td>≥6 to 12 years: 54 mg daily 13 to 17 years: 72 mg daily (not to exceed 2 mg/kg/day) &gt;17 years: 72 mg daily</td>
</tr>
<tr>
<td>Focalin® and Focalin® XR</td>
<td>≥6 to 12 years: 20 mg daily &gt;12 years: 20 mg daily</td>
</tr>
<tr>
<td>Adderall® Dextedrine® Liquadd™ (or generic equivalent), Dextedrine Spansule CD® (or generic equivalent)</td>
<td>≥6 to 12 years: 40 mg daily &gt;12 years: 60 mg daily</td>
</tr>
<tr>
<td>Adderall® XR</td>
<td>≥6 to 12 years: 30 mg daily &gt;12 years: 30 mg daily</td>
</tr>
<tr>
<td>Celexa (or generic equivalent)</td>
<td>&gt;12 years to &lt;18 years: 40 mg daily* &gt;18 years: 40 mg daily</td>
</tr>
<tr>
<td>Lexapro (or generic equivalent)</td>
<td>&gt;12 years: 20 mg daily</td>
</tr>
<tr>
<td>Risperdal (or generic equivalent)</td>
<td>&gt;12 years to &lt;18 years: 6 mg daily &gt;18 years: 6 mg daily (bipolar); 16 mg daily (schizophrenia)</td>
</tr>
<tr>
<td>Zoloft (or generic equivalent)</td>
<td>&gt;12 years: 200 mg daily</td>
</tr>
<tr>
<td>Prozac (or generic equivalent)</td>
<td>&gt;12 years to &lt;18 years: 60 mg daily &gt;18 years: 80 mg daily</td>
</tr>
<tr>
<td>Paxil immediate release (or generic equivalent)</td>
<td>&gt;12 years to &lt;18 years: 50 mg daily** &gt;18 years: 60 mg daily</td>
</tr>
<tr>
<td>Paxil CR controlled release (or generic equivalent)</td>
<td>&gt;12 years to &lt;18 years: 50 mg daily** &gt;18 years: 75 mg daily</td>
</tr>
</tbody>
</table>

*Doses of up to 40 mg daily have been studied in adolescents off-label**Doses of up to 50 mg daily have been studied in adolescents off-label

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 selected psychiatric medications (“study drugs”). 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 RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx).

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 24 hours.

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 psychiatric 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 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 RSC (Regulatory Support Center) website at RSCSafety@tech-res.com.

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 RSC website: RSCSafety@tech-res.com. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@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 formulations of methylphenidate, amphetamine/dextroamphetamine, citalopram, escitalopram, risperidone, sertraline, fluoxetine and paroxetine 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 RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.
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. 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:

- Under Version 1.0: methylphenidate, amphetamine/dextroamphetamine
- Under Version 2.0: citalopram, escitalopram, risperidone, sertraline, fluoxetine and paroxetine

Subjects will be replaced if the 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 (t1/2), pre-dose concentration (C_pre), maximum concentration (C_max), corresponding time of maximum concentration (T_max), elimination rate constant (k_e), 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. (Applies only to subjects enrolled under Version 1.0.)

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

Under Version 1.0, planned accrual was forty-five subjects in each of two arms (Arms 1 and 2) for a total of 90 subjects. Under Version 2.0, forty-five subjects will be enrolled in each of 4 arms, for a total of 180 subjects; total planned accrual in both versions: 270 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 each arm, and secondary objectives are to estimate mean oral clearance for each psychiatric medication for HIV-1 infected versus uninfected and in each cell.
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></td>
<td></td>
<td></td>
<td></td>
<td>N=5</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>0.4 (L/h/kg)</td>
<td>30%</td>
<td>0.12</td>
<td>±0.15</td>
</tr>
<tr>
<td>Amphetamine/dextroamphetamine</td>
<td>30 (L/h)</td>
<td>30%</td>
<td>9.00</td>
<td>±11.17</td>
</tr>
<tr>
<td>Citalopram</td>
<td>15.2 (L/hr)</td>
<td>10%</td>
<td>1.5</td>
<td>±1.86</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>34.9 (L/hr)</td>
<td>41%</td>
<td>14.2</td>
<td>±17.63</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.18 (L/kg/hr)</td>
<td>50%</td>
<td>0.09</td>
<td>±0.11</td>
</tr>
<tr>
<td>Paroxetine (20 mg)</td>
<td>0.54 (L/kg/hr)</td>
<td>76%</td>
<td>0.41</td>
<td>±0.51</td>
</tr>
<tr>
<td>Risperidone + 9-OH-risperidone</td>
<td>EM*: 5 (L/h)</td>
<td>40%</td>
<td>2.00</td>
<td>±2.48</td>
</tr>
<tr>
<td></td>
<td>PM 3.2 (L/h)</td>
<td></td>
<td>1.28</td>
<td>±1.59</td>
</tr>
<tr>
<td>Sertraline</td>
<td>EM: 148 (L/h)</td>
<td>20%</td>
<td>29.60</td>
<td>±36.75</td>
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<tr>
<td></td>
<td>PM: 105 (L/h)</td>
<td></td>
<td>21.00</td>
<td>±26.07</td>
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</table>

*EM = CYP2D6 Extensive metabolizer, PM = CYP2D6 poor metabolizer

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 ratio of 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 ratio of 50% between cells if the CV in each cell was similar to published studies at ≤30%.[68] 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 Ratio of Mean Clearance With 80% Power and a Type I Error of 5% for a Range of CVs.

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

For the fourth secondary objective, which applies only to participants enrolled under Version 1.0, 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 visit. 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, which applies only to participants enrolled under Version 1.0, 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 selected psychiatric medications 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. (Applies only to participants enrolled under Version 1.0.)

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

9.21  Deferral of Pharmacokinetic (PK) Visit

The pharmacokinetic visit 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 PK visit 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 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) Visit**

Subjects, who are ineligible for the PK visit based on the following reasons, will be discontinued from study:

- Pregnancy
- 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)
- Any other exclusion criteria is met (see Section 4.3 for additional exclusion criteria)

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 visit is 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 (Vd/F), half-life (t1/2), pre-dose concentration (Cpre), maximum concentration (Cmax), corresponding time of maximum concentration (Tmax), elimination rate constant (ke), 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, which apply only to subjects enrolled under Version 1.0, 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 270 subjects across Versions 1.0 and 2.0 of the protocol. 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 [69]. A sample size of 45 pediatric subjects completing a pharmacokinetic visit should provide an accurate estimate of the population oral clearance and its variability both between and within subjects for the agents in the study arms.

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 background section, the pharmacokinetics of these psychiatric agents has not been described in HIV-1 infected youth.

In addition to modeling the typical variables described above, for subjects enrolled under Version 1.0, 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.
10.0 HUMAN SUBJECTS

10.1 Institutional Review Board and Informed Consent

This protocol, the informed consent document (Appendices III-A, III-B, III-C, and III-D), and any subsequent modifications must be reviewed and approved by the IRB responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the 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


# APPENDIX I-A - SCHEDULE OF EVALUATIONS FOR SUBJECTS ENROLLED UNDER VERSION 1.0

<table>
<thead>
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<th>Screening¹</th>
<th>Entry¹</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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<td>+ 4 weeks</td>
<td>± 2 weeks</td>
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<td>± 2 weeks</td>
<td>± 2 weeks</td>
<td>± 2 weeks</td>
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<td>37-43mL</td>
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Footnotes

1. 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.

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%; 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. 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. 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.

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 Entry 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. 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.

10. Urine toxicology screen is for disallowed drugs. These include barbiturates, benzodiazepines, opiates, and phencyclidine for all study subjects. For methylphenidate arm subjects, amphetamines are also disallowed. Though propoxyphene is not exclusionary, if it is currently part of the sites’ routine screening panel, the result should be recorded on the CRF. 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.

11. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase, albumin. 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.

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 24 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 a CLIA-certified laboratory.
17. This is for HIV-1 infected cohort only. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at a CLIA-certified laboratory. 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.
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. 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.
20. The Vanderbilt Scale Questionnaire can be administered via telephone at the Entry Visit.
# APPENDIX I-B - SCHEDULE OF EVALUATIONS FOR SUBJECTS ENROLLED UNDER VERSION 2.0

<table>
<thead>
<tr>
<th>Evaluation Type</th>
<th>Screening¹</th>
<th>Entry¹</th>
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<tbody>
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<td>+ 4 weeks</td>
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<td><strong>Clinical Evaluations</strong></td>
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</tr>
<tr>
<td>Physical exam³</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adherence Questionnaire⁵</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Instructions and planning for PK Visit</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic Visit (incl. pre-visit phone call)⁶</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Laboratory Evaluations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology⁷</td>
<td></td>
<td>1mL</td>
<td>1mL</td>
</tr>
<tr>
<td>Toxicology Screen⁸</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemistries⁹</td>
<td></td>
<td>2mL</td>
<td>2mL</td>
</tr>
<tr>
<td>Pregnancy test¹⁰</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PBMC pellets for genotypic analysis</td>
<td></td>
<td></td>
<td>0-6mL¹¹</td>
</tr>
<tr>
<td><strong>Virology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 Antibodies, HIV-1/HIV-2, EIA¹²</td>
<td></td>
<td>5mL</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA PCR¹³</td>
<td></td>
<td></td>
<td>3mL</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets¹⁴</td>
<td></td>
<td>1mL</td>
<td>1mL</td>
</tr>
<tr>
<td><strong>Pharmacology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK samples¹⁵</td>
<td></td>
<td></td>
<td>0-36mL¹¹</td>
</tr>
<tr>
<td>Dextromethorphan Dose and 4-Hour Urine Collection¹⁶</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Total Blood Volumes</strong></td>
<td></td>
<td>5mL</td>
<td>4mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49mL</td>
</tr>
</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. 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. A targeted history is sufficient at the PK visit; 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.
4. Physical exam should include height, weight, and vital signs. 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.
5. Adherence Questionnaire is to be completed by a member of the site staff in a face-to-face interview at the PK visit 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.
6. Approximately two days prior to the PK visit, 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.
7. Hematology for Entry Visit should include CBC with differential and platelet count. For HIV-1 positive subjects at the PK visit, WBC and % lymphocytes should be included if needed for dual platform flow cytometer lymphocyte subsets results. 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.
8. Urine toxicology screen is for disallowed drugs. These include methamphetamine, methadone, barbiturates, benzodiazepines, opiates, and phencyclidine, for all study subjects. Though propoxyphene is not exclusionary, if it is currently part of the sites’ routine screening panel, the result should be recorded on the CRF.
9. Chemistries should include AST, ALT, total bilirubin, BUN, electrolytes, glucose, creatinine, total amylase, albumin. 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.
10. 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 PK visit. If the screening and entry visits are completed within 72 hours, a pregnancy test does not have to be repeated at the entry visit.

11. Non-viable PBMC pellets for DNA genotypic analysis should be collected at the PK visit for all subjects who have provided consent for genetic testing.

12. 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.

13. This is for HIV-1 infected cohort only, and must be performed at a CLIA-certified laboratory.

14. This is for HIV-1 infected cohort only. Lymphocyte subsets include CD4/CD8 counts and percentages. Must be performed at a CLIA-certified laboratory. 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.

15. PK sampling time points are pre-dose, and 2, 4, 6, 12 and 24 hours post-dose. Depending on date of enrollment in relation to the PK visit, sites should contact subjects by telephone for the two days prior to the PK visit to encourage adherence. If the subject reports missing doses in the two days prior to the PK visit day, reschedule the PK visit.

16. 4-Hour urine collection for CYP 2D6 and 3A4 metabolic phenotyping; to include measurement of dextromethorphan, 3-hydroxy-morphinan and dextrorphan. 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.
### APPENDIX II

**PHARMACOKINETIC SAMPLING SCHEDULE FOR SELECTED PSYCHIATRIC MEDICATIONS / FORMULATIONS FOR SUBJECTS ENROLLED UNDER VERSION 1.0**

<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>Methyl™ (methylphenidate) Immediate-Release chewable tablets or oral solution</td>
<td>6 hours</td>
</tr>
<tr>
<td>Ritalin® (methylphenidate) Immediate-Release tablets (or generic equivalent Immediate-Release tablets)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Ritalin® SR (methylphenidate) Extended-Release tablets (or generic equivalent Sustained-Release tablets)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Metadate® ER (methylphenidate) Extended-Release tablets (or generic equivalent Sustained-Release tablets)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Ritalin® LA (methylphenidate) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Metadate® CD (methylphenidate) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td>Concerta® (methylphenidate) Extended-Release tablets</td>
<td>12 hours</td>
</tr>
<tr>
<td>Focalin® (dextmethylphenidate) Immediate-Release tablets</td>
<td>6 hours</td>
</tr>
<tr>
<td>Focalin® XR (dextmethylphenidate) Extended-Release capsules</td>
<td>12 hours</td>
</tr>
<tr>
<td><strong>AMPHETAMINE/DEXTROAMPETAMINE</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>Dexedrine® (dextroamphetamine sulfate) Immediate-Release tablets or Liquadd™ oral solution (or generic equivalent Immediate-Release tablets or oral solution)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Dexedrine Spansules® (dextroamphetamine sulfate) Extended-Release capsules (or generic equivalent Extended-Release capsules)</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

**6 Hour Sampling Schedule:** 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.

**12 Hour Sampling Schedule:** Pre-dose, and at 2, 4, 6 and 12 hours post-dose.
DAIDS SAMPLE INFORMED CONSENT for HIV-1 INFECTED CHILDREN and ADOLESCENTS WHO ENROLLED UNDER VERSION 1.0

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 2.0, Dated 22 April 2014

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

INTRODUCTION

You are/your child is being asked to re-consent 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 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 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></td>
</tr>
<tr>
<td><strong>ARM 2</strong></td>
</tr>
<tr>
<td>Amphetamine/ dextroamphetamine</td>
</tr>
<tr>
<td></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 entry 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 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, 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 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol.

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 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. The NIH does not provide direct compensation for research related injury. 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.

<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) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>Father’s Name (If father’s consent is required)</td>
<td>Father’s Signature and Date (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 WHO ENROLLED UNDER VERSION 1.0

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in
HIV-1 Infected and Uninfected Children and Adolescents
Version 2.0, Dated 22 April 2014

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

INTRODUCTION

You are/your child is being asked to re-consent 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 ADHD 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 in the past year, 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 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><strong>ARM 1</strong></td>
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<tr>
<td><strong>ARM 2</strong></td>
</tr>
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</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 entry 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 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 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, 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 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol.
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 $XXX 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. The NIH does not provide direct compensation for research related injury. 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.

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

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

DAIDS SAMPLE INFORMED CONSENT for HIV-1 INFECTED CHILDREN and ADOLESCENTS WHO ENROLL UNDER VERSION 2.0

P1080: A Pilot Study of Psychiatric and Antiretroviral Medication Concentrations in HIV-1 Infected and Uninfected Children and Adolescents
Version 2.0, Dated 22 April 2014

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 psychiatric medication (citalopram [Celexa®], escitalopram [Lexapro®], risperidone [Risperdal®], sertraline [Zoloft®], fluoxetine [Prozac® or Sarafem®] or paroxetine [Paxil®, Paxil CR®, Pexeva®, or Brisdelle®]). The main purpose of this study is to find out how these psychiatric 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 psychiatric 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 psychiatric medicines are broken down by children and adolescents who are not HIV-1 infected, and compare the results to the way the same psychiatric medicines are broken 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 psychiatric 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 psychiatric 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 may be up to three study visits described below.

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 psychiatric 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’)

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 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); the Screening and Entry visits may be on the same day.

- 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.

- 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.

**Pharmacokinetic (PK) Visit** (this visit will take about 24 hours). Within 8 weeks after your/your child’s Entry Visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visit, the staff will contact you/your child by phone to ask about missed doses and to encourage medication adherence. At this clinic visit, the following will take place:

- Approximately 2 teaspoons of blood will be drawn to check your/your child’s white blood cells (the cells that help your body fight infection), chemistry levels (tests which help us see how well your liver and kidneys are working), as well as CD4 or T-cell count and HIV viral load (amount of HIV measured in you/your child’s blood). 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. Study staff will ask you/your child some questions about medications you have/your child has taken within the three days before the visit.

- Approximately 1 teaspoon of blood will be collected at the 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 psychiatric medication.

- A total of about 3 tablespoons of blood will be collected to look at how your body breaks down both your psychiatric medications and your antiretroviral medications. This blood will be collected over 24 hours – for this testing about 1 teaspoon will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours, 6 hours, 12 hours, and 24 hours, after you/your child takes the medication. To obtain the 24 hour specimen, study staff will discuss with you whether the option of staying overnight is available or you should return the next day. These results will be made available to your healthcare provider upon request.

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

If you provide additional consent, at the pharmacokinetic visit, 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 psychiatric 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 psychiatric 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 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol.

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

You/your child will be in this study for up to eight weeks.

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 psychiatric 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 psychiatric 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 psychiatric 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 psychiatric medications.

WHAT ABOUT CONFIDENTIALITY?
Your/your child’s records will be identified only by a coded number and will be kept in a private area to maintain 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 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. The NIH does not provide direct compensation for research related injury. 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.

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

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 2.0, Dated 22 April 2014

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 psychiatric medication (citalopram[Celexa®], escitalopram [Lexapro®], risperidone [Risperdal®], sertraline [Zoloft®], fluoxetine [Prozac® or Sarafem®] or paroxetine [Paxil®, Paxil CR®, Pexeva®, or Brisdelle®]). The main purpose of this study is to find out how these psychiatric 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 to see how psychiatric 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 psychiatric 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 psychiatric medicines are processed by children and adolescents who are not HIV-1 infected, and compare the results to the way the same
psychiatric medicines are processed by HIV-1 infected children and adolescents who are also taking other medications.

Management of your/your child’s psychiatric 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 may be up to three study visits described below.

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 psychiatric 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 in the past year, about 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’)

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 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); the Screening and Entry visits may be on the same day.

- 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

- 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.

Pharmacokinetic (PK) Visit (this visit will take about 24 hours.)
Within 8 weeks after your/your child’s entry visit, you/your child will return to the clinic before taking your/your child’s usual medicine. Approximately two days prior to the PK visit, the staff will contact you/your child to encourage medication adherence. At this visit, the following will take place:

- Approximately 1 teaspoon of blood will be drawn to check your/your child’s blood count 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. 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].

- Approximately 1 teaspoon of blood will be collected at the 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 psychiatric medication.

- A total of about 3 tablespoons of blood will be collected to look at how your body breaks down your medication. This blood will be collected over 24 hours – for this testing, about 1 teaspoon will be collected just before you/your child take(s) your medication; about 1 teaspoon will be collected at 2 hours, 4 hours, 6 hours, 12 hours, and 24 hours, after you/your child takes the medication. To obtain the 24 hour specimen, study staff will discuss with you whether the option of staying overnight is available or you should return the next day. These results will be made available to your healthcare provider upon request.

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

If you provide additional consent, at the PK visit, 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 psychiatric care.

However, in case researchers learn new information that makes them believe that a certain study result is important for your/your child’s psychiatric 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 270 subjects will take part in this study, across versions 1.0 and 2.0 of the protocol.

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

You/your child will be in this study for up to eight weeks.

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 psychiatric 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 psychiatric 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 psychiatric 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 psychiatric medications.

WHAT ABOUT CONFIDENTIALITY?

Your/your child’s records will be identified only by a coded number and will be kept in a private area to maintain 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. The NIH does not provide direct compensation for research related injury. 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.

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<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
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</thead>
<tbody>
<tr>
<td>Participant’s Legal Guardian (print) (As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print) (As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
<tr>
<td>Father’s Name (If father’s consent is required)</td>
<td>Father’s Signature and Date (If father’s consent is required)</td>
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