Phase I/II, Dose-Finding Investigation of the Pharmacokinetics and Safety of Atorvastatin for Treatment of PI-Associated Increased LDL-Cholesterol in HIV-Infected Children and Adolescents

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

This file contains the current IMPAACT P1063 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #3, dated 07 November 2013
- Clarification Memorandum #2, dated 25 April 2013
- Clarification Memorandum #1, dated 27 September 2012
- Letter of Amendment #2, dated 04 April 2012
- Letter of Amendment #1, dated 17 October 2011
- Protocol Version 2.0, dated 28 May 2010
This is Clarification Memo #3 for IMPAACT P1063 “Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol in HIV-infected Children, Adolescents, and Young Adults” Version 2.0, dated, May 28, 2010.

This Clarification Memo can be obtained from the P1063 Protocol Specific Web Page (http://www.impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1063] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to clarify the following:

**Lipitor® brand atorvastatin 10 mg and 20 mg tablets are no longer available from the Clinical Research Products Management Center (CRPMC). Generic atorvastatin 10mg tablets (but not 20 mg tablets) manufactured by Apotex are available from the CRPMC for P1063.**

Please contact the Protocol Team at actg.teamp1063@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1063.
This is Clarification Memo #2 for IMPAACT P1063 “Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol in HIV-infected Children, Adolescents, and Young Adults” Version 2.0, dated, May 28, 2010.

This Clarification Memo can be obtained from the P1063 Protocol Specific Web Page (http://www.impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1063] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to clarify the following:

The protocol language in Sections 4.21 and 6.11 require revision to clarify the management of elevated total bilirubin levels in subjects taking atazanavir.

The protocol text in section 4.21 and 6.11 has been revised as follows:

4.21 Screening LFTs ≥ Grade 1. **Entry of subjects with ≤ Grade 3 total bilirubin will be permissible if the subject is taking atazanavir and the direct bilirubin*, ALT and AST are < Grade 1.**

6.11

**Grade 2 toxicity**

- Continue atorvastatin
- Monitor closely and repeat abnormal test within 14 days (grade 2 total bilirubin does not need to be repeated if the subject is on atazanavir and the direct bilirubin*, ALT and AST are < Grade 1)
- Work-up to exclude other causes.

*Grade 1 direct bilirubin is 1.1 – 1.5 x ULN

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1063@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1063.
DATE: 27 September 2012
RE: CLARIFICATION MEMO #1 for P1063
TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in P1063
FROM: P1063 Protocol Team

This is Clarification Memo #1 for IMPAACT P1063 “Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol in HIV-infected Children, Adolescents, and Young Adults” Version 2.0, dated, May 28, 2010.

This Clarification Memo can be obtained from the P1063 Protocol Specific Web Page (http://www.impaactgroup.org/). Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1063] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

The purpose of this memo is to clarify the following:

1. Throughout the P1063 protocol LDL-C is used generically for LDL cholesterol and does not distinguish between direct and calculated LDL. Direct and calculated LDL cholesterol refers to different assay methods. The direct method, LDL-C, is performed in the central laboratory and is the result that should be used for decisions regarding final eligibility (screening central LDL-C) and for dose escalation (week 4 central LDL-C).

2. A subject meets the criterion for dose escalation at week 8 if the week 4 direct LDL-C is > 110 mg/dL AND there is <30% decline from baseline to week 4. Note that Section 5.11, pg 35, “Dose Escalation Visit (Dose level 2)” was inaccurately written with OR used in the statement rather than AND.

3. As outlined in footnote 1 of Appendix 1B, Hepatitis C RNA PCR is only required to determine eligibility for potential patients who are HepC antibody positive. For U.S. sites, HepC RNA PCR must be performed in a CLIA certified lab. Non-U.S. sites do not have access to CLIA-certified labs in which to run the HepC RNA PCR, so participants who are HepC antibody positive at these sites would need to be excluded.

4. Sites should report total bilirubin with the other chemistries specified in Appendix IA-C, as both direct and indirect bilirubin are required chemistries.

This clarification will be included in the next version of the protocol when it is amended. Please contact the Protocol Team at actg.teamp1063@fstrf.org with any questions about this correspondence.

Thank you for your participation in IMPAACT P1063.
To: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1063

From: IMPAACT P1063 Protocol Team

Date: April 4, 2012


IND-Exempt Protocol, DAIDS ES #: 10167

THE FOLLOWING INFORMATION IMPACTS THE P1063 STUDY AND MUST BE forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their review. This letter of amendment must be approved by your IRB/EC before implementation.

THE FOLLOWING INFORMATION MAY IMPACT THE SAMPLE INFORMED CONSENT. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Upon receiving final IRB/EC and any other applicable regulatory entity (RE) approval(s) for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site’s regulatory files.

This Letter of Amendment can be obtained from the P1063 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1063] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Version 2.0, Dated May 28, 2010.

This Letter of Amendment is being issued to alert participating site IRBs and study participants about the U.S. Food and Drug Administration (FDA)- issued drug safety communication of March 1, 2012 [http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm]. The FDA has issued updated recommendations concerning drug-drug interactions between drugs for human
immunodeficiency virus (HIV) or hepatitis C virus (HCV) known as protease inhibitors and certain cholesterol-lowering drugs known as statins. Protease inhibitors and statins taken together may increase the risk for muscle injury (myopathy) and its most serious form rhabdomyolysis. The updated FDA safety communication also specifically recommends avoiding concomitant atorvastatin and the fibrate gemfibrozil, due to an increased risk of myopathy/rhabdomyolysis.

The P1063 Protocol Team would like to emphasize that the current study design already limits atorvastatin daily dosage to within the new limits recommended by the FDA.

1. The following has been added to Section 1.5 (Atorvastatin Pharmacokinetics), Subsection 1.53 (Interactions with protease inhibitors):

Due to the interactions between atorvastatin and protease inhibitors, the atorvastatin package insert recommends the following dosing for atorvastatin when administered concurrently with protease inhibitors.

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Atorvastatin dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Use with caution and lowest dose necessary</td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>Do not exceed 20mg daily</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Do not exceed 40mg daily</td>
</tr>
<tr>
<td>Tipranavir/ritonavir</td>
<td>Avoid atorvastatin</td>
</tr>
</tbody>
</table>

2. The following have been added to the list of Disallowed Medications (Section 4.3)
   a. Tipranavir/
   b. Gemfibrozil

3. As generic atorvastatin is now available, “Lipitor®” has been changed to “atorvastatin” throughout the protocol and sample informed consent document.

4. Section 5.2 has been changed to remove the reference to “white, elliptical, non-scored tablets”

This information will be incorporated into the next protocol version when a new version is issued. Please contact the P1063 Protocol Team (actg.teamp1063@fstrf.org) with any questions concerning this correspondence.

Thank you for your interest in P1063.
To: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1063

From: IMPAACT P1063 Protocol Team

Date: October 17, 2011

Re: Letter of Amendment #1 for IMPAACT P1063, Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol In HIV-Infected Children, Adolescents and Young Adults, Version 2.0 dated 5/28/2010.

DAIDS ES #: 10167

THE FOLLOWING INFORMATION IMPACTS THE P1063 STUDY AND MUST BE forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their review. This letter of amendment must be approved by your IRB/EC before implementation.

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

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

The following exclusion criterion has been REMOVED:

4.28: Pharmacologic treatment for depression or other mental health disorder excluding Attention Deficit Disorder within thirty days of study entry.

This exclusion criterion was initially included due to the requirement that the subjects also be treated with protease inhibitors and the concern for potential drug interactions. Firstly, the requirement that the participants also be treated with protease inhibitors was removed in Version 2.0 and secondly, if a potential participant was on a medication for a mental health disorder which is contraindicated with protease inhibitors or atorvastatin, this is already captured under exclusion criteria 4.214.
This Letter of Amendment may be obtained from the P1063 Protocol Specific Webpage of the IMPAACT Website (http://www.impaactgroup.org).

Please contact the P1063 Protocol Team (actg.teamp1063@fstrf.org) with any questions concerning this correspondence. This information will be incorporated into the next protocol version when a new version is issued.

Thank you for your interest in P1063.
IMPAACT P1063

PHASE I/II SAFETY AND EFFICACY INVESTIGATION OF ATORVASTATIN FOR TREATMENT OF INCREASED LDL CHOLESTEROL IN HIV-INFECTED CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

A Multicenter Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group

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)

Pharmaceutical Support Provided by: Pfizer Inc.

IND-Exempted Protocol

The IMPAACT Complications Scientific Committee:
Sharon Nachman, M.D., Chair

Protocol Chair: Ann Melvin, M.D.

Protocol Co-Chair: Marilyn Crain, M.D., M.P.H.

NIAID Medical Officer: Paul Sato, M.D., M.P.H.

NICHD Medical Officer: George Siberry, M.D., M.P.H.

Protocol Manager: Elizabeth Hawkins

Version 2.0
FINAL
May 28, 2010
All questions concerning this protocol should be sent via e-mail to actg.teamp1063@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.teamp1063@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 material can be sent electronically to epr@tech-res.com or by fax at 1-800-418-3544 or 301-897-1701. For EAE questions, e-mail rccsafetyoffice@tech-res.com or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710. To order study drug, call the Clinical Research Products Management Center at 301-294-0741. For randomization or enrollment questions, contact the Data Management Center at 716-834-0900 or by e-mail at sdac.random.desk@fstrf.org.

Protocol Chair
Ann Melvin, M.D.
Assistant Professor Pediatrics
Division of Infectious Diseases
Children’s Hosp and Reg Med Center
Mailstop 8G-1
4800 Sand Point Way, N. E.
Seattle, WA 98105-0371
Phone: 206-987-2535
Fax: 206-987-3890
e-mail: ann.melvin@seattlechildrens.org

NIAID Medical Officer
Paul A Sato, M.D., M.P.H.
Medical Officer
International Maternal Adolescent and Pediatric Branch
Therapeutics Research Program
NIAID Division of AIDS
6700B Rockledge Dr, room 5218
MSC 7624
Bethesda, MD 20892-7624
Phone: 301-435-3750
Fax: 301-435-9282
email: satop@niaid.nih.gov

Protocol Co-Chair
Marilyn Crain, M.D., M.P.H.
University of Alabama at Birmingham
Pediatric Infectious Diesese
1600 7th Avenue South
CHB 304
Birmingham, AL 35233
Phone: 205-996-7780
Fax: 205-975-6549
e-mail: mcrain@peds.uab.edu

NICHD Medical Officer
George Siberry, M.D., M.P.H.
Pediatric, Adolescent, and Maternal AIDS Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, DHHS
6100 Executive Boulevard, Room 4B11H
MSC 7510
Bethesda, MD 20892-7510
Phone: 301-496-7350
Fax: 301-496-8678
e-mail: siberryg@mail.nih.gov
IMPAACT P1063 PROTOCOL TEAM ROSTER (Cont.)

Protocol Virologist
William A. Meyer III, Ph.D.
Technical Director
Quest Diagnostics Incorporated
1901 Sulphur Spring Rd.
Baltimore, MD 21227-0580
Phone: 410-536-1593
Fax: 410-536-1639
e-mail: William.A.Meyer@questdiagnostics.com

Protocol Manager
Elizabeth Hawkins
IMPAACT Operations Office
8757 Georgia Avenue
Silver Spring, MD 20910
Phone: 301-628-3335
Fax: 301-628-3304
e-mail: ehawkins@s-3.com

Protocol Manager
Ashley Buchanan, M.S.
Statistical & Data Analysis Center
Harvard School of Public Health
FXB Building, Fifth floor, Room 604A
651 Huntington Avenue
Boston, MA 02115
Phone: 617-432-1075
Fax: 617-432-2843
e-mail: buchanan@sdac.harvard.edu

Protocol Pharmacologist
Brookie M. Best, Pharm.D., M.A.S.
University of California, San Diego
900 Gilman Drive, MC 0719
San Diego, CA 92093-0719
Phone: 858-822-5550
Fax: 858-246-0007
e-mail: brookie@ucsd.edu

Protocol Pharmacologist
Grace Montepiedra, Ph.D.
Harvard School of Public Health
Statistical and Data Analysis Center
651 Huntington Avenue
Boston, MA 02115
Phone: 617-432-1141
Fax: 617-432-3163
e-mail: gmontepie@sdac.harvard.edu

Protocol Data Manager
Bobbie Graham, B.S.
Data Manager
Frontier Science & Technology Research Foundation
4033 Maple Road
Buffalo, NY 14228-1056
Phone: 716-834-0900 x7265
Fax: 716-834-8675
e-mail: graham.bobbie@fstrf.org

Protocol Data Manager
Bobbie Graham, B.S.
Data Manager
Frontier Science & Technology Research Foundation
4033 Maple Road
Buffalo, NY 14228-1056
Phone: 716-834-0900 x7265
Fax: 716-834-8675
e-mail: graham.bobbie@fstrf.org
IMPAACT P1063 PROTOCOL TEAM ROSTER (Cont.)

Investigator
Nehali Patel, M.D..
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mailstop 600
Memphis, TN 38105
Phone: 901-595-4646
Fax: 901-595-5067
e-mail: nehali.patel@stjude.org

Laboratory Technologist
Patricia Anthony, B.S., C.L.S.
University of Southern California
Maternal Child Adolescent Virology Research Lab
1801 Marengo Street
Los Angeles, CA 90033
Phone: 323-226-4161
Fax: 323-226-4168
e-mail: paanthony@usc.edu

Investigator
Myron Levin, M.D.
U of Colorado Health Sciences Center
Dept. of Pediatric Infectious Disease
Campus Box C227
4200 East Ninth Avenue
Denver, CO 80220-3706
Phone: 303-315-4620
Fax: 303-315-7909
e-mail: myron.levin@uchsc.edu

Laboratory Data Coordinator
James Tutko, B.S.
Frontier Science and Technology Research Foundation
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 ext: 7382
Fax: 716-833-0655
e-mail: tutko@fstrf.org

Investigator
Peggy R. Borum, Ph.D.
University of Florida
Food Science and Human Nutrition
409 FSHN, PO 110370
Gainesville, FL 32611
Phone: 352-392 7553
Fax: 352-392 8957
e-mail: prb@ufl.edu

Westat Clinical Research Associate
Scott Watson, R.N., B.S.
Westat, Inc.
1441 W. Montgomery Ave.
Rockville, Maryland 20850
Phone: 415-494-5575
Fax: 415-859-9029
e-mail: scottwatson@westat.com

Protocol Pharmacist
Katherine Shin, Pharm.D.
Pharmaceutical Affairs Branch
Division of AIDS, NIAID, NIH
6700-B Rockledge Drive, MSC 7620
Bethesda, MD 20892-7620
Phone: 301-594-1517
Fax : 301-402-1506
e-mail: kashin@niaid.nih.gov

Field Representative
Eric Cagwin, R.N.
Chicago Children’s Memorial Hospital
2300 Children’s Plaza
Chicago, IL 60614-3394
Phone: 773-880-4757
Fax: 773-880-3208
e-mail: ecagwin@childrensmemorial.org
# TABLE OF CONTENTS

SUMMARY OF CHANGES ............................................................................................................ 7

GLOSSARY ................................................................................................................................... 10

SCHEMA ........................................................................................................................................ 12
  1.1 Background ........................................................................................................................ 14
  1.2 Rationale for Drug Therapy for Hyperlipidemia .............................................................. 15
  1.3 Rationale for use of atorvastatin ....................................................................................... 18
  1.4 Safety and Efficacy of Atorvastatin .................................................................................. 19
  1.5 Atorvastatin Pharmacokinetics ......................................................................................... 23
  1.6 Rationale for measuring markers of inflammation ........................................................... 27
  1.7 Rationale for Urine 6β-hydroxycortisol/cortisol ratio ...................................................... 27

2.0 STUDY OBJECTIVES ......................................................................................................... 28
  2.1 Primary Objective .............................................................................................................. 28
  2.2 Secondary Objectives ........................................................................................................ 28

3.0 STUDY DESIGN .................................................................................................................. 29

4.0 SELECTION AND ENROLLMENT OF SUBJECTS ......................................................... 29
  4.1 Inclusion Criteria ............................................................................................................... 29
  4.2 Exclusion Criteria .............................................................................................................. 31
  4.3 Disallowed Medications .................................................................................................... 33
  4.4 Enrollment Procedures ...................................................................................................... 34
  4.5 Co-Enrollment Guidelines ................................................................................................. 34

5.0 STUDY TREATMENT ........................................................................................................ 35
  5.1 Drug Regimens, Administration and Duration .................................................................. 35
  5.2 Drug Formulation and Storage .......................................................................................... 36
  5.3 Drug Supply, Distribution, and Pharmacy ........................................................................ 36

6.0 SUBJECT MANAGEMENT ................................................................................................ 37
  6.1 Toxicity Management ........................................................................................................ 37
  6.2 Study Management Plan ................................................................................................... 42
  6.3 Criteria for Study Discontinuation ..................................................................................... 43
  6.4 Criteria for Study Drug Discontinuation .......................................................................... 44

7.0 EXPEDITED ADVERSE EVENT REPORTING ................................................................. 44
  7.1 Adverse Event Reporting to DAIDS ............................................................................... 44
  7.2 Reporting Requirements for this Study .......................................................................... 44
7.3 Grading Severity of Events ................................................................. 45
7.4 Expedited AE Reporting Period .......................................................... 45

8.0 STATISTICAL CONSIDERATIONS ........................................ 46
  8.1 General Design Issues ................................................................. 46
  8.2 Outcome Measures ................................................................. 46
  8.3 Randomization And Stratification ............................................... 46
  8.4 Sample Size And Accrual .......................................................... 47
  8.5 Dose Escalation Strategy ............................................................ 47
  8.6 Interim Analyses ....................................................................... 47
  8.7 Monitoring ............................................................................... 49
  8.8 Analysis ................................................................................. 51

9.0 CLINICAL PHARMACOLOGY PLAN ......................................... 53
  9.1 Pharmacology Objectives .......................................................... 53
  9.2 Primary and Secondary Data to be Accessioned ......................... 54
  9.3 Study Design, Modeling and Data Analysis ................................. 54
  9.4 Anticipated Outcomes ............................................................... 56

10.0 HUMAN SUBJECTS ................................................................. 56
  10.1 Institutional Review Board (IRB) Review and Informed Consent .. 56
  10.2 Subject Confidentiality .............................................................. 56
  10.3 Study Discontinuation .............................................................. 57

11.0 PUBLICATION OF RESEARCH FINDINGS ................................. 57

12.0 BIOHAZARD CONTAINMENT .................................................. 57

13.0 REFERENCES ........................................................................... 58

APPENDICES:
  I. SCHEDULE OF EVALUATIONS
     IA. ON STUDY VISITS FOR 10MG PER DAY DOSE
     IB. ON STUDY VISITS FOR 20MG PER DAY DOSE
     IC. SCHEDULE OF EVALUATIONS: Subjects who discontinue study provided atorvastatin due to drug related toxicity or pregnancy
  II. INSTRUCTIONS FOR THE PROCESSING, STORAGE, AND SHIPPING OF SERUM SPECIMENS FOR REAL TIME FASTING LIPID AND FUTURE INFLAMMATORY MARKER/SECONDARY LIPID MARKER TESTING
  III. SITE RESOURCES FOR NUTRITIONAL COUNSELING
IV. SAMPLE INFORMED CONSENT

V. INFORMATION SHEET – NICHD SITES ONLY

VI. FACT SHEET AND TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (Parent Fact Sheet)

VII. FACT SHEET AND TEMPLATE CONSENT FORM for Specimen Storage at Repositories funded by the National Institute of Child Health and Human Development (Youth Fact Sheet)
SUMMARY OF CHANGES

P1063, Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol in HIV-infected Children, Adolescents, and Young Adults

All changes in this version appear in boldface type. Major changes are listed below. Editorial changes, including corrections of typographical errors and other changes required to update information not affecting regulatory issues or the Sample Informed Consent may also be included. Information from Clarification Memo #1 (October 23, 2009), Letter of Amendment #1 (August 12, 2008), Letter of Amendment #2 (May 19, 2009), and Letter of Amendment #3 (June 24, 2009) are included.

1. The title of the protocol has been changed to delete “PI-Associated and add “Young Adults.”
2. The team roster has been updated.
3. The major changes include: increasing the upper age limit from <19 to <24 years; removing the requirement that subjects be on PI-containing ART; and lowering the restriction for required LDL-cholesterol level at entry to 130mg/dl without the need for additional risk factors. These changes appear throughout the protocol, when appropriate in the Schema, and Sections 3.0, 4.1, 6.2, 8.0 and 9.0.
4. A Glossary has been added.
5. Schema and Section 8.3: Added: Enrollment of subjects between the ages of ≥18 - < 24 years of age will be limited to 10.
6. Section 1.0 (background and rationale) have been updated with additional information and references to justify removing the restriction that subjects be on PI-containing ART regimens and for lowering the required LDL-cholesterol level.
7. Section 3.0: First paragraph revised to describe enrollment stratums.
8. Section 3.0: Second paragraph added to explain registration to steps.
9. Section 4.11: Revised per IMPAACT Laboratory Committee standard definition.
10. Section 4.113: Revised: Negative pregnancy test at screening.
11. Section 4.21: Allowable total bilirubin was changed from ≤Grade 2 to ≤Grade 3.
12. Section 4.26: Added: Stable static encephalopathy is not an exclusion.
13. Section 4.27: Added: of study entry.
16. Section 4.215: Added: Any laboratory or unresolved clinical toxicity ≥Grade 3 unless prior approval obtained from the protocol team.
18. Section 5.1: Added: In addition to receiving a new prescription, the site pharmacist must receive a new Study Identification (SID) number when re-registering subjects to Step II and Step III.
19. Section 6.11: Revised to account for potential of elevated bilirubin for subjects on atazanavir.
20. Section 6.1: The RCC website hyperlink is updated to: http://rcc.tech-res.com/safetyandpharmacovigilance/.
21. Section 7.0: Expedited adverse event reporting procedures have been updated.
22. Section 9.3: Corrected to read: All subjects will have 3mLs of blood obtained at weeks 4, 12, 24 and 48.
23. Section 10.0: Appendix V changed to Appendix IV and information on confidentiality of pregnancy testing added.
24. Section 13.0: The references have been updated.
25. Appendices IA and IB: Study visit windows have been added.
26. Appendices IA, IB and IC: Revised to correct footnotes and clarify procedures.
27. Appendix IV (3-Day Diet History) has been deleted. Note: The deletion of this appendix shifted the numbering of the subsequent appendices, which is adjusted accordingly.
28. Appendix IV (Sample Informed Consent)
   WHAT DO I /DOES MY CHILD HAVE TO DO IF I AM/MY CHILD IS IN THIS STUDY? (Screening)
   • To indicate that a pregnancy test will be done at screening, the 2nd paragraph has been revised to read: A pregnancy test will be done. A small amount of urine or blood (less than 1 teaspoon) will be taken for this test. You/your child will be told the test result as soon as it is available. If you are/your child is pregnant, you/your child cannot be in this study.
   • Assurance of confidentiality of pregnancy testing has been added.
   • To account for additional blood draw at screening, the 3rd paragraph has been revised to read: You/your child will have about 1 ½ teaspoons of blood taken to check the amount of LDL cholesterol (a type of fat) in the blood, to check how well your/your child’s immune system is working, to check the amount of HIV in your/your child’s blood, and for other routine tests. You/your child should not eat for 8 hours before these tests. You/your child should drink water and continue taking anti-HIV medications during the 8 hour fasting period. You will be informed of results of routine blood tests and screening evaluations. If you agree to it, a little more than ½ tablespoon of blood will be drawn and stored for future IMPAACT approved, HIV-related research.
   WHAT DO I/DOES MY CHILD HAVE TO DO IF I AM/MY CHILD IS IN THIS STUDY? (During Study)
   • Because the 3-day diet history will not be done, “keeping a diet log” has been deleted from the 1st paragraph.
   WHAT ARE THE RISKS OF THE STUDY?
   • The risks for the use of combination antiretroviral drugs and protease inhibitors have been deleted.
   ARE THERE RISKS RELATED TO PREGNANCY
• To clarify effective birth control if on protease inhibitors, the 3rd paragraph has been revised to read: Lipitor can increase the blood levels of some oral birth control pills by 20-30%. On the other hand, protease inhibitors can make hormonal birth control pills less effective. If you are taking a protease inhibitor, hormonal birth control alone would not be considered adequate.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT

• Revised last sentence: Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

29. Appendix V (Information Sheet for NICHD Sites Only) has been added.
30. Appendix VI (FACT SHEET AND TEMPLATE CONSENT FORM for Specimen Storage at Repositories Funded by the National Institute of Child Health and Human Development (Parent Fact Sheet) has been added.
## Glossary

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>CARRA</td>
<td>Childhood Arthritis and Rheumatology Research Alliance</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CIMT</td>
<td>Carotid intima media thickness</td>
</tr>
<tr>
<td>CK</td>
<td>Creatinine kinase</td>
</tr>
<tr>
<td>CLIA</td>
<td>Clinical Laboratory Improvement Amendments Act</td>
</tr>
<tr>
<td>C_MIN</td>
<td>Plasma concentration at end of dosing interval</td>
</tr>
<tr>
<td>CR</td>
<td>Creatinine</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CRPMC</td>
<td>Clinical Research Products Management Center</td>
</tr>
<tr>
<td>CTU</td>
<td>Clinical trials unit</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DAERS</td>
<td>DAIDS Adverse Event Reporting System</td>
</tr>
<tr>
<td>DAIDS</td>
<td>Division of AIDS, NIAID</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>EAE</td>
<td>Expedited Adverse Event</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-Linked ImmunoSorbent Assay</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High-density lipoprotein-cholesterol</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMG CoA</td>
<td>Hepatic hydroxymethyl glutaryl coenzyme A</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IMPAACT</td>
<td>International Maternal Pediatric Adolescent AIDS Clinical Trials Group</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein-cholesterol</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function test</td>
</tr>
</tbody>
</table>
LPV/r  Lopinavir/ritonavir
NFV  Nelfinavir
NCEP  National Cholesterol Education Program
NIAID  National Institute of Allergy and Infectious Diseases
NICHD  Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH  National Institutes of Health
NNRTI  Non-nucleoside reverse transcriptase inhibitor
NRTI  Nucleoside reverse transcriptase inhibitor
OHRP  Office for Human Research Protections
PI  Protease inhibitor
PK  Pharmacokinetic(s)
RCC  Regulatory Compliance Center
RNA  Ribonucleic Acid
RTV/SQV  Ritonavir/saquinavir
SAE  Serious Adverse Event
SDMC  Statistical and Data Management Center
SDAC  Statistical Data Analysis Center
SEM  Standard error of the estimated mean percent change
SID  Study Identification Number
SMC  Study Monitoring Committee
SOC  Scientific Oversight Committee
SREBP  Sterol regulatory element binding protein
TC  Total cholesterol
ULN  Upper limit of normal
**SCHEMA**

**PHASE I/II SAFETY AND EFFICACY INVESTIGATION OF ATORVASTATIN FOR TREATMENT OF INCREASED LDL CHOLESTEROL IN HIV-INFECTED CHILDREN, ADOLESCENTS, AND YOUNG ADULTS.**

**DESIGN:** Phase I/II safety and efficacy study of atorvastatin in patients on stable antiretroviral regimens.

**SAMPLE SIZE:** 40 subjects ages ≥ 10 to < 24 years of age.

**POPULATION:** HIV-infected subjects ages ≥ 10 to < 24 years of age stable on an antiretroviral regimen for at least six months with fasting LDL-C ≥ 130 mg/dL (calculated or directly measured) at least twice over the previous six months.

**STRATIFICATION:** Subjects will be stratified by age. Target accrual will be 20 subjects for each of the following strata: (a) ≥ 10 - <15 years old and (b) ≥ 15 - < 24 years old. If the first six subjects pass an initial safety review, the remaining subjects will be enrolled so as to achieve the target accrual for each of the two age groups above. The first six subjects will be enrolled from the ≥ 15 - < 24 year old strata. Enrollment of subjects between the ages of ≥ 18 - < 24 years of age will be limited to 10.

**REGIMEN:** Atorvastatin (Lipitor®), added to existing stable antiretroviral therapy. Each subject will be followed independently according to a dose escalation algorithm for atorvastatin. Atorvastatin dosing will begin at 10 mg per day and if efficacy criteria are not met, will increase to a maximum dose of 20 mg per day. An initial safety review will be conducted after six subjects have completed 8 weeks of therapy.

**TREATMENT DURATION:** Maximum 48 weeks.

**OBJECTIVES:**

**Primary:**

1. To evaluate the safety and efficacy (based on direct LDL-cholesterol levels) of escalating doses of atorvastatin in HIV-1-infected subjects treated with stable antiretroviral therapy.
SCHEMA (cont.)

Secondary:

1. To evaluate changes from baseline in fasting total cholesterol, triglycerides, HDL-cholesterol, Apolipoprotein A1 and B, and lipoprotein (a) after initiation of atorvastatin.
2. To evaluate changes from baseline in inflammatory-associated cardiac risk markers (e.g. high-sensitivity CRP) after initiation of atorvastatin.
3. To describe the pharmacokinetics of atorvastatin when administered concurrently with protease inhibitors.
4. To evaluate changes from baseline in plasma HIV-1 RNA levels after initiation of atorvastatin.
1.0 INTRODUCTION

1.1 Background

Hypercholesterolemia in HIV-infected children on HAART

Treatment of HIV-1 infection with combination regimens including protease inhibitors (PI) frequently results in the suppression of HIV-1 plasma RNA to below the level of detection, significant immune reconstitution, and delayed disease progression (1;2). However, when patients remain on these regimens for long periods, several potentially significant side effects commonly occur. Treatment with combination antiretroviral therapy, particularly PIs, has been associated with significant increases in cholesterol and triglycerides in HIV-1-infected adults and children (3-5). Data from two cross-sectional cohort studies of HIV-infected children treated with PIs have demonstrated fasting cholesterol levels above the 95th percentile for age in 47-65% of treated children (3;6), with the primary elevation occurring in the LDL-C fraction.

A somewhat lower prevalence of hypercholesterolemia was found in the IMPAACT 219C cohort (7). Among 1812 HIV-infected participants in 219C between 4 and 19 years of age at first cholesterol measurement date, 229 children had total cholesterol (TC) > 95th percentile (prevalence 12.8 %, 95% CI 11.1-14.3). The prevalence was higher, 16%, in those taking a PI when tested. In a multivariate logistic regression model with hypercholesterolemia status as the categorical dependent variable, the following independent variables were highly statistically significant (all p < 0.004): present PI usage; report of no missed doses in the past 3 days; younger age; and white/hispanic ethnicity. Current PI usage increased the risk of TC > 95th percentile by 5.3-fold. Prevalence of hypercholesterolemia was somewhat more common among those prescribed ritonavir (23%, 95% C.I. 18-29%) or ritonavir with 1-2 additional PIs (21%, 95% C.I. 16-26%), but not uncommon among those prescribed nelfinavir (15%, 95% C.I. 12-18%). Duration of PI use was not associated with increased risk. NRTI use was not independently associated with hypercholesterolemia.

The finding of increased risk for hypercholesterolemia among younger children with optimal virologic suppression, and the strong association between elevated total and LDL-C and the development of atherosclerosis and cardiovascular disease (8;9), underscore the need to evaluate potential interventions to address hypercholesterolemia. Although for the majority, the cholesterol levels were not significantly above the 95th percentile for age and the likelihood of significant short-term risk is low, as many of these children are treated with combination antiretroviral regimens from a young age, the development of persistent lipid abnormalities could place them at risk for premature cardiovascular disease. There
is reason to believe that hyperlipidemia may be more problematic in HIV-infected children than in otherwise healthy children (10). Hypercholesterolemia is known to lead to atherogenesis, which in turn has been found to cause endovascular inflammation (11). There is growing evidence that chronic inflammation plays a role in the development of cardiovascular disease (12) and there is increased risk of death from coronary artery disease in several chronic illnesses such as rheumatoid arthritis and systemic lupus erythematosus (13).

The mechanism by which the PIs cause hyperlipidemia is not clearly understood. Identification of a homologous sequence between the HIV-1 protease and two proteins involved in lipid metabolism led to the suggestion that partial inhibition of the low density lipoprotein-receptor-related protein and the cytoplasmic retinoic-acid binding protein type 1 by the PIs could lead to alterations in serum lipid concentrations (5). Alternatively, there could be direct mitochondrial effects disrupting the normal cholesterol metabolism. Recent work by Riddle et al demonstrated increased fatty acid and cholesterol biosynthesis in the liver and adipose tissue of ritonavir-treated mice (14). The abnormalities, which were more prominent in mice fed a high-fat diet, were the result of ritonavir-induced accumulation of the activated forms of sterol regulatory element binding protein (SREBP)-1 and –2 in the nucleus of liver and adipose cells. Induction of activated SREBP-1 and –2 increased the expression of genes responsible for lipid biosynthesis in adipocytes and hepatocytes. Interestingly, cholesterol levels were significantly lower in the ritonavir-treated mice fed a low-fat, low-cholesterol diet than in those fed a Western type high fat diet (14).

There are currently no validated recommendations for treatment of HAART-associated hyperlipidemia in HIV-infected children. Options include modifying the HAART regimen to include agents which are less likely to lead to hyperlipidemia; dietary modification; or treatment with lipid-lowering medications. Although switching to an NNRTI-based regimen from one including a PI has been shown to be safe without leading to viral rebound in some studies (15), for many children this is not a viable option because of the presence of viral resistance mutations (16).

1.2 Rationale for Drug Therapy for Hyperlipidemia

Review of the 219C database documents indicates that there are HIV-infected children who are being treated with lipid-lowering agents. The currently available agents for the treatment of hyperlipidemia include cholesterol binding agents, niacin and HMG-CoA reductase inhibitors. As treatment with cholesterol binding agents and niacin can result in significant, unpleasant side effects, the HMG-CoA reductase inhibitors, or statins, are the drugs of choice in the general population
and in children (AHA and AAP guidelines) for the therapy of hyperlipidemia unresponsive to diet therapy.

HMG-CoA reductase inhibitors reduce cholesterol biosynthesis through their competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis. Through their effect on HMG-CoA reductase activity, HMG-CoA reductase inhibitors such as atorvastatin reduce cholesterol synthesis in the liver. They also increase the number of hepatic LDL cell-surface receptors and enhance uptake and catabolism of LDL. In most studies, in both adults and children, treatment with HMG-CoA reductase inhibitors reduces total and LDL-C by 20-60%.

Hyperlipidemia may become an even more significant problem for HAART-treated HIV-1-infected children as they age into adolescence (17). Understanding the safety and efficacy of statin therapy for HIV-1-infected children is essential for developing recommendations for the treatment of hyperlipidemia in this group.

It is possible that HIV-infection itself is a risk factor for early cardiovascular disease. As early as 1987, there were reports of coronary artery pathology with endothelial inflammation and atherosclerotic lesions in children and adults with HIV disease (18;19). Markers of endothelial cell dysfunction, such as von Willebrand factor and tissue plasminogen activator, are elevated in HIV-infected adults independent of antiretroviral treatment (20). In addition, there is growing evidence relating chronic inflammation to the development of cardiovascular disease. In particular, elevated c-reactive protein (CRP) levels are an independent and even stronger predictor of cardiovascular events than LDL-C(21). HIV-infected adults have higher levels of CRP and other acute-phase reactants than the general population (22). There is also evidence to suggest that PIs may promote atherosclerotic lesion formation independent of their effects on blood lipid levels (23).

Recently, a record review of the Medi-Cal population, which included over 28,000 HIV-infected and 3,000,000 HIV-uninfected individuals, found a significantly increased risk of the development of coronary heart disease (CHD) in HIV-infected young adults ages 18-24 years (24). Over a median of 2.5 years of follow-up, the relative risk of developing CHD in HIV-infected men ages 18-24 was 6.76 (p < 0.0001) compared to uninfected men and 2.47 (p < 0.01) for women in the same age group. The co-variate adjusted RR for the development of CHD in individuals receiving ART compared with those not receiving ART was 2.06 (p<0.001) in HIV-infected individuals in the 18 - 33 year age group (24). This suggests that HIV-infected children may be at a greater risk for early cardiovascular disease than previously appreciated.
Treatment with HMG Co-A reductase inhibitors appears to have a greater protective effect against progression of cardiovascular disease than is predicted based on reduction of cholesterol levels alone. HMG Co-A reductase inhibitors in adults have been found to significantly decrease CRP levels independent of their effect on LDL-C in several studies (21;25), which could contribute to their ability to prevent cardiovascular events.

**Statins**

Statin therapy reduces risk for cardiovascular disease both through effectively decreasing cholesterol levels and chronic inflammation. There is compelling evidence that inflammation plays an important role in the development of cardiovascular disease (26). While the immune mechanisms resulting in increased atherosclerosis are complex, CRP (C-reactive protein) has been shown to be a relevant surrogate marker for immune activation and is a significant independent risk factor for myocardial infarction and peripheral vascular disease (27;28). Multiple studies have demonstrated that statins lower CRP levels and the clinical efficacy in reducing cardiovascular disease is independently related to the ability of statins to reduce both blood lipid levels and CRP (29-31). The mechanisms through which statins exert an anti-inflammatory effect are not completely delineated; however, statins have been shown to improve endothelial function, reduce the number of leukocytes in experimental atherosclerosis, reduce T-cell activation, and to inhibit vascular smooth muscle proliferation (32). A recent meta-analysis of primary prevention trials involving over 70,000 adults concluded that statins significantly reduced the risk of all cause mortality, major coronary events and major cerebrovascular events in adults with risk factors for cardiovascular disease but without established disease (33).

The National Cholesterol Education Program (NCEP) guidelines, proposed in 1992, recommend that drug therapy be provided for children age 10 years and older who have LDL-C levels ≥190 mg/dL in spite of dietary modification. For those children with a strong family history of early cardiovascular disease and who also have other risk factors, the LDL-C level at which drug therapy should be considered is >160 mg/dL. Recently, revised recommendations have been issued by the American Heart Association (34) and the American Academy of Pediatrics (35). These recommendations, based on 10 years more data on the long-term cardiovascular consequences of hyperlipidemia in children and adolescents (36;37) and the effectiveness of alternative therapies and the safety of statins in children, lower the LDL-cholesterol level at which drug therapy should be considered for many affected children.

There is growing evidence that HIV-infected children and youth are at increased cardiovascular risk: There is accumulating evidence that HIV-infection (both ARV-treated and treatment naïve) results in an increased risk
for early cardiovascular disease in adults (38-42). Studies in HIV-1 infected children have also shown evidence of increased risk factors for cardiovascular disease (dyslipidemia, increased inflammatory markers) and markers of early atherosclerosis (increased carotid artery intima media thickening) (43-45). While the significance of these findings is not yet clear, they suggest that HIV-infected children and youth may be at greater risk for early cardiovascular disease than previously recognized.

The American Heart Association guidelines specifically include HIV disease in the list of high-risk conditions for which the cutpoint LDL cholesterol level for initiation of drug therapy and the desired target LDL cholesterol level should be lowered. The American Academy of Pediatrics guidelines recommend that for children with chronic inflammatory disease (Tier II, moderate risk), statins should be initiated for LDL cholesterol levels ≥ 130 mg/dl. We propose to use an LDL-C level of ≥ 130 mg/dL which is refractory to dietary modification as the entry criteria for this study, with the goal of therapy being a LDL cholesterol level of ≤ 110 mg/dl or a ≥ 30% decrease in LDL-C level regardless of baseline LDL-C level (34).

While adult guidelines for the treatment of hyperlipidemia is based on the 10 year risk for the development of symptomatic cardiovascular disease, no such risk score is available for children. In addition, there is no data to support a particular level of childhood cholesterol that predicts risk of adult cardiovascular disease (CVD). This makes it difficult to determine a specific cholesterol level where the benefit of drug treatment clearly outweighs the risk. Nevertheless, as discussed above, atorvastatin has been shown to have a good safety profile in adults and children so the risk of early therapy with atorvastatin is not expected to be significant. There is likely to be a cumulative benefit from early attention to decreasing the risk of early cardiovascular disease in HIV-infected children and young adults. Studies have shown that aggressive atorvastatin therapy can cause regression of atherosclerotic plaques and improvement in the carotid intima media thickness (CIMT) as well as slowing the rate of coronary atherosclerosis progression. HIV-infected children and young adults have both the additional risk of early cardiovascular disease caused by HIV itself and in addition have the iatrogenic risk related to ART. As the goal of HIV therapy is not just to keep the virus under control, but also to maintain optimal long-term health, identification and early treatment to prevent the long-term consequences of HIV disease and its therapy will hopefully optimize the long-term health of HIV infected children and young adults.

1.3 Rationale for use of atorvastatin
Atorvastatin will be used in this investigation because it is likely to be a more effective agent for the treatment of hyperlipidemia based on adult studies. Atorvastatin appears to be significantly more potent than the other currently available HMG-CoA inhibitors (46). In addition, atorvastatin lowers plasma triglyceride levels as well as cholesterol levels (47) (atorvastatin package insert) which is important as many HIV-infected children with hyperlipidemia also have elevated triglyceride levels.

1.4 Safety and Efficacy of Atorvastatin

1.4.1 HIV- uninfected adults:

The safety of widespread use of atorvastatin was examined through a retrospective analysis using pooled data from 44 trials comprising 16,495 dyslipidemic adults and children treated with atorvastatin (n = 9,416, given in the 10 – 80 mg dose range), placebo (n = 1,789) and other statins (n = 5,290). Only 3% of atorvastatin subjects withdrew from trials compared to 1% on placebo and 4% on other statins. Only 0.5% of atorvastatin-treated subjects developed elevated hepatic transaminases to > 3 x ULN and the incidence of myalgia was low at 1.9% in the atorvastatin-treated subjects vs 0.8% in the placebo treated subjects (48). The frequency of myalgia did not increase across the atorvastatin dose range and no subjects experienced myopathy or rhabdomyolysis (9). Although efficacy and toxicity of atorvastatin are generally related to dose, there is no direct correlation between atorvastatin serum levels and efficacy or toxicity (49).

Increasing doses of atorvastatin up to 80 mg/day were given to 919 adults with risk factors for cardiovascular disease (50). There was a dose-dependent decrease in LDL-C (35-52% decrease) and triglycerides (16-38% decrease) during the 8 week study. Adverse effects were similar across all groups, with 12.6% of subjects reporting any treatment-associated adverse events. Reported AEs were not dose related. Clinically significant increases in creatinine kinase levels were reported in 2.6% of the subjects, with only two subjects (0.2%) experiencing CK levels 10x ULN. Myalgias were reported by 2.7% of subjects and ALT/AST levels > 3x ULN occurred in 0.7% of subjects. No subjects developed myopathy or rhabdomyolysis. A suggested mechanism for statin-induced myopathy is an increase in intracellular Ca^{2+} levels which activate a pathway of skeletal muscle cell apoptosis (51). Large follow-up cohort studies have confirmed the safety of atorvastatin in adults even at the higher dosing level of 80mg daily (52).
Atorvastatin was more effective than other statins in adult cardiac transplant recipients, with a low incidence of adverse events. Two studies reported on 87 adults post-cardiac transplant treated with both cyclosporin and atorvastatin. The rate of hepatotoxicity, rhabdomyolysis and asymptomatic increased CK levels was reported as 0%, 0% and 4.5% respectively (53).

A review of the atorvastatin package insert reveals the following as the primary adverse events reported with atorvastatin treatment:

- Thrombocytopenia, irritability, confusion, memory loss, increased LFTs – each < 1%
- Headache – 2-16%
- Insomnia, dizziness – ≥ 2%
- GI abnormalities – abdominal pain, constipation, diarrhea, nausea – 2-5%
- Hepatitis/liver failure – reported
- Dyspnea/diaphragmatic muscle pain – reported
- Myalgias – 1-6%
- Arthralgia – 2-5%
- Increased CK levels – 0.2-5%
- Rhabdomyolysis (occasionally fatal) – rare
- Rash 1-4% - case reports of Stevens-Johnson Syndrome reported in post-marketing surveillance.

Increases in liver transaminases of greater than 3 times the upper limit of normal have been reported in 0.7% of subjects participating in atorvastatin clinical trials. In the 40% of subjects who stopped the atorvastatin the transaminase levels fell to normal or baseline in all of the subjects. For the 60% of subjects who continued treatment with atorvastatin the LFTs decreased despite continued use of atorvastatin (atorvastatin package insert).

Although the majority of data suggest that statin use may lead to improved cognition in elderly patients (54), there have been a few reports of cognitive impairment and/or memory loss associated with statin use. Wagstaff et al reviewed statin-associated memory loss and found 60 reported cases in the literature. In the majority of cases, the adverse event was noted within 2 months of statin treatment initiation and was reversible upon discontinuation of the statin (55).

1.42 HIV- uninfected children and adolescents:
HMG Co-A reductase inhibitors have comparable efficacy and safety in children and adolescents as in adults. Although in general, the number of subjects included in most studies has been small and the length of treatment short, significant reductions in LDL-C (27-40%) have been reported with statin treatment and no adverse effects have been noted on growth or pubertal development (56;57). In one large study of statins in children, 214 children with familial hypercholesterolemia ages 8-18 years were treated with pravastatin vs placebo over a 2-year period. Mean LDL-C levels were reduced in the pravastatin-treated group compared with placebo (-24% vs + 0.3%, respectively p = 0.001) (58). Significantly, there was a decrease in the carotid artery intima-media thickness in the treated group. There were no differences between the two groups in growth, sexual maturation, liver toxicity or myopathy.

Three HMG Co-A reductase inhibitors are FDA-labeled for use in children: pravastatin, lovastatin and atorvastatin. Lovastatin will not be used in this trial because lovastatin levels are significantly increased when administered concurrently with PIs and their concurrent use is contraindicated (59). Atorvastatin was chosen over pravastatin because as seen in adult trials, atorvastatin lowers blood cholesterol levels more effectively than pravastatin.

One hundred eighty-seven children, ages 10 - 17 years, with familial hypercholesterolemia were treated with 10 or 20 mgs of atorvastatin. LDL-C levels decreased 40% in the atorvastatin-treated subjects after 26 weeks of therapy. The goal of therapy was an LDL-C level of < 130 mg/dL. Subjects were started on 10 mg atorvastatin; 55% required an increase to 20mg after 4 weeks for failure to reach the study goal. No significant adverse events were associated with atorvastatin treatment in these subjects, although 1% had elevations in ALT and/or AST of > 3x ULN (60).

A recent summary of published studies of statin use in children and adolescents, ages 4 – 18 years, including 156 children on atorvastatin, demonstrated short term efficacy and safety of statin therapy. Treatment with atorvastatin resulted in the largest decrease in LDL-C compared with the other statins studied (61). Adverse drug effects reported were similar to those reported in adults. Mild increases in CK and LFTs were reported. In this series there were no cases of symptoms of myalgia, myositis or rhabdomyolysis. Judging the relationship of mild CK elevations to statin therapy in this population is difficult, as CK elevations occur commonly due to excessive exercise or participation in sports. One placebo recipient
in the controlled study of pravastatin (58) had an asymptomatic increase in CK levels to >16,000 U/L after 168 days of therapy.

There are several small studies of atorvastatin therapy in pediatric renal transplant recipients with hyperlipidemia secondary to drug therapy. Doses of 2.5 mg – 10 mg of atorvastatin were associated with reductions in LDL-C of up to 57% and no clinically significant side effects were noted (62) (63). **Atorvastatin has been successfully used in children after cardiac transplantation and with limited toxicity, in spite of concurrent immunosuppressive agents (64;65).** Thirty-eight children ages 8-16 were treated with 0.2 mg/kg/day of atorvastatin following cardiac transplant. Significant reductions were seen in total and LDL-C and triglycerides. None of the children developed increased liver enzymes; however 2 (5%) developed rhabdomyolysis with CK levels >10x normal (65).

**A recent meta-analysis of placebo-controlled trials using statins for the treatment of familial hypercholesterolemia in children reported on 798 children treated with statins vs placebo: there was no difference between the two groups in the number of adverse events reported (66). Fifty-one diabetic children treated with 20 mg of atorvastatin developed no serious toxicity over 12 weeks of therapy (LFTs less than 2 times normal and no increase in CK) (67). In addition, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) recently completed a placebo controlled investigation of the safety and efficacy of atorvastatin in 240 children ages 10 – 21 years with systemic lupus erythematosus. Subjects were treated on the study for 3 years. There were no serious adverse events related to atorvastatin in this study (APPLE study - personal communication, manuscript pending – ClinTrials.gov reference - http://www.clinicaltrials.gov/ct/show/NCT00065806?order=2)**

There are no studies on the use of statins in HIV-infected children with HAART-associated hyperlipidemia.

**1.43 Atorvastatin in HIV-infected adults:**

A few studies have investigated the safety and efficacy of statins in HIV-infected adults. Lipid values decreased by 21 – 30% after 24 weeks of treatment with rosuvastatin. Mild gastrointestinal adverse events were reported, with no laboratory abnormalities (68). In the study by Moyle, median total cholesterol fell from 7.5 to 6.3 mmol/l after 24 weeks of treatment with pravastatin, a 16% reduction. No adverse events were recorded and no subject experienced virologic rebound during the study. No
pharmacokinetic studies were performed (69). In another study, total cholesterol levels were decreased an average of 24% in 24 HIV-infected adults treated with a variety of statins (2 on atorvastatin) after a median of 8 months of therapy. No serious adverse events were noted except for two lovastatin-treated subjects who developed reversible myalgia (70). In another study, LDL-C levels decreased 37% after 24 weeks of treatment with atorvastatin in 20 HIV-1 infected adults with antiretroviral-associated hypercholesterolemia (71), without myalgias or myositis being reported and with stable CK levels. In addition, no significant changes in LFTs, CD4 count or viral load were noted. A group of 29 HIV-infected patients taking PIs started taking atorvastatin alone (n = 10) or with gemfibrozil (n = 19)(72). After a median of 6 months, decreases in total cholesterol and triglycerides were 19% and 21%, respectively in the patients taking atorvastatin alone and 30% and 60% in the patients taking atorvastatin plus gemfibrozil. No myopathy or liver toxicities were reported. Murillas and colleagues followed 15 patients who experienced lipid abnormalities after beginning a regimen including ritonavir. Atorvastatin 10 mg daily was started at a median of 7 months after starting the PI. Total cholesterol decreased by about 25% by month 3, and responses were sustained over the first year. One patient experienced increased liver enzymes which normalized by month 3, and no patients reported myalgia (73).

1.44 HIV-infected children and adolescents:

No published data are available on the safety and efficacy of atorvastatin in HIV-infected children and adolescents.

1.5 Atorvastatin Pharmacokinetics

1.51 HIV-uninfected adults:

Atorvastatin is rapidly absorbed after oral administration. The extent of absorption increases in proportion to the dose of PI concomitantly administered. The approximate bioavailability of the parent compound is 14% and the systemic bioavailability of HMG-CoA reductase inhibitory activity is 30%. Most pharmacokinetic (PK) studies report “atorvastatin equivalent” concentrations measured by enzyme inhibition assays, meaning that the PK parameters reported are a sum of the parent compound, all active metabolites, and any other endogenous substrates that inhibit HMG Co-A reductase. Atorvastatin undergoes extensive first pass metabolism to numerous active metabolites. Plasma atorvastatin and active metabolite
concentrations are approximately 30% lower after evening dose administration than after morning dosing, however the LDL-C reduction is the same regardless of time of day of administration (74). Administration with food decreases the rate and extent of absorption by approximately 25% and 9% respectively (75). Moreover, LDL-C reductions are similar regardless of food intake with dose. Therefore, atorvastatin may be administered with or without food (76). Approximately 70% of the circulating inhibitory activity for HMG-CoA reductase is attributed to the atorvastatin active metabolites. Several single and multiple dose PK studies of doses ranging from 2.5 mg – 120 mg have demonstrated greater than dose-proportional increases in maximum equivalent concentration ($C_{\text{max}}$) and area under the concentration-time curves (AUC) (74;77). However, a multiple dose study using the same patients at different doses demonstrated dose-proportionality of AUC, and less than proportional increases in minimum equivalent concentrations ($C_{\text{min}}$) with increasing doses (78). Reported half-lives range from approximately 7 to 45 hours, with the majority between 10 – 20 hours. Steady-state is reached in about 3 days (75;77;79-82). Systemic exposure to atorvastatin is greater in elderly patients than in young adults, and small differences in exposure profiles have also been seen between women and men. However, the age and gender-related changes are modest and do not necessitate dose adjustments (80). Atorvastatin and its metabolites are primarily eliminated in bile after hepatic or extra hepatic metabolism. Less than 2% is excreted in the urine, and dose adjustments for renal dysfunction are not necessary (81).

Several studies have found that plasma concentration does not correlate with LDL-C lowering capacity but rather that the efficacy of atorvastatin is better predicted by drug dose than by $C_{\text{max}}$ and AUC (78;82). Likewise, the risk of rhabdomyolysis appears to be dose-related rather than plasma equivalent concentration related. (49).

Atorvastatin is metabolized by cytochrome P450 3A4 to two primary active metabolites (o-hydroxyatorvastatin and p-hydroxyatorvastatin). The two metabolites are responsible for ~ 70% of the lipid-lowering activity. Single and multiple dose studies have evaluated doses of 0.5 mg – 120 mg daily in HIV-uninfected adults. The FDA-approved safe and effective dose range for adults is 10 – 80 mg once daily.
Reported pharmacokinetic parameters after multiple doses (using atorvastatin equivalents, or total active atorvastatin) are summarized below.

<table>
<thead>
<tr>
<th></th>
<th>10mg</th>
<th>20mg</th>
<th>40mg</th>
<th>80mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>7</td>
<td>13-23</td>
<td>66-95</td>
<td>187-252</td>
</tr>
<tr>
<td>AUC (ng*hr/mL)</td>
<td>78</td>
<td>161-205</td>
<td>461-649</td>
<td>1159-1293</td>
</tr>
</tbody>
</table>

Of note, plasma concentrations (Cmax and AUC) do not correlate with LDL-C lowering capacity or the risk of rhabdomyolysis. Drug dose is a better predictor than plasma exposure.

1.52 Interactions with non-nucleoside reverse transcriptor inhibitors:

In adults, efavirenz and atorvastatin administered together yielded a decrease in atorvastatin of 43%, and a decrease of all active compounds (atorvastatin + the 2 main metabolites) of 34% (83).

1.53 Interactions with protease inhibitors:

Most of the statins currently in use are metabolized via the cytochrome P450 3A4 (CYP) system; therefore the risk for drug interactions with PIs is significant. Adult subjects were treated concurrently with ritonavir/saquinavir (RTV/SQV) or nelfinavir (NFV) and atorvastatin, simvastatin or pravastatin through ACTG A5047. The AUC of simvastatin increased over 3000% when given in conjunction with RTV/SQV. Atorvastatin parent compound concentrations increased 300%, however, the sum of concentrations of the parent compound and active metabolites (total active atorvastatin) only increased 79% when given in conjunction with RTV/SQV as the formation of the active metabolites responsible for 70% of the cholesterol-lowering activity is decreased (84). In contrast, pravastatin, which is not significantly metabolized by the CYP system, had a decreased AUC when given with RTV/SQV. Importantly, treatment with atorvastatin did not affect the exposure to ritonavir or saquinavir (59). Healthy subjects taking tipranavir/ritonavir with atorvastatin demonstrated that atorvastatin had no effect on the PIs, but that tipranavir/ritonavir increased atorvastatin AUC by 9-fold, and inhibited the formation of atorvastatin active metabolites (85). Nelfinavir, 1250 mg twice daily, with atorvastatin 10 mg daily in healthy subjects increased equivalent Cmax and AUC of atorvastatin & metabolites by 74% after two weeks of coadministration(86). Concomitant administration of LPV/r and atorvastatin increased the parent compound AUC and Cmax, decreased ortho-hydroxy metabolite formation, increased para-hydroxy metabolite formation, and resulted in an overall increase in atorvastatin equivalent
C<sub>max</sub> and AUC by 4.5 and 2.5 fold, respectively (87). The lack of effect of atorvastatin on the pharmacokinetics of PIs is consistent with the low affinity of atorvastatin for the human liver CYP3A4 enzyme <i>in vitro</i> (88). Atorvastatin does inhibit human p-glycoprotein-mediated transport at high concentrations and may affect exposure to p-glycoprotein substrates (88;89).

1.54 HIV-infected adults

Pharmacokinetic data for atorvastatin in HIV-infected adults have not been published.

1.55 HIV-uninfected children

Pharmacokinetic data for atorvastatin in HIV-uninfected children have not been published.

1.56 HIV-infected children

Pharmacokinetic data for atorvastatin in HIV-infected children have not been published. Synthesizing the above adult data, we would predict that children taking a protease inhibitor without a non-nucleoside agent, along with atorvastatin will have an 80% - 250% increase in plasma exposure to atorvastatin with commonly used protease inhibitors as below:

<table>
<thead>
<tr>
<th></th>
<th>10 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>13 – 18</td>
<td>23-58</td>
</tr>
<tr>
<td>AUC (ng*hr/mL)</td>
<td>140 – 195</td>
<td>290-513</td>
</tr>
</tbody>
</table>

These will be the highest expected total atorvastatin concentrations, as subjects taking a non-nucleoside agent along with the protease inhibitor will likely have some attenuation of the increased atorvastatin and subjects who are not taking protease inhibitors would be expected to have even lower atorvastatin exposure. The C<sub>max</sub> for both doses is below the C<sub>max</sub> observed for the 80 mg dose in adults.

Cytochrome P450 3A4 activity is consistently higher in children than adults, and slowly decreases to adult values in mid-late adolescence. (90) Because atorvastatin is a CYP 3A4 substrate, higher clearance and lower exposures of the parent drug are expected in childhood and early adolescence. Therefore, the C<sub>max</sub> and AUC for HIV-infected children listed in the table above may be over-predictions. However, the formation of the active metabolites may be increased for this same reason.
Furthermore, the concomitant antiretroviral therapy that may induce or inhibit CYP 3A4 complicates our ability to predict total active atorvastatin exposure.

1.6 Rationale for measuring markers of inflammation

The role of inflammation as a factor associated with the risk of developing coronary artery disease has been studied intensively in various HIV-uninfected populations (91). A still somewhat controversial proposal is that inflammatory processes interact with “traditional” metabolic risk factors (e.g., elevated lipids) in the development and/or progression of atherosclerotic disease. Recent studies indicate that inflammatory cytokines and acute phase reactants are predictive markers of those who are at increased risk of developing coronary heart disease. For example, a prospective study of a subset of subjects in the Nurses’ Health Study and the Health Professionals Follow-Up Study found that elevated levels of inflammatory markers at baseline (particularly high sensitivity C-reactive protein) place subjects at increased risk for the development of coronary heart disease (92). Another study found that intervention with intensive statin treatment for HIV-uninfected adults with documented coronary artery disease led to a reduced rate of disease progression and to reductions in the levels of atherogenic lipoproteins and high sensitivity CRP (93). Others have additionally published that adult subjects with acute coronary syndromes who have low levels of high sensitivity CRP after statin therapy have better clinical outcomes than those with higher levels (21).

Several inflammatory markers and acute phase reactants have been evaluated as correlates for the development of coronary artery disease. Some of these circulating blood markers include: high sensitivity CRP (detailed above), fibrinogen and other plasma proteins (94), as well as soluble adhesion molecules such as P-selectin, soluble intercellular adhesion molecule 1, and VCAM-1 (95). A comprehensive analysis of all candidate inflammatory markers studied to date in the HIV-uninfected populations is beyond the scope of the current pediatric HIV Phase I/II study. However, evaluation of the subjects’ inflammatory responses to atorvastatin administration, using commonly available blood markers (e.g., high sensitivity CRP), will provide valuable information for the HIV-infected, hyperlipidemic pediatric population under study.

1.7 Rationale for Urine 6β-hydroxycortisol/cortisol ratio

Cytochrome P4503A (CYP3A) is the most abundant hepatic oxidative enzyme. The isoforms CYP3A4 and CYP3A5 are the most important CYP3A isoforms in humans. CYP3A4 accounts for 30-40% of the P450 content in the human liver and intestine and is involved in the metabolism of almost 30% of clinically used drugs. Protease inhibitors, in particular ritonavir, are potent inhibitors of CYP3A4, thus
increasing blood levels of many concurrently administered agents. In contrast, non-nucleoside reverse transcriptase inhibitors such as efavirenz, induce CYP3A4 enzymes, thus decreasing blood levels of many concurrently administered agents. As atorvastatin is primarily metabolized through the CYP3A4 pathway, the pharmacokinetics of atorvastatin will be impacted by the degree of inhibition or induction of CYP3A4.

We hypothesize that subjects with inhibited CYP3A4 activity will require fewer dose escalations to achieve the target cholesterol reduction whereas subjects with higher CYP3A4 activity will require more dose escalations. Knowing the CYP3A4 activity status of each subject will assist in the analysis of the pharmacokinetics of atorvastatin and interpretation of the dose escalation strategy proposed by this investigation.

Biotransformation of endogenous cortisol to its metabolite 6β-hydroxycortisol is mediated through CYP3A4, and the ratio of 6β-hydroxycortisol to cortisol in the urine has been used as a surrogate marker of CYP3A4 activity (96),(97). We propose to determine baseline CYP3A4 activity by measuring the 6β-hydroxycortisol to cortisol ratio in spot urine collected as a first morning void. This has been shown to have a good correlation with the measurement in a 24-hour urine (98).

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the safety and efficacy (based on direct LDL-cholesterol levels) of escalating doses of atorvastatin in HIV-1-infected subjects with stable antiretroviral treatment regimens.

2.2 Secondary Objectives

2.21 To evaluate changes from baseline in fasting total cholesterol, triglycerides, HDL cholesterol, Apolipoprotein A1 and B, lipoprotein (a) after initiation of atorvastatin.

2.22 To evaluate changes from baseline in inflammatory-associated cardiac risk markers (e.g. high-sensitivity CRP) after initiation of atorvastatin.

2.23 To describe the pharmacokinetics of atorvastatin when administered concurrently with protease inhibitors.
2.24 To evaluate changes from baseline in plasma HIV-1 RNA levels after initiation of atorvastatin.

3.0 STUDY DESIGN

This is a Phase I/II dose escalation study designed to examine the safety and efficacy of atorvastatin for treatment of increased LDL-Cholesterol in HIV-infected subjects ≥ 10 to < 24 years of age on stable antiretroviral regimens. The primary objective of the study is to evaluate the safety and efficacy of a dose escalation strategy for atorvastatin, where efficacy is defined as the achievement of an LDL-C level of ≤ 110mg/dL or a ≥ 30% decline in LDL-C from baseline within 4 weeks of treatment. Subjects meeting the entry criteria will be started on atorvastatin at 10mg per day. This dose will be increased to 20mg on Week 8 if the subject has not achieved a LDL-C level ≤ 110mg/dL or a ≥ 30% decline in LDL-C from baseline at week 4 and has not developed an atorvastatin-related Grade 3 or Grade 4 (LFTs ≥ Grade 2) toxicity by Week 8. The first six subjects enrolled should be ≥15-<24 years old, with enrollment of the remaining 34 subjects resumed and opened up to the younger stratum if safety criteria on these six subjects are met. Secondary objectives include determination of the effects of atorvastatin on fasting lipids, high sensitivity CRP and HIV-1 RNA levels and measurements of population pharmacokinetics.

P1063 subjects will have to re-register if the atorvastatin dose is increased to 20 mg per day as the study will be treated as a stepwise study. Step I will be for all subjects enrolling at the 10mg dose (Appendix IA). Step II will be for subjects requiring a dose increase to 20mg (Appendix IB). Step III will be for any subject that must continue on the follow-up schedule (Appendix IC) due to treatment related toxicity or pregnancy. Registration to the new steps will be done using the Data Management Center Subject Enrollment System.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.11 Documentation of HIV-1 infection defined as positive results from two samples collected at different time points. The same method may be used at both time points. All samples tested must be whole blood, serum or plasma.

Subjects ≤ 18 months of age

The first test may be any of the following:
- One HIV DNA PCR
- One HIV RNA (quantitative >5,000 copies/mL or qualitative)
• One HIV culture (prior to August 2009)
• One total HIV nucleic acid

If the first test(s) is positive, a second sample collected and tested using any of the tests listed above (except for qualitative RNA assays) in a laboratory participating in an appropriate external quality assurance program and NIH-approved.

Subjects > 18 months of age

The first test may be any of the following:
• Two rapid antibody tests from different manufacturers or based on different principles and epitopes
• One rapid antibody test AND one [enzyme immunoassay (EIA) OR Western blot (WB) OR immunofluorescence OR chemiluminescence]
• One EIA AND one [WB OR immunofluorescence OR chemiluminescence]
• One HIV DNA PCR
• One HIV RNA (quantitative >5,000 copies/mL or qualitative)
• One HIV culture (prior to August 2009)
• One total HIV nucleic acid

If the first test(s) is positive, a second sample collected and tested using any of the tests listed above (except for qualitative RNA assays) in a laboratory participating in an appropriate external quality assurance program and either CAP/CLIA approved (for US laboratories) or NIH-approved (for international laboratories).

4.12 Subjects ≥ 10 to < 24 years of age at study entry.

4.13 CD4% at screening ≥ 15%.

4.14 HIV-1 plasma RNA ≤ 10,000 copies/ml at screening.

4.15 On a stable antiretroviral therapy regimen for at least 6 months.

4.16 Tanner Stage ≥ 2

4.17 LDL-C ≥ 130 mg/dL (fasting specimen required, if LDL-C calculated; no fasting requirement if LDL-C directly measured) at least twice over the previous 6 months prior to screening with at least one of the
measurements within 30 days prior to screening and after documented attempts at modifying diet and other risk factors by the site, for at least 3 months. In addition to the required 2 LDL-C ≥130 mg/dL obtained through clinical care, the screening fasting direct LDL-C results obtained from the P1063 Central Metabolic Laboratory must be ≥ 130 mg/dL.

4.18 Able to fast overnight at least 8 hours.

4.19 Parent or legal guardian able and willing to provide informed consent and subject willing and able to provide assent when appropriate.

4.110 Female subjects who are sexually active and able to become pregnant must use two methods of birth control while on study. Hormonal birth control alone (e.g. pills, shots, patches, or slow release inserts placed under/on the skin) would not be considered adequate. An effective, medically accepted barrier method of contraception (e.g., female/male condoms, diaphragm or cervical cap with a cream or gel that kills sperm, intrauterine device (IUD), also must be used during the study. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission. Use of an IUD may increase the risk of pelvic inflammatory disease. Female subjects who smoke cigarettes and cannot refrain from smoking should not be placed on hormonal contraception. Contraception must be continued for 4 weeks after stopping study medication.

4.111 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 through alternative methods and agree to consistently use contraception (as stated in section 4.110).

4.112 Males participating in the study must not attempt to impregnate a female, or participate in sperm donation programs. Males engaging in sexual activity that could lead to pregnancy must use a condom.

4.113 Negative pregnancy test at screening.

4.2 Exclusion Criteria
4.21 Screening LFTs ≥ Grade 1. **Entry of subjects with ≤ Grade 3 total bilirubin will be permissible if the subject is taking atazanavir and the direct bilirubin and other LFTs are < Grade 1.**

4.22 Screening creatinine kinase ≥ Grade 1

4.23 Screening creatinine ≥ Grade 2

4.24 Unlikely to remain on current antiretroviral therapy for at least six months after study entry

4.25 Use of a statin, fibrate, or niacin within the 3 months prior to enrollment

4.26 Evidence of chronic ongoing myositis or history of myopathy or neuromuscular disorder. **Stable static encephalopathy is not an exclusion.**

4.27 Symptomatic peripheral neuropathy within 6 months **of study entry**

4.28 Pharmacologic treatment for depression or other mental health disorder excluding Attention Deficit Disorder within thirty days **of study entry**

4.29 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

4.210 Chemotherapy for malignancy within three months **of study entry**

4.211 Hepatitis B Surface Antigen positive

4.212 Hepatitis C viremia (presence of HCV RNA in plasma)

4.213 Insulin-dependent diabetes mellitus

4.214 Required treatment with an agent contraindicated with either atorvastatin or PIs. (See 4.3)

**4.215 Any laboratory or unresolved clinical toxicity ≥ Grade 3, unless prior approval obtained from the protocol team.**
4.3 Disallowed Medications

- alprazolam   XANAX®
- amiodarone  CORDARONE®
- astemizole   HISMANAL®
- bepridil     VASCOR®
- bupropion    WELLBUTRIN®, ZYBAN®
- carbamazepine TEGRETOL®
- cisapride    PROPULSID®
- clorazepate  TRANXENE®
- clozapine    CLOZARIL®
- diazepam     VALIUM®
- dexamethasone DECADRON®
- encainide    ENKAID®
- estazolam    PROSOM®
- ergot alkaloids and derivatives: BELLERGAL®, CAFERGOT®, ERGOSTAT®, WIGRAINE®, and others
- flecainide acetate TAMBOCOR®
- fluticasone  FLONASE®
- flurazepam   DALMANE®
- ketoconazole NIZORAL®
- isotretinoin ACCUTANE®
- itraconazole SPORANOX®
- lovastatin   MEVACOR®
- meperidine   DEMEROL®
- midazolam    VERSED®
- phenobarbital SOLFOTON®
- phenytoin    DILANTIN®
- pimozide     ORAP®
- piroxicam    FELDENE®
- propafenone  RYTHMOL®
- propoxyphene DARVON®, DARVOCET®
- quinidine    QUINAGLUTE®
- rifabutin    MYCOBUTIN®
- rifampin     RIFADIN®, RIMACTANE®
- Saint John’s wort
- simvastatin  ZOCOR®
- terfenadine  SILDANE®
• trazodone DESYREL®
• triazolam HALCION®
• zolpidem AMBIEN®

Additional disallowed medications: fibrates, clarithromycin, cyclosporine, delavirdine, erythromycin, fluconazole, niacin, nefazodone, any alternative (herbal) medications unless preapproved by protocol chair, Quinopristin/dalfopristin and voriconazole. In addition, grapefruit juice is disallowed.

4.4 Enrollment Procedures

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

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

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

4.5 Co-Enrollment Guidelines
Co-enrollment is permitted except for protocols that would violate the exclusion criteria. All co-enrollments require the assent of the protocol chairs of IMPAACT P1063 and the co-enrollment protocols.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration and Duration

At study entry, subjects will be administered atorvastatin (Lipitor®) study product in combination with subject’s stable antiretroviral therapy. Atorvastatin will be provided through the study. The site pharmacist must receive a new prescription from an authorized prescriber for each dose increase of atorvastatin. **In addition to receiving a new prescription, the site pharmacist must receive a new Study Identification (SID) number when re-registering subjects to Step II and Step III.**

5.11 Regimens

All subjects will be started on atorvastatin (Lipitor®) 10mg orally once daily.

Atorvastatin dosing will begin at 10 mg per day and if efficacy criteria are not met, will increase the dose to a maximum dose of 20 mg per day. Subjects will be maintained on their efficacious dose throughout the study treatment weeks, unless there is a toxicity event which requires discontinuation of the atorvastatin.

Once the subject is found to have reached an efficacious dose at a Dose Escalation Visit, the subject will then enter the Dose Maintenance Phase and return to clinic in 4 Week Study Visit.

See Table 1: Atorvastatin Dose Escalation Schedule.

**Study Baseline Visit (Dose Level 1):**
- Atorvastatin 10mg orally once daily.

**Dose Escalation Visit (Dose Level 2):**
If LDL-C remains > 110mg/dL or a < 30% decline from baseline to Week 4 and the subject has not developed an atorvastatin-related Grade 3 or Grade 4 toxicity (LFTs ≥ Grade 2) by Week 8, then increase to:
- Atorvastatin 20mg orally once daily at Week 8.
If atorvastatin 10mg once daily dose is found to be efficacious at Week 4, then continue on this dosing regimen to Study Week 48.

Table 1
Atorvastatin Dose Escalation Schedule

<table>
<thead>
<tr>
<th>Dose Escalation Week #</th>
<th>Dose Level</th>
<th>Dose</th>
<th># of Tablets per Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1</td>
<td>10 mg</td>
<td>1 x 10 mg tablet</td>
<td>Once Daily</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>20 mg</td>
<td>2 x 10 mg tablet (or 1 x 20mg tablet)</td>
<td>Once Daily</td>
</tr>
</tbody>
</table>

5.12 Administration
Atorvastatin is administered orally as a single dose at any time of the day, with or without food.

5.13 Duration
Subjects will remain on atorvastatin study drug regimen until Study Week 48.

5.2 Drug Formulation and Storage
Atorvastatin (Lipitor®) 10 mg and 20 mg tablets are provided as white, elliptical, film-coated, non-scored tablets.

Store atorvastatin tablets at controlled room temperature between 20 - 25º C (68 - 77º F).

5.3 Drug Supply, Distribution, and Pharmacy

5.31 Study Product Acquisition
Atorvastatin 10 mg and 20 mg tablets will be provided by Pfizer. Atorvastatin will be available through the NIAID Clinical Research Products Management Center. The IMPAACT clinical trials unit (CTU) pharmacist can obtain the study products for this protocol by following instructions in the manual, Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, in the section on Study Product Control.

5.32 Study Product Accountability
The IMPAACT CTU pharmacist is required to maintain complete records of all study products 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 on Study Product Control.

5.33 Study Product Dispensing

Atorvastatin tablets should be dispensed to subjects in a prescription vial.

Subjects must bring back to clinic all study medications at each visit.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009, must be used for screening eligibility and for grading all adverse events, and is available on the RCC website (http://rcc.tech-res.com/safetyandpharmacovigilance/)

Alternate explanations for clinical and laboratory abnormalities must be sought prior to study drug discontinuation. Toxicities related to antiretroviral therapy will be managed by the subject’s HIV care provider.

6.11 General Toxicity Management Guidelines

The following important exceptions to Section 6.11, General Toxicity Management Guidelines, must be managed as per specific guidelines described in Sections 6.12 – 6.15:

- Increase in AST or ALT – See 6.12.
- Neuromuscular weakness – See 6.15.

Grade 1 toxicity
- Continue atorvastatin
- Routine monitoring.
Grade 2 toxicity
- Continue atorvastatin
- Monitor closely and repeat abnormal test within 14 days
- Work-up to exclude other causes.

Grade 3 toxicity
Send an e-mail to the protocol team at actg.teamp1063@fstrf.org within 48 hours of the event.
- Discontinue atorvastatin (except for grade 3 total bilirubin if the subject is taking atazanavir and the direct bilirubin and other LFTs are < Grade 1)
- Repeat lab test within 72 hours for confirmation.
- Work-up to exclude other causes.
- If repeat clinical observation or laboratory test confirms Grade 3 toxicity, and the toxicity is definitely NOT related to atorvastatin, resume atorvastatin after the toxicity has resolved to <Grade 2 (<Grade 1 lipase). If the toxicity IS thought to be related to atorvastatin, atorvastatin should be discontinued. If atorvastatin is resumed after being stopped for toxicity, subject should be monitored closely upon restarting drug (e.g. weekly for 2 weeks). If toxicity > Grade 1 recurs, permanently discontinue atorvastatin.

Grade 4 toxicity
- STOP atorvastatin and notify the protocol team at actg.teamp1063@fstrf.org.
- Provide protocol team with ALL toxicity related laboratory results.
- Repeat clinical observation or laboratory test within 72 hours and notify study team of those results.
- Work-up to exclude other causes.
- If the toxicity is definitely not related to atorvastatin resume atorvastatin after the toxicity has resolved to <Grade 2 (<Grade 1 lipase) or <Grade 4 total bilirubin if the subject is taking atazanavir and the direct bilirubin and other LFTs are < Grade 1)
- If atorvastatin is resumed after being stopped for toxicity, subject should be monitored closely upon restarting drug (e.g. weekly for 2 weeks). If toxicity > grade 1 recurs, permanently discontinue atorvastatin.
- If the toxicity is related to atorvastatin subjects should permanently discontinue atorvastatin, subject will go off-study treatment. Grade 4 toxicity should be followed until resolution to < Grade 2.
6.12 Increase in AST or ALT

**Grade 1 toxicity**
Continue atorvastatin

**Grade 2 toxicity**
Continue atorvastatin – repeat LFTs in 72 hours.
If the repeat level confirms Grade 2 toxicity, notify the protocol team actg.teamp1063@fstrf.org and discontinue atorvastatin. Atorvastatin may be restarted if the toxicity has resolved to <Grade 1 within 14 days. LFTs should be checked weekly for the first 3 weeks after restarting the atorvastatin. If Grade 2 toxicity recurs, permanently discontinue atorvastatin and notify the protocol team actg.teamp1063@fstrf.org.

**Grade 3 toxicity**
Discontinue atorvastatin and repeat LFTs within 72 hours.
Notify the protocol team actg.teamp1063@fstrf.org.
If the toxicity is definitely not related to atorvastatin resume study drug after the toxicity has resolved to <Grade 1. If no definitive alternate etiology can be determined, permanently discontinue atorvastatin. Subject will go off-study treatment. Grade 3 toxicity should be followed until resolution.

**Grade 4 toxicity**
Discontinue atorvastatin.
Notify the protocol team actg.teamp1063@fstrf.org and repeat LFTs within 72 hours.
If the toxicity is definitely not related to atorvastatin, resume atorvastatin after the toxicity has resolved to <Grade 1. If no definitive alternate etiology can be determined, permanently discontinue atorvastatin. Subject will go off-study treatment. Grade 4 toxicity should be followed until resolution.

6.13 Myalgia

**Grade 1 toxicity**
No accompanying muscle tenderness/weakness and/or limited to single muscle group, and/or associated with compatible history of trauma to include strenuous exercise within 10 days – check CK, electrolytes, BUN, CR and urinalysis – if normal, continue atorvastatin, repeat observation in 7-10 days.
If myalgia is persistent contact protocol team at actg.teamp1063@fstrf.org.

**Grade 2 toxicity**
• Generalized, minimal/no accompanying muscle tenderness/weakness, and/or associated with compatible history of trauma.

Check CK, electrolytes, BUN, CR and urinalysis— if normal, continue study drug, repeat observation in 7-10 days. If persistent contact protocol team at actgteamp1063@fstrf.org.

• Grade 2, generalized, moderate accompanying muscle tenderness/weakness, not associated with compatible history of trauma to include strenuous exercise within 10 days.

Discontinue atorvastatin, check CK, electrolytes, BUN, CR and urinalysis, repeat observation within 72 hours.

If no improvement is noted and no definitive alternate etiology can be determined, permanently discontinue atorvastatin. Subject will go off-study treatment. Toxicity should be followed until resolution. If it is determined that the toxicity was caused by some alternate etiology, atorvastatin may be continued. If the toxicity occurs again, permanently discontinue atorvastatin.

Grade 3 toxicity
Generalized, with accompanying muscle tenderness/weakness, discontinue atorvastatin, check CK, electrolytes, BUN, CR and urinalysis, repeat observation within 72 hours.

If no definitive alternate etiology can be determined, permanently discontinue atorvastatin. Subject will go off-study treatment. Toxicity should be followed until resolution.

Grade 4 toxicity
Generalized, with accompanying muscle tenderness/weakness, discontinue atorvastatin. Check CK, electrolytes, BUN, CR and urinalysis; repeat observation within 72 hours.

If no definitive alternate etiology can be determined, permanently discontinue atorvastatin. Subject will go off-study treatment. Toxicity should be followed until resolution. Subject will remain on study follow-up.

6.14 Increased CK levels

Grade 1 toxicity
No muscle tenderness, myalgia or weakness and/or associated with compatible history of trauma to include strenuous exercise within 10 days - continue study drug, repeat CK and repeat observation in 7-10 days.
If CK elevation is persistent contact protocol team at actg.teamp1063@fstrf.org.

Grade 2 toxicity

- Minimal/no accompanying muscle tenderness, myalgia or weakness, and/or associated with compatible history of trauma to include strenuous exercise within 10 days.

  Check urinalysis, electrolytes, BUN, CR – if normal, continue atorvastatin and contact the subject by telephone within 72 hours. Repeat observation in 7-10 days. If Grade 2 persists, contact the protocol team at actg.teamp1063@fstrf.org.

- Grade 2, moderate accompanying muscle tenderness, myalgia or weakness, NOT associated with compatible history of trauma to include strenuous exercise within 10 days.

  Discontinue atorvastatin, check urinalysis, electrolytes, BUN, CR, repeat within 72 hours.

  If no definitive alternate etiology can be determined, permanently discontinue atorvastatin. Subject will go off-study treatment. Toxicity should be followed until resolution. If it is determined that the toxicity was caused by some alternate etiology, atorvastatin may be continued. If the toxicity occurs again, permanently discontinue atorvastatin.

Grade 3 toxicity

- Discontinue atorvastatin. Check urinalysis, electrolytes and BUN, CR. Repeat CK within 72 hours. If no definitive alternate etiology can be determined, PERMANENTLY discontinue atorvastatin. Contact the protocol team at actg.teamp1063@fstrf.org. Subject will go off-study treatment. Toxicity should be followed until resolution.

Grade 4 toxicity

Permanently discontinue atorvastatin
Subject will go off-study treatment but continue on-study. Toxicity should be followed until resolution. Notify protocol team at actg.teamp1063@fstrf.org.

NOTE: For all grades of toxicity for myalgias and increased CK levels discussed above, if laboratory findings or symptoms suggest rhabdomyolysis (CK > 10,000 IU/L, myoglobinuria, rising creatinine, hyperkalemia, hyperphosphatemia, hypocalcemia), atorvastatin should be permanently
discontinued and the event followed until its resolution. Notify the protocol team actg.teamp1063@fstrf.org.

6.15 Neuromuscular weakness (if associated with myalgia or increased CK, see sections 6.13 and 6.14).

Grade 1 toxicity
Continue atorvastatin.

Grade 2 toxicity
Continue atorvastatin.

Monitor closely, repeat observation in 7 days

Work-up to exclude other causes

If alternate cause cannot be determined, and weakness does not resolve, notify protocol team at actg.teamp1063@fstrf.org and permanently discontinue atorvastatin.

Grade 3 toxicity
Discontinue atorvastatin

Work-up to exclude other causes.

If the toxicity is definitely not related to atorvastatin resume atorvastatin after the toxicity has resolved to <Grade 2.

If alternate cause cannot be determined, notify protocol team at actg.teamp1063@fstrf.org and permanently discontinue atorvastatin. Subject will go off-study treatment. Toxicity should be followed until resolution.

Grade 4 toxicity

If alternate cause cannot be determined, notify protocol team at actg.teamp1063@fstrf.org and permanently discontinue atorvastatin. Subject will go off-study treatment. Toxicity should be followed until resolution.

6.2 Study Management Plan

Subjects ≥ 10 to < 24 years of age will receive 10 mg atorvastatin as a starting daily dose. Dose escalation will be in 10 mg increments until a maximum atorvastatin dose of 20mg per day is reached. Enrollment will occur sequentially and each subject will be managed independently for dose escalation. Fasting direct LDL-C will be measured after 4 weeks of atorvastatin therapy. Those subjects whose direct LDL-C is ≤ 110mg/dL or a ≥ 30% decline in LDL-C from baseline will be considered to have met the efficacy criteria and will continue on that dose of atorvastatin until week 48, as long as the subject does not develop any related
toxicities ≥ Grade 3 (Grade ≥ 2 LFTs). If the subjects direct LDL-C remains > 110mg/dL or a < 30% decline in LDL-C from baseline at 4 weeks and the subject has not developed any Grade 3 toxicities (Grade ≥ 2 LFTs) by week 8, the atorvastatin dose will be increased by 10 mg at week 8. Subjects will be seen for repeat fasting lipid levels and safety labs 4 weeks after the dose increase. Subjects who achieve efficacy criteria four weeks (week 12) after dose escalation to 20 mg will continue on that dose of atorvastatin until week 48 as long as the subject does not develop any Grade 3 toxicities (Grade ≥ 2 LFTs).

The first six subjects to be enrolled in the study will strictly be in the age range of ≥15 - < 24 years old. After the first six subjects have enrolled, study accrual will be held until all six subjects have reached 8 weeks of therapy to complete the initial safety assessment. The first six subjects will have passed the week 8 safety criteria if there are no life-threatening toxicities and no more than one subject experiences a non-life threatening ≥ Grade 3 toxicity (Grade ≥ 2 LFTs) attributable to the study treatment. After the initial 8 week safety assessment, enrollment will continue, and will now include subjects from ≥10 - < 24 years old. Enrollment will continue unless the subsequent safety assessments indicate any safety concerns.

Real-time safety monitoring during the first 24 weeks will be closely followed. Further accrual will be suspended, pending thorough investigation by the protocol team, if one of the following events occurs on or before week 24:

- The first life-threatening toxicity attributable to the study treatment in any of the first 12 subjects
- The second non-life threatening ≥ Grade 3 toxicity (Grade ≥ 2 LFTs) attributable to the study treatment in any of the first 6 subjects
- The third non-life threatening ≥ Grade 3 toxicity (Grade ≥ 2 LFTs) attributable to the study treatment in any of the first 12 subjects

The team will decide whether it is safe to proceed or if the study has to be closed. Any team decision will be reviewed by the Study Monitoring Committee (SMC). The SMC will review these adverse events on a quarterly basis.

6.3 Criteria for Study Discontinuation

- The subject or legal guardian refuses further treatment and/or follow-up evaluations.
- The investigator determines that further participation would be detrimental to the subject’s health or well-being.
• The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.

• The subject requires treatment with medications that are disallowed while on study.

• The subject stops taking antiretroviral therapy.

6.4 Criteria for Study Drug Discontinuation

• Subjects who become pregnant will be followed until outcome of pregnancy.

• The subject experiences drug toxicity as defined in Section 6.1. Subjects will be followed until resolution of toxicity or end of study, whichever is later.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting to DAIDS

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

The DAERS, an 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. Site queries may also be sent from within the DAERS application itself.

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

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

The study agent for which expedited reporting is required is atorvastatin.

In addition to reporting all SAE’s as defined above, other events that sites must report in an expedited fashion include all malignancies, seizures and hepatotoxicities whether or not symptomatic or related to study drug, and all other Grade 3 or 4 related toxicities (except Grade 3 neutropenia and anemia) for which a relationship to study drug cannot be ruled out.

The death of any subject after enrollment or within 30 days of study completion, regardless of the cause, must be reported within 1 working day of first becoming aware of the death. After the 30-day period, deaths need to be reported only as part of long-term follow-up studies. If an autopsy is performed, the report must be provided. Reports of all deaths must be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

For all SAE’s submitted to RCC, sites must file an updated SAE report to RCC with the final or stable outcome (Status Code p. 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification August 2009, must be used and is available on the RCC website at http://rcc.tech-res.com/safetyandpharmacovigilance/.

7.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

After the protocol-defined AE reporting period, unless otherwise noted, only Suspected Unexpected Serious Adverse Reactions 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 a Phase I/II study designed to examine the safety and efficacy of escalating doses of atorvastatin for treatment of LDL-C persistently ≥130 mg/dL in HIV-infected children ≥10 to <24 years old who are on stable ART. The primary objective of the study is to assess the safety and efficacy of escalating doses of atorvastatin after 12, 24 and 48 weeks of treatment. Secondary objectives include using population pharmacokinetics to describe the pharmacology of atorvastatin in HIV-1-infected children and adolescents and to evaluate the effects of atorvastatin on fasting lipids, high sensitivity CRP and HIV-1 RNA levels.

Since dose-escalations are done within subjects, inferences on safety and efficacy rates will be on the dose-escalation regimen overall and not on individual doses. However, safety and efficacy rates of the starting dose can still be estimated (10 mg per day) after 8 weeks on atorvastatin.

8.2 Outcome Measures

8.2.1 Safety:
1. Grade 3 or 4 toxicity (Grade ≥ 2 LFTs).
2. Grade 3 or 4 toxicity (Grade ≥ 2 LFTs) attributed to study treatment.

8.2.2 Efficacy Targets:
1. Success: LDL-C ≤ 110mg/dL or ≥ 30% decline from baseline
2. Failure: LDL-C > 110mg/dL or < 30% decline from baseline

8.2.3 Secondary Outcome Measures:
1. Atorvastatin PK parameters
2. Fasting lipids
3. High sensitivity CRP, adiponectin, and potentially other inflammatory markers of cardiac disease risk
4. HIV-1 RNA levels

8.3 Randomization And Stratification

Subjects will not be randomized in this study. Subjects will be stratified by age. Target accrual will be 20 subjects for each of the following strata: (a) ≥ 10 - <14 years old, and (b) ≥ 15 - < 24 years old. The first 6 subjects will only be accrued from the second stratum (≥ 15 - < 24 years old). If the first six subjects pass the
initial safety review at week 8, the remaining subjects will be enrolled from both age groups. **Enrollment of subjects between the ages of ≥ 18 - < 24 years of age will be limited to 10.**

### 8.4 Sample Size And Accrual

The study will enroll 40 subjects. The team will monitor study feasibility quarterly, first based on site registration and then on accrual. Initially, the team will monitor site registration quarterly to ensure that an adequate number of sites have registered to complete the protocol. Once one-third of eligible sites have registered sites start to accrue subjects, the team will assess accrual on a quarterly basis. If the study has not accrued 50% (i.e. 20 subjects) by 12 months after the opening of the protocol, then the progress and the prospect for completion of accrual will be reviewed by the Study Monitoring Committee. Consideration will be given as to whether sufficient accrual to yield evaluable data can be achieved in a reasonable time. If any stratum has not accrued half of its subjects within 12 months after opening, the team will identify the reasons for lack of accrual and possibly amend the protocol accordingly.

### 8.5 Dose Escalation Strategy

Each subject will follow a dose-escalation regimen as follows:

At study entry, each subject will have fasting lipid profile and baseline safety labs. The subject will then start on 10 mg of atorvastatin daily. Safety laboratory studies and fasting lipid profiles will be obtained at four weeks following initiation of atorvastatin dosing. Safety profiles will be obtained again at week 8. A subject whose LDL-C is ≤ 110mg/dL or ≥ 30% decline from baseline to week 4 will remain on the same dose and will continue to be on study until week 48, as long as the subject does not experience any toxicity ≥ Grade 3 (Grade ≥ 2 LFTs). A subject who fails to achieve this efficacy endpoint at week 4 and who does not have any atorvastatin-related life-threatening or non-life-threatening Grade ≥ 3 toxicity (Grade ≥ 2 LFTs) by week 8 will have the atorvastatin dose increased to 20 mg daily at week 8. Subjects will be seen for repeat fasting lipid levels and safety labs 4 weeks after the dose increase (week 12).

### 8.6 Interim Analyses

#### 8.6.1 Safety

After the first six subjects have enrolled, study accrual will be held until all six subjects have reached 8 weeks of therapy to complete the initial safety assessment.
Further accrual may proceed if the following conditions are met:

⇒ none of these 6 study subjects experience life threatening toxicities attributable to study treatment, and
⇒ fewer than 2 of these 6 study subjects experience non-life-threatening grade 3 or 4 toxicity (Grade ≥ 2 LFTs), attributable to the study treatment

After the initial 8 week safety assessment, enrollment will continue unless the subsequent safety assessments indicate any safety concerns.

In addition, real time safety monitoring during the first 24 weeks will also be implemented as follows: further accrual will be suspended, pending thorough investigation by the Protocol Team, if one of the following occurs on or before week 24:

- the first life-threatening toxicity attributable to the study treatment in any of the first twelve subjects
- the second non-life threatening ≥Grade 3 toxicity (Grade ≥ 2 LFTs) attributable to the study treatment in any of the first six subjects
- the third non-life threatening ≥ Grade 3 toxicity (Grade ≥ 2 LFTs) attributable to the study treatment in any of the first 12 subjects

The Protocol Team will then decide whether it is safe to proceed or if the study has to be closed.

Given the small sample size, the information available for safety decisions will be imperfect. Two types of sampling errors are possible: 1) with a dose-escalation strategy whose true rate of toxicity is unacceptable, the sample data may pass the safety criteria or 2) with a dose-escalation strategy whose true rate of toxicity is warranted by the potential benefits of the medication, the sample data may fail the safety criteria.

Table 2 presents the probability that the sample will fail the safety criteria, under various assumptions concerning the true failure rates that would occur in large populations that undergo the dose-escalation strategy used in this study.
TABLE 2. Probability of Failing Safety Criteria Under Potential Rates of True Toxicity in the Population from which the Sample (N = 6) was Drawn

<table>
<thead>
<tr>
<th>True Rate of Toxicity:</th>
<th>Probability of Failing Safety Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Grade 3 Not Life Threatening</td>
<td>.50</td>
</tr>
<tr>
<td></td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td>.30</td>
</tr>
<tr>
<td></td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>.00</td>
</tr>
<tr>
<td></td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>.00</td>
</tr>
</tbody>
</table>

NOTE: The 6 subjects fail safety criteria if one of the following occurs:
- at least one life threatening toxicity attributable to study treatment, or
- at least 2 non-life threatening ≥ Grade 3 toxicities attributable to study treatment

This table indicates that if the dose-escalation strategy has a true toxicity rate > 30% or if the true rate of life threatening toxicity is ≥ 10%, then it will likely fail the safety criteria after the first 6 study patients have been accrued. If the dose-escalation strategy has a true toxicity rate that is 10% or less and if the true rate of life threatening toxicity approaches zero, then it will have a low probability of failing after the first 6 study subjects have been accrued.

8.7 Monitoring

Data monitoring and data quality reports presenting laboratory and clinical events that reflect safety and efficacy of the study agent will be generated and reviewed by the study team. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available.
Reports compiled by the Statistical Data Management Center (SDMC) will be reviewed and discussed by the Protocol Team on regularly scheduled conference calls. Adverse events, accrual, study conduct and adherence to dose escalation algorithm will be reviewed. In addition, conference calls will also be scheduled as needed in response to any adverse event that requires the immediate attention of the protocol team. Notification of core team members will be normally by email, possibly by phone or fax, if necessary. Data on overall and stratum accrual, toxicity and efficacy data will be reviewed.

A Study Monitoring Committee (comprised of the Chair, Co-chair, NIAID and NICHD Medical Officers, statisticians, data manager, protocol manager, lab data coordinator and independent representatives from the Complications Scientific Committee) will review the progress of the trial, adherence to the dose escalation algorithm and the safety data as follows:

- A first interim report will be prepared after the first 6 subjects have reached 8 weeks. Summaries of toxicity and efficacy data, as well as dose escalation histories will be included. Once completed, the report will be reviewed by the SMC, which will then make recommendations, primarily on whether the protocol should continue accrual to the target sample size of 40 evaluable participants or be closed to accrual and/or follow-up of patients already in the study, or whether it should be modified. In addition to the specific points above the SMC will review these adverse event data on a quarterly basis. These recommendations will be brought to the Scientific Oversight Committee (SOC) and DAIDS for approval.

- A second interim report will be prepared after all 40 subjects have reached 24 weeks. Summaries of toxicity and efficacy data, as well as dose escalation histories will be included. The report will also include preliminary analyses of the primary objectives of the study. The review committee will make recommendations, primarily on whether the study should continue follow-up or whether it should be closed to follow-up, or whether it should be modified. These recommendations will be brought to the SOC for approval.

Adverse events will be monitored throughout the follow-up period. If the protocol team identifies any potentially treatment-related toxicities, which may compromise subject safety, it will determine whether the study needs to be suspended or modified.
8.8 Analysis

8.81 Primary Analysis

The proportion of subjects experiencing treatment related $\geq$ Grade 3 adverse events at weeks 12, 24 and 48 of the study will be calculated for the entire cohort of subjects. The proportion of subjects who meet the LDL-C threshold of $\leq 110$mg/dL or $\geq 30\%$ decline from baseline from baseline at week 12, 24, and 48 and did not experience life-threatening or atorvastatin-related $\geq$ Grade 3 (Grade $\geq 2$ LFTs) will be calculated for the entire sample of subjects. Similar proportions will be calculated for each subgroup of subjects under different age groups and the presence of NNRTI treatment at the same weeks specified above.

Ninety percent confidence intervals will be placed around each of the toxicity and treatment success proportions described above. The proportion of subjects who meet the LDL-C threshold of $\leq 110$mg/dL or $\geq 30\%$ decline from baseline from baseline to weeks 12, 24, 48 and did not experience life-threatening or Grade 3 or Grade 4 (Grade $\geq 2$ LFTs) will also be estimated. Tables 3A, B, C and Table 4 show the relative precision with which these rates will be estimated, given various potential sample sizes ($n = 60, 40, 15$).

**TABLE 3A: 90% Confidence Limits Around Potential Rates (N = 60)**

<table>
<thead>
<tr>
<th>Observed Toxicity/Efficacy rate</th>
<th>90% Confidence Limits$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>0.00 (0/60)</td>
<td>0.00</td>
</tr>
<tr>
<td>0.20 (12/60)</td>
<td>0.12</td>
</tr>
<tr>
<td>0.40 (24/60)</td>
<td>0.29</td>
</tr>
<tr>
<td>0.50 (30/60)</td>
<td>0.39</td>
</tr>
<tr>
<td>0.70 (42/60)</td>
<td>0.59</td>
</tr>
<tr>
<td>0.90 (54/60)</td>
<td>0.81</td>
</tr>
<tr>
<td>1.00 (60/60)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

$^1$Based on binomial distribution
TABLE 3B: 90% Confidence Limits Around Potential Rates (N = 40)

<table>
<thead>
<tr>
<th>Observed Toxicity/Efficacy rate</th>
<th>90% Confidence Limits¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>0.00 (0/40)</td>
<td>0.00</td>
</tr>
<tr>
<td>0.10 (4/40)</td>
<td>0.03</td>
</tr>
<tr>
<td>0.20 (8/40)</td>
<td>0.10</td>
</tr>
<tr>
<td>0.30 (12/40)</td>
<td>0.20</td>
</tr>
<tr>
<td>0.40 (16/40)</td>
<td>0.27</td>
</tr>
<tr>
<td>0.50 (20/40)</td>
<td>0.36</td>
</tr>
<tr>
<td>0.60 (24/40)</td>
<td>0.46</td>
</tr>
<tr>
<td>0.70 (28/40)</td>
<td>0.56</td>
</tr>
<tr>
<td>0.80 (32/40)</td>
<td>0.67</td>
</tr>
<tr>
<td>0.90 (36/40)</td>
<td>0.79</td>
</tr>
<tr>
<td>1.00 (40/40)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

¹Based on binomial distribution

TABLE 3C: 90% Confidence Limits Around Potential Rates (N = 15)

<table>
<thead>
<tr>
<th>Observed Toxicity/Efficacy rate</th>
<th>90% Confidence Limits¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>0.00 (0/15)</td>
<td>0.00</td>
</tr>
<tr>
<td>0.20 (3/15)</td>
<td>0.06</td>
</tr>
<tr>
<td>0.40 (6/15)</td>
<td>0.20</td>
</tr>
<tr>
<td>0.60 (9/15)</td>
<td>0.36</td>
</tr>
<tr>
<td>0.80 (12/15)</td>
<td>0.56</td>
</tr>
<tr>
<td>1.00 (15/15)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

¹Based on binomial distribution

The lower limit of the interval indicates the threshold above which the true toxicity or efficacy rate will lie with 95% probability, given the sample data. For example, if the proportion of the total sample meeting the criterion for treatment success is at least 0.5 (30/60), then we can be 95% certain that the true rate within the population represented by this sample is at least 0.39.

Additionally, the mean percent change in LDL-C from baseline to week 12 (or week 24 or week 48) will be estimated. Assuming an observed standard deviation of 20, Table 4 below shows the estimated SEM (standard error of the estimated mean percent change) and the corresponding margins for error associated with 90% confidence limits, under different sample sizes.
TABLE 4: 90% Confidence Limits for the True Mean Percent Change in LDL-C from Baseline

<table>
<thead>
<tr>
<th>N</th>
<th>90% Confidence Limits Parameters²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEM</td>
</tr>
<tr>
<td>15</td>
<td>5.2</td>
</tr>
<tr>
<td>40</td>
<td>3.2</td>
</tr>
<tr>
<td>60</td>
<td>2.6</td>
</tr>
</tbody>
</table>

² Based on Student's t distribution

For example, suppose that a sample of 60 subjects shows a 40% observed mean percent decrease from baseline in LDL-C, with an observed standard deviation in percent decrease of 20%. Then the lower 90% confidence limit for the true mean percent change in LDL-C is 35.7% and the upper limit is 44.3%. Then we can be 95% certain that the true mean percent change within the population represented by this sample is at least 35.7%.

Descriptive analyses will present toxicity and efficacy rates. In addition the mean percent change in LDL-C from baseline will be studied in a linear regression model adjusting for baseline LDL-C, age group and ARV class.

8.82 Secondary Analysis

Secondary analysis will examine the changes from baseline in fasting lipids, high sensitivity CRP, adiponectin, potentially other inflammatory markers of inflammatory cardiac disease risk, and HIV-1 RNA after initiation of atorvastatin. Change from baseline to weeks 12, 24 and 48 in other fasting lipids, high sensitivity CRP, adiponectin, potentially other inflammatory markers of cardiac disease risk, and HIV-1 RNA will be studied in a linear regression model adjusting for baseline LDL-C, age group and ARV class (99).

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Pharmacology Objectives

No published studies describe the pharmacokinetics of atorvastatin in HIV-infected adults, HIV-uninfected or HIV-infected children, either alone or with anticipated interacting medications. A secondary objective of this study is to determine the pharmacokinetics (PK) of atorvastatin when administered concurrently with protease inhibitors. Understanding the
pharmacokinetics and drug interactions of this common agent used in HIV-infected children is necessary to design safe and effective treatment regimens.

Most of the statin drugs currently in use, including atorvastatin, are extensively metabolized by the cytochrome P450 enzyme system; therefore, the risk for drug interactions with protease inhibitors and non-nucleoside reverse transcriptase inhibitors is significant. Several studies in adult healthy subjects demonstrated that exposure to atorvastatin and its active metabolites increases significantly when coadministered with protease inhibitors, while the exposure to the protease inhibitors was unchanged by atorvastatin (84). When atorvastatin is given in combination with delavirdine, the risk of myopathy, including rhabdomyolysis, is increased due to the inhibition of atorvastatin metabolism (100). In contrast, nevirapine co-administration with atorvastatin may decrease the efficacy of the statin due to induction of metabolism (101).

9.2 Primary and Secondary Data to be Accessioned

Population apparent clearance (Cl/F), and apparent volume of distribution (V/F) will be estimated. Inter- and intrapatient variability will be determined.

9.3 Study Design, Modeling and Data Analysis

This study will evaluate the population pharmacokinetics of atorvastatin in children ≥ 10 to < 24 years of age on a stable antiretroviral regimen. The study will enroll 40 subjects. Each subject will begin on 10 mg of atorvastatin, and each subject will be dose-escalated independently based on safety and efficacy endpoints to a maximum of 20 mg (See Section 8.5).

Laboratory Analysis and Reporting

Site: All PK plasma samples will be sent to the central repository and forwarded batched to Advion BioServices, Inc. for assay of atorvastatin and active metabolites. All PK samples will be destroyed after the primary assays have been completed for the pharmacokinetic studies.

Methods to be used: All methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions. These methods are the ones currently used at the University of San Diego Pharmacology Laboratory or will be derived from published methods.
Atorvastatin, o-hydroxyatorvastatin and p-hydroxyatorvastatin will be assayed in plasma samples by turbo ion spray LC/MS/MS at Advion BioServices, Inc. The assay validation range is 0.27 to 25 ng/mL. Accuracy ranges from -4.4 to 8.4% for all three compounds, and precision is ≤ 3.3%.

**PK Sampling Schedules and Analysis**

A sparse or population sampling approach will be used in this study. **All subjects will have 3 mLs of blood obtained at weeks 4, 12, 24, and 48.** These scheduled evaluations allow obtaining blood samples without requiring additional needle sticks. The exact time at which the sample is drawn will be recorded. The study drug may be taken at home. Subjects will be strongly encouraged to arrange a set time in the day to take their doses. The time elapsed since ingestion of the last three doses and whether taken with or without food must be recorded.

Population analysis of the atorvastatin and active metabolite concentrations will be performed by fitting these data to a pharmacokinetic model using the computer program NONMEM. NONMEM employs NON-linear Mixed Effects Modeling to analyze data comprised of repeated measurements in non-linear systems. The intra-individual variation will be accounted by the structural model and measurement error. The inter-individual variation will be accounted by the assumption of separate and random pharmacokinetic parameters for each individual since part of this inter-individual variation will likely depend on certain individual attributes as well as underlying random effects. For example, individual variation in drug in clearance may be explained in part by individual differences in liver function (a fixed effect). This combination of "fixed" and "random" effects makes up the "mixed" effects. Various fixed effects will be tested, such as size (height and weight), AST, ALT, bilirubin, ethnicity and sex, along with random intra- and inter- individual effects in the model. By describing these fixed effects, the relationships among the pharmacokinetic parameters and patient attributes will be determined. The variability explained by each fixed effect (clinical attribute) will be assessed in the pharmacokinetic model both statistically and graphically. Only clinical attributes which significantly influence pharmacokinetic parameters will be kept in the model. The proposed model development process is analogous to step-forward multivariate regression analysis and will lead to identification of clinical attributes that independently explain inter-subject variability. NONMEM (version IV level 1.0 double precision) will be run on an IBM-compatible personal computer. Model development will be performed in 3 steps, as described by Mandema, et al., with oversight by Dr. Edmund Capparelli of the UCSD Pharmacology Laboratory, Vice-Chair of the IMPAACT Pharmacology Lab Committee (102). Final parameter estimates will be compared with those from HIV-uninfected adult populations.
9.4 Anticipated Outcomes

The data from this study will describe atorvastatin population pharmacokinetics as well as the variability observed in this patient population of HIV-infected older children and adolescents on antiretroviral therapy. Relationships between atorvastatin dose, exposure, clinical characteristics and toxicities will be described. This knowledge will help to determine the appropriate dose selection and treatment of dyslipidemia in HIV-infected children on ART.

10.0 HUMAN SUBJECTS

10.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent document (Appendix IV), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. Written informed consent must be obtained from the 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 MB, local and state 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, parent or guardian, except as necessary
for monitoring by Pfizer Inc, (the pharmaceutical sponsor), the Office for Human Research Protections (OHRP), the NIAID, the local IRB or Ethics Committee.

This protocol is focused on youth between the ages of 10-18 when a parent/guardian will usually be granting permission for their participation through older ages when the subjects will generally consent for themselves. Since pregnancy testing is included in the protocol, adolescents are entitled to confidential testing and care for reproductive health and substance abuse in many jurisdictions, and, in general, access to confidential care is thought to improve the ability for adolescents to access this care. As a result, information collected in this study (including for screening for this study) related to pregnancy will not be shared with parents (or other adults consenting for youth’s participation) without permission of the youth, and study staff must ensure that the subject is referred to his or her medical provider for appropriate counseling and management if the subject tests positive.

10.3 Study Discontinuation

The study may be discontinued at any time by the NIAID, Pfizer, Inc., the IRB, or other government agencies (such as the OHRP) 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

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention.

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


(34) McCrindle BW, Urbina EM, Dennison BA et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of


(57) Kwiterovich PO, Jr. Safety and efficacy of treatment of children and adolescents with elevated low density lipoprotein levels with a step two diet or with lovastatin. Nutr Metab Cardiovasc Dis 2001; 11 Suppl 5:30-34.


(85) van Heeswijk R, Sabo JP, Cooper C, Cameron W, MacGregor TR, Elgadi M. The pharmacokinetic interactions between tipranavir/ritonavir 500 mg/200 mg bid (TPV/r) and atorvastatin, antacid and CYP3A4 in healthy volunteers. 5th International Workshop on Clinical Pharmacology of HIV Therapy, Rome, Italy. 2004. Ref Type: Abstract


Ref Type: Catalog


APPENDIX IA: ON STUDY VISITS FOR 10 MG PER DAY DOSE

Begin 10mg dose at study entry and register subject to Step 1: If week 4 labs show dose meets criteria for efficacy, then continue 10mg dose to week 48.

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen&lt;sup&gt;1&lt;/sup&gt; (up to 30 days prior to entry)</th>
<th>Entry</th>
<th>On Treatment: Study Week/Visit&lt;sup&gt;12&lt;/sup&gt;</th>
<th>End of Study (week 48)</th>
<th>Early Discontinuation&lt;sup&gt;13&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>x                      x x x x x x x x x x x x X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>x                      x x x x x x x x x x x x X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence Questionnaire</td>
<td></td>
<td>x                      x x x x x x x x x x x x X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1 ml</td>
<td>1 mL</td>
<td>1 mL                    1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Chemistries&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1 ml</td>
<td>1 mL</td>
<td>1 mL                    1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>Fasting Lipids&lt;sup&gt;6&lt;/sup&gt; (Appendix II)</td>
<td>2 ml</td>
<td>2 mL</td>
<td>2 mL                    2 mL</td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Urinalysis (dip only)</td>
<td>x</td>
<td>x x x x x x x x x x x x X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine beta6hydroxycortisol ratio&lt;sup&gt;7&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Serum Storage, Future Inflammatory Markers, Secondary Lipid Markers&lt;sup&gt;8&lt;/sup&gt; (Appendix II)</td>
<td>8.5 mL</td>
<td>12 mL</td>
<td>12 mL</td>
<td>12 mL</td>
<td>12 mL</td>
</tr>
<tr>
<td>Beta HCG (serum/urine)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>x</td>
<td>x x x x x x x x x x x x X X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HepB and HepC testing&lt;sup&gt;10&lt;/sup&gt;</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VIROLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1 to 4 mL</td>
<td>1 to 4 mL</td>
<td>1 to 4 mL</td>
<td>1 to 4 mL</td>
<td>1 to 4 mL</td>
</tr>
<tr>
<td><strong>IMMUNOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2 mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHARMACOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC/MS/MS&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (ml)</td>
<td>15.5-18.5 mL</td>
<td>17-20 mL</td>
<td>6 mL                    1 mL</td>
<td>20-23 mL</td>
<td>20-23 mL</td>
</tr>
</tbody>
</table>
APPENDIX IB: ON-STUDY VISITS FOR 20 MG PER DAY DOSE

Begin 10mg dose at study entry; if week 4 labs show dose does not meet criteria for efficacy and safety criteria are met at week 8, **register subject to Step 2**, increase to 20 mg dose at week 8 and continue 20mg dose to week 48.

<table>
<thead>
<tr>
<th>Event</th>
<th>On Treatment: Study Week/Visit</th>
<th>End of Study (week 48)</th>
<th>Early Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 (+/− 7 days)</td>
<td>12 (+/− 14 days)</td>
<td>24 (+/− 14 days)</td>
</tr>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>History</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Adherence Questionnaire</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Instruct to Increase Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LABORATORY EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
</tr>
<tr>
<td>Chemistries</td>
<td>1mL</td>
<td>1mL</td>
<td>1mL</td>
</tr>
<tr>
<td>Fasting Lipids (Appendix II)</td>
<td>2 mL</td>
<td>2mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Urinalysis (dip only)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Fasting Serum Storage, Future Inflammatory Markers, Secondary Lipid Markers (Appendix II)</td>
<td>12mL</td>
<td>12mL</td>
<td>12mL</td>
</tr>
<tr>
<td>Beta HCG (serum/urine)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>VIROLOGY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA</td>
<td>1 to 4 mL</td>
<td>1 to 4 mL</td>
<td>1 to 4 mL</td>
</tr>
<tr>
<td>IMMUNOLOGY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>2mL</td>
<td>2mL</td>
<td></td>
</tr>
<tr>
<td>PHARMACOLOGY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC/MS/MS</td>
<td>3mL</td>
<td>3mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (ml)</td>
<td>1 mL</td>
<td>20-23 mL</td>
<td>20-23mL</td>
</tr>
</tbody>
</table>
1. Evaluations should be completed within 30 days prior to study entry. **Subjects are required to have 2 values of LDL-cholesterol ≥ 130 mg/dL (fasting if calculated; non-fasting if directly measured) within the previous 6 months within 30 days prior to screening with at least one of the measurements within 30 days prior to screening and after documented efforts by the site to modify diet and other risk factors (see Appendix III).** Hepatitis BsAg testing should be done if the subject has no prior evidence of positive HepBsAb. HepC RNA should be done in subjects who are Hepatitis CAb positive.

2. Height, weight, and vital signs. Physical exam will include a neuromuscular assessment.


4. Complete blood count, cell differential, platelet count. Assays may be performed at any **CLIA (Clinical Laboratory Improvement Amendments Act, 1988)** licensed laboratory.

5. Indirect bilirubin, direct bilirubin, AST, ALT, electrolytes, glucose, BUN, creatinine, amylase, creatinine kinase, albumin. Assays may be performed at any CLIA licensed laboratory.

6. Includes total cholesterol, direct LDL cholesterol, triglyceride, and HDL cholesterol. Subjects must be fasting, limiting consumption to only water and required medications for at least 8 hours prior to blood collection. Ship frozen serum samples in Real-Time (no less frequently than once per week) to the P1063 Central Metabolic Laboratory.

7. Collect first morning void in a sterile container without preservatives. Refrigerate urine after collection. Prepare ten (1 mL) aliquots and freeze. Ship samples monthly as per the Laboratory Processing Chart, available on the P1063 web page. **If unable to collect at entry, samples can also be collected at week 4.**

8. Serum Storage for Future Inflammatory Marker and Secondary Lipid Marker Testing. Subjects must be fasting, limiting consumption to only water and required medications for at least 8 hours prior to blood collection. Frozen serum samples are prepared as per the Laboratory Processing Chart and shipped monthly to the respective NIAID or NICHD IMPAACT Specimen Repositories.

9. Pregnancy test must be negative.

10. The laboratory that is performing the HIV-1 RNA can utilize any FDA-cleared (approved) method, as directed by the requesting physician. A single method should be employed for a particular subject throughout the entire protocol if possible (i.e., do not shift between kit methods for any particular study subject). The HIV-1 RNA results should not be reported as “greater than a particular value”. Instead, the results should be reported with an actual endpoint value. Note: 1mL to 4mL of blood should be collected and processed, depending on what HIV RNA method is used.

11. Basic lymphocyte phenotyping, including CD3/CD4, CD3/CD8 should be performed in a laboratory that is duly certified by both the CLIA and the Division of AIDS Immunology Quality Assessment (IQA) programs.

12. See Appendices IA-IB for each dose escalation scenario. Confirm toxicity lab results prior to escalating dosage. All subjects will remain on study for 48 weeks.

13. If Early Discontinuation occurs after 24 weeks, the following labs will not be required if they were completed within the past month: hematology, lipids, secondary lipid endpoints, HIV RNA, lymphocyte subsets, or serum storage.

15. For insufficient blood draws, priorities are as follows:
   1. Safety (hematology, chemistries)
   2. Fasting lipid studies
   3. Pharmacology
   4. Serum Storage
   5. Virology
   6. Immunology
APPENDIX IC

SCHEDULE OF EVALUATIONS:

For subjects who discontinue study provided atorvastatin (register subject to Step 3)

For subjects who discontinue study provided atorvastatin due to DRUG RELATED TOXICITY

<table>
<thead>
<tr>
<th>Event</th>
<th>Q 3 months (+/- 4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>x</td>
</tr>
<tr>
<td>History</td>
<td>x</td>
</tr>
<tr>
<td>Hematology</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Chemistries</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Fasting Lipids</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (mL)</td>
<td>4.0 mL</td>
</tr>
</tbody>
</table>

For subjects who discontinue study provided atorvastatin due to PREGNANCY

<table>
<thead>
<tr>
<th>Event</th>
<th>Q 3 months (+/- 4 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone Call</td>
<td>x</td>
</tr>
</tbody>
</table>

1. Height, weight, and vital signs. Physical exam will include a neuromuscular assessment.
2. Current medical history, diagnosis, and symptoms.
3. Complete blood count, cell differential, platelet count. Assays may be performed at any CLIA licensed laboratory.
4. Indirect bilirubin, direct bilirubin, AST, ALT, electrolytes, glucose, BUN, creatinine, amylase, creatinine kinase, albumin. Assays may be performed at any CLIA licensed laboratory.
5. Includes total cholesterol, direct LDL cholesterol, triglyceride, and HDL cholesterol. Subjects must be fasting, limiting consumption to only water and required medications for at least 8 hours prior to blood collection. Ship frozen serum samples in Real-Time (no less frequently than once per week) to the P1063 Central Metabolic Laboratory. Fasting lipids need to be done only at the first visit after discontinuing atorvastatin.
6. For subjects who experience a drug related toxicity requiring drug discontinuation, visits will occur every 3 months until study week 48 or resolution of toxicity, whichever is later.
7. Subjects who become pregnant will ONLY receive a telephone call every 3 months until pregnancy outcome is determined.
APPENDIX II

INSTRUCTIONS FOR THE PROCESSING, STORAGE, AND SHIPPING OF SERUM SPECIMENS FOR REAL TIME FASTING LIPID AND FUTURE INFLAMMATORY MARKER /SECONDARY LIPID MARKER TESTING

1.0 OVERVIEW OF LIPID/INFLAMMATORY MARKER EVALUATIONS

1.1 REAL TIME TESTING FOR FASTING LIPID PROFILE

Specimens for the lipid profile will be collected fasting, processed, and shipped in real-time to the P1063 Central Metabolic Laboratory (Quest Diagnostics—Baltimore).

1.2 STORED SERUM FOR FUTURE INFLAMMATORY MARKER/SECONDARY LIPID MARKER TESTING

Blood will be collected fasting, processed, and stored for future Inflammatory Marker/Secondary Lipid Marker testing. Frozen serum will be shipped monthly to the clinical site’s respective NIAID or NICHD IMPAACT Central Specimen Repository for storage. At the end of the study these samples will be withdrawn from the Central Specimen Repositories and sent to the designated testing laboratory.

2.0 SPECIMEN COLLECTION, PROCESSING, AND STORAGE

2.1 Real Time Fasting Lipid Profile (Total Cholesterol, direct LDL cholesterol, HDL cholesterol and triglycerides):

Subjects must be fasting limiting consumption to only water and required medications for at least 8 hours prior to blood collection.

Collect at least 2 mL of blood in an SST tube (red tiger top serum separator tube; no anticoagulant). Invert tube 5 times immediately after collection to initiate clotting. Allow blood to clot at room temperature (18°C-24°C) in a vertical position for 30 minutes. Centrifuge at 1,100-1,200 g for 10 minutes within 1 hour of specimen collection. Store centrifuged SST at refrigerator temperatures up to 8 hours prior to preparation of frozen serum aliquots. Prepare two 0.5-mL aliquots of serum in cryovials and freeze at -70°C. Label each aliquot as noted below with the LDMS spec. code BLD/SER/SST. Ship 2 aliquots in real time to
the P1063 Central Metabolic Laboratory along with the P1063 Real Time Lipid testing custom requisition (see section 3.1 below). Ship samples for testing no less frequently than once per week.

2.2 Stored Serum for Future Inflammatory Marker/Secondary Lipid Marker Testing

Subjects must be fasting, limiting consumption to only water and required medications for at least 8 hours prior to blood collection.

Collect at least 8.5 to 12 mL of blood in SST tubes (red tiger top serum separator tube; no anticoagulant) (See Appendix I for specimen volume requirements per the specific week in study). Note: Blood for Serum Storage can be collected in the same SST tubes as are used for Real Time Lipid Testing (see section 2.1 above). Invert tube 5 times immediately after collection to initiate clotting. Allow blood to clot at room temperature (18°C-24°C) in a vertical position for 30 minutes. Centrifuge at 1,100-1,200 \times g for 10 minutes. within 1 hour of specimen collection. Store centrifuged SST at refrigerator temperatures up to 8 hours prior to preparation of frozen serum aliquots. Prepare twelve 0.5-mL aliquots of serum in cryovials and freeze at -70°C. Label each aliquot as noted below with the LDMS specification code BLD/SER/SST. Ship all serum aliquots on a monthly basis to the site’s designated NIAID or NICHD IMPAACT Central Specimen Repository.

3.0 SPECIMEN TRACKING, LABELING, AND SHIPPING

All specimens should be logged into the LDMS by the processing laboratory and computer labels should be generated that have the LDMS spec. number, labeled with Patient Identification Number (PID), Protocol Number or Study Identification Number (SID), Visit Identification Number (VID), date and time of draw, and the LDMS spec. code.

3.1 Real Time Lipid Serum Aliquot Shipment to the P1063 Central Metabolic Laboratory:

Each registered clinical site must contact the P1063 Central Metabolic Laboratory (Quest Diagnostics—Baltimore, MD) at least 2 weeks prior to shipment of their first P1063 Real Time Lipid specimen. Contact the Quest Diagnostics’ Special Studies Service Representative (Larry Hirsch) at 410-536-1622 in order to arrange for an account to be created to allow for appropriate specimen receipt and result reporting to a particular clinical site. A custom P1063 Real Time Lipid testing requisition will be provided to the clinical site to use with specimen submission.
The clinical site specific P1063 custom requisition form includes the demographic data entry fields (e.g., PID/SID, Date/Time of Specimen Collection, etc.) that must be completed by site personnel when sending the study subject’s specimen aliquots.

Ship two 0.5 mL serum aliquots for each subject’s blood collection event for the Real Time Lipid panel (total cholesterol, direct LDL cholesterol, HDL cholesterol and triglyceride). Ship serum aliquots on dry ice via overnight courier.

The site will pack and ship the box according to IATA regulations. The shipment must contain an LDSM diskette, manifest, and boxmap. Ship samples via overnight courier on a Monday through Thursday schedule. Do not ship on days that occur before a national holiday.

The site must FAX a notification to the P1063 Central Metabolic Laboratory (Quest Diagnostics—Baltimore at 410-536-1474) prior to shipping using the “IMPAACT Specimen Shipment Notice” from the IMPAACT website http://IMPAACT.s-3.com/specrepos.htm. The laboratory can be contacted by telephone at 410-247-9100 ext 2270.

Ship package to:

Quest Diagnostics
Retrovirology Dept
Attn: Dr. William Meyer/Denise Bopst
1901 Sulphur Spring Road
Baltimore, MD 21227
Phone: 410-536-1713
FAX: 410-536-1474
Email: BALresearch@questdiagnostics.com
larry.a.hirsch@questdiagnostics.com

Note: This is LDMS Lab 33

3.2 Shipping of Stored Serum for Future Inflammatory Marker/Secondary Lipid Marker Testing to the Respective NIAID and NICHD IMPAACT Central Specimen Repository:

All specimens must be labeled according to the IMPAACT specifications as described above and entered into the LDMS.

Sites should send specimens to their respective Central Specimen Repository once a month following the schedule listed in the “Instructions for Shipping to the
Repository” document available on the Web at http://IMPAACT.s-3.com/specrepos.htm. At least one week prior to shipping, sites should order shipping containers from the Central Specimen Repository using the Shipping Container Order Form on the Web at http://IMPAACT.s-3.com/specrepos.htm. Ship only full boxes of specimens to the Central Specimen Repository. Boxes may be filled with specimens from multiple protocols. Ship specimens on dry ice via overnight courier. Shipments to the Central Specimen Repository should be limited to Monday through Wednesday of your designated week. Do not ship the day before a holiday. The Central Repository is closed on weekends and holidays and will not be able to receive specimens. Please call the Central Repository around a holiday to determine the available days for shipping.

When ready to ship specimens, the site will call the Central Repository to request shipping materials to provide the name, address, and phone number of the site contact person.

The site will pack and ship the box according to IATA regulations. The shipment must contain an LDSM diskette, manifest, and boxmap. Prior to shipping, ensure that the specimens, manifest, and boxmap match. Boxes with greater than 10% discordance will be returned to the site for reconciliation. Returned boxes will be reported to the DMC on the Problem Shipping Form.

The site must FAX a notification to the Central Repository prior to shipping using the “IMPAACT Specimen Shipment Notice” located on the IMPAACT website: http://IMPAACT.s-3.com/labs.htm.

Upon request for shipment from the Protocol Team at the end of the study, stored serum specimens will be sent from the Central Repositories to the testing laboratory.

4.0 INFORMATION TO ACCOMPANY SHIPMENT OF SERUM SPECIMENS.

4.1 Real Time Lipid Serum Aliquots Shipment to the P1063 Central Metabolic Laboratory:

Include a completed site specific P1063 custom test requisitions along with each study subjects specimen.

The shipment must also contain an LDMS diskette, manifest, and boxmap.

4.2 Stored Serum for Future Inflammatory Marker/Secondary Lipid Marker Testing Shipment to the Respective IMPAACT Central Specimen Repository.
4.21 For NIAID Clinical Site Specimens

The shipment must contain an LDMS diskette, manifest, and boxmap.

The paperwork should not be placed in the dry ice, but between the inner container and outer box.

The samples and appropriate documentation should be sent to:

John C. Ward, Jr.
Biomedical Research Institute
12264 Wilkins Avenue, Bay F
Rockville, MD 20852
Phone: 301-881-7636
FAX: 301-770-9811
e-mail: brirepository@aol.com

Prior to shipment, please fax the IMPAACT Specimen Shipment Notice to John C. Ward at 301-770-9811 (a copy should also be included with all shipments in addition to the other paperwork).

- If the fax does not seem to be transmitting, please call the laboratory at 301-881-7636 to advise that a shipment has been sent and provide the airway bill number.
- Any questions related to specimen handling, shipping, or identification should be directed to John C. Ward at 301-881-7636.

Shipments may occur Monday through Wednesday only by overnight courier service. Please call the laboratory around holiday times to check available days for shipping.

4.22 For NICHD Clinical Site Specimens

The shipment must contain an LDMS diskette, manifest, and boxmap.

The paperwork should not be placed in the dry ice, but between the inner container and outer box.

The samples and appropriate paperwork should be sent to:

Hannah Elson
Fisher Biological Services
Lab 243
625 Lofstrand Lane
5.0 REPORTING OF REAL TIME LIPID RESULTS

Each clinical site will receive their subject’s Real Time Lipid results via FAX within one week of specimen receipt at the P1063 Central Metabolic Laboratory (Quest Diagnostics—Baltimore). If there are any issues with laboratory result reporting, please contact the Quest Diagnostics’ Special Studies Service Representative (Larry Hirsch) at 410-536-1622 for assistance, Monday through Friday.
APPENDIX III

SITE RESOURCES FOR NUTRITIONAL COUNSELING

The National Cholesterol Education Program (NCEP) has recommended that children with elevated low-density lipoprotein (LDL) cholesterol levels be treated primarily by modification of diet. The initial recommended approach is to use the NCEP step 1 diet. This diet provides calories and nutrients that support normal growth and development but limits saturated fat and total fat intake to no more than 10 and 30 percent of total calories, respectively, and cholesterol intake to no more than 100 mg per 1,000 kcal per day, to a maximum of 300 mg. The protocol team recognizes that proper counseling and management of patients on the NCEP step 1 diet is very difficult without ongoing counseling and patient supervision by a nutritionist. The following resources are suggested as nutritional counseling resources for sites without a nutritionist available as alternatives to comply with inclusion criterion 4.17, however other appropriate counseling is acceptable. In addition to dietary modifications, patients should be counseled regarding smoking cessation (if applicable), weight reduction (if obese), and increased physical activity.

Nutritional counseling resources:

A. Utilization of a food diary to identify foods high in saturated fats to be avoided. *(American Family Physician, Vol 61, No 3, February 1, 2000, page 4 http://www.aafp.org/afp/20000201/675.html*).

B. Use of patient education materials listed on the National Cholesterol Education Program website and available at no or minimal cost (http://hin.nhlbi.nih.gov/cholmonth/). These resources include: *Questions and Answers About the New Food Label, Be Heart Smart: Eat Foods Lower in Saturated Fat and Cholesterol, Heart Healthy Home Cooking: African American Style, and Delicious Heart Health Latino Recipes.*

C. Use of the individual food pyramid calculator on the U.S. Dept. of Agriculture web site (http://www.mypyramid.gov/).

D. Referral to a registered dietitian using the ‘Find a Nutrition Professional’ link on the American Dietetic Association’s website (http://www.eatright.org).
APPENDIX IV
DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC ADOLESCENT AIDS CLINICAL TRIAL
GROUP (IMPAACT)
SAMPLE INFORMED CONSENT

For protocol:

PHASE I/II SAFETY AND EFFICACY INVESTIGATION OF ATORVASTATIN FOR TREATMENT OF INCREASED LDL-CHOLESTEROL IN HIV-INFECTED CHILDREN, ADOLESCENTS, AND YOUNG ADULTS
P1063, Version 2.0, dated May 28, 2010

SHORT TITLE FOR THE STUDY: SAFETY AND EFFICACY OF ATORVASTATIN FOR TREATMENT OF INCREASED LDL CHOLESTEROL

INTRODUCTION

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

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

WHY IS THIS STUDY BEING DONE?

This study is being done to study the safety of Lipitor (atorvastatin is the generic name for Lipitor), a medicine that lowers cholesterol, in HIV-infected children and adolescents, and to find out how well Lipitor lowers the LDL cholesterol levels in children and adolescents who are on anti-HIV treatment (medicines that decrease the level of HIV in the blood).

High levels of LDL cholesterol can increase the risk of developing cardiovascular (heart) disease. Anti-HIV medicines have been found to increase LDL cholesterol in some people. Sometimes, changes in diet and exercise can lower levels of LDL cholesterol in people’s blood. Lipitor is a type of medicine used to lower cholesterol in people who have tried changing their diet and exercising, but still have high cholesterol levels. It is FDA approved in adults, and in uninfected children in doses of 10mg and 20mg. It has not been studied in HIV-infected children. One type of anti-HIV medicines, protease inhibitors, can increase the level of Lipitor in your/your child’s
blood. This study will look at the effect Lipitor can have on other types of cholesterol and fats in
the blood. The study will also look how the anti-HIV medications you’re taking/your child is
taking can affect blood levels of Lipitor and how they can affect the level of HIV in your/your
child’s blood.

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

Screening:

If you decide/allow your child to join this study, and you sign this consent form, the following
procedures will be done to see if you/your child can participate in this study:

A medical history will be taken, which will include questions about your/your child’s health and
what symptoms, medications, and illnesses you have/your child has had in the past. A special
blood test may be done to see if you/your child is infected with Hepatitis. Hepatitis is a type of
liver disease which causes the liver to swell, yellowing of the skin and eyes, and liver failure. A
physical exam will be done, which will include height, weight, vital signs, temperature, blood
pressure, pulse respiratory rate, and neuromuscular exam (a physical exam to check your muscles
and nerves). A pregnancy test will be done. A small amount of urine or blood (less than 1
teaspoon) will be taken for this test. You/your child will be told the test result as soon as it
is available. If you are/your child is pregnant, you/your child cannot be in this study.

Information collected in this study (including for screening for this study) that is related to
pregnancy will not be shared with parents (or other adults consenting for your child’s
consent) without permission of the your child and study staff will ensure that the your child
is referred to his or her doctor for appropriate counseling and management if your child
tests positive for pregnancy.

You/your child will have about 1 ½ teaspoons of blood taken to check the amount of LDL
cholesterol (a type of fat) in the blood, to check how well your/your child’s immune system
is working, to check the amount of HIV in your/your child’s blood, and for other routine
tests. You/your child should not eat for 8 hours before these tests. You/your child should
drink water and continue taking anti-HIV medications during the 8 hour fasting period.
You will be informed of results of routine blood tests and screening evaluations. If you
agree to it, a little more than ½ tablespoon of blood will be drawn and stored for future
IMPAACT approved, HIV-related research.

During Study:

If you are/your child is eligible for this study, you/your child will come to the clinic at least 8
times during the study, over 11 months. The first study visit will be within 4 weeks of the
screening visit. At each visit, a medical history will be taken, which will include questions about
you/your child’s health and what symptoms, medications and illnesses you/your child have had in
the past and a physical exam. Blood will be drawn at 4-8 of these visits to check the amount of
HIV in your/your child’s blood, to check the amount of cholesterol in your /your child’s blood, to check how your body is responding to the study medicine, to see how well your immune system is working and for other routine tests; urine will be taken to check the amount of study medicine in your body. At 4 of these visits, you/your child should not eat for 8 hours before these tests. You/your child should drink water and continue taking anti-HIV medications during the 8 hour fasting period. You will be informed of results of routine blood tests. The amount of blood drawn at the different study visits will vary from 1 to 5 teaspoons. You/your child will be asked questions about dietary habits, medication taking, and any missed doses of anti-HIV medications. You/your child will be offered counseling on proper nutrition and exercise.

You/your child will be given a dose of 10 mg of Lipitor to take each day, beginning at the first visit on study. After you’ve/your child has been taking the 10 mg dose of Lipitor for 4 weeks, you/your child will have blood drawn to see if the cholesterol level in your/your child’s blood has changed. If it has decreased to 110mg/dL, or by at least 30% you/your child will continue on the 10 mg dose and will continue to be monitored for the rest of the study. If it has not decreased, your/your child’s dose of Lipitor will be increased to 20 mg per day. If you reach/your child reaches a dose of 20 mg per day and the cholesterol level in your/your child’s blood has still not decreased to 110mg/dL, or by at least 30% you/your child will not increase the dose again and will be monitored until the end of the study.

You/your child must continue to take your anti-HIV medications during the study as prescribed by your/your child’s HIV care provider. If your/your child’s HIV care provider changes your/your child’s anti-HIV medications during the study, you/your child can still have the study drug Lipitor. If you/your child’s HIV care provider changes you/your child’s anti-HIV medications, you/your child must inform the study staff.

You/your child will be tested for pregnancy again during study visits. A small amount of urine or blood (less than 1 teaspoon) will be taken for this test. You/your child will be informed of the test result as soon as it is available. If you are/your child is pregnant, you/your child can not receive the study drug Lipitor. If you think you/your child may be pregnant at any time during the study, tell the study staff right away. If you are/your child becomes pregnant, you/your child will be taken off the study. The study staff will talk to you about your choices. The study staff will contact you/your child by phone every 3 months until you/your child is no longer pregnant.

For NIAID Sites Only:

Storage of Blood & Urine Samples

Some of your/your child’s blood and urine will be stored (with usual protectors of identity) and used for future IMPAACT-approved, HIV-related research. About 1 tablespoon of blood and 2 teaspoons of urine will be taken for this purpose. These tests are a part of the study and will be done at a later date.
Your/your child’s samples will be stored at a special laboratory facility. Only approved researchers will have access to them. People who work at the facility will also have access to your/your child’s samples to keep track of them. These people won’t have information that directly identifies you/your child. Your/your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your child’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your/your child’s samples will be stored.

The researchers do not plan to contact you or your/your child’s regular doctor with the results of studies done using your/your child’s stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your/your child’s medical care. If the researchers decide that the result of a certain study provides important information for your/your child’s medical care, your/your child’s study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your/your child’s samples stored for future research studies. You/your child can still participate in this study even if you make this decision. You may withdraw your consent for the storage and use of your/your child’s samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

I agree to allow my/my child’s blood and urine samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes  __________ No  __________ Date

FOR NICHD Sites:

Some of your/your child’s blood specimens collected as part of this study will be stored for testing at a later date as part of this study. There is a separate consent form to explain this and get your/your child's consent.

OTHER INFORMATION:

The information collected in this study may be used for other IMPAACT-approved HIV-related research.

Information provided throughout this study about pregnancy will not be shared with parents or caretakers of adolescent participants.
HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 40 people will take part in this study.

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

You/your child will be in this study for 48 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 cancelled by the Office for Human Research Protections (OHRP), National Institutes of Health (NIH), the drug company supporting this study, a safety and monitoring board, or the site’s Institutional Review Board (IRB) recommends that the study be stopped early. An IRB is a committee that watches over the safety and rights of research subjects.

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

- continuing the study drug(s) may be harmful to you/your child
- you/your child need(s) a treatment that you/your child may not take while on the study
- you are/your child is not able to take the study drug as required by the study
- you/your child becomes pregnant
- you/your child stops taking antiretroviral medicines

During the study:
If you/your child must permanently stop taking Lipitor before your/your child’s study participation is over, the study staff will discuss other options that may be of benefit to you/your child. If you stop/your child stops taking Lipitor or anti-HIV medicines before the end of the study, you/your child will be asked to come to the clinic for a final study visit. At this visit, you/your child will have a medical history, a physical examination, a pregnancy test, a urine test, some routine blood tests, and special blood tests to check how your body responded to the study medicine, to see how well your immune system is working. If you stop/your child stops taking Lipitor because you/your child had a bad side effect from the Lipitor, you/your child will be asked to come to the clinic every 3 months until the end of the study or until the side effect has resolved. At these visits, a physical examination, medical history, and special blood tests will be done.

After the study:
After you/your child have/has completed study participation, the study will not be able to continue to provide you/your child with the Lipitor that was provided during the study. If continuing to take this or a similar cholesterol-lowering medication would be of benefit to you/your child, the study staff will discuss how you may be able to obtain it.

WHAT ARE THE RISKS OF THE STUDY?

Use of Lipitor
Lipitor has been tested in animals and in humans, and is approved by the FDA. These studies show that the study drug appears to be safe in the doses we will be using in this study. These studies involved routine safety tests to see if there were any bad reactions to the drug. Lipitor sometimes causes muscles or joints to become sore. If this happens, it is important to tell clinic staff about your symptoms. Lipitor can rarely cause a condition called hepatitis, which is swelling of liver, yellowing of the skin and eyes, and liver failure. Lipitor can rarely cause a condition called rhabdomyolysis, which is a breakdown of muscle that can cause kidney damage. Other problems that have been caused by Lipitor include headaches, rash, abdominal pain, constipation, diarrhea and nausea. All these problems are uncommon.

Risks of Drawing Blood
You/your child may feel faint or may feel some discomfort while having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of infection forming where the needle goes into the skin to take blood.

ARE THERE RISKS RELATED TO PREGNANCY?

Lipitor is unsafe for unborn babies. If you are a female and are having sex that could lead to pregnancy, you must agree not to become pregnant from the time you start taking the study drug until 4 weeks after the last study visit or the time at which you stop taking the study medication. If you are a male and are having sex with a partner who can become pregnant, you must agree to use condoms from the date you start taking the study drug until 4 weeks after the last study visit or the time at which you stop taking the study medication. If you/your child become pregnant while on this study, you/your child should seek treatment from you/your child’s medical provider.

Because of the risk involved, you and your partner must use at least two method of birth control from the list below. You may choose any of these birth control methods:
- male or female condoms with a cream or gel that kills sperm
- diaphragm with a cream or gel that kills sperm, or cervical cap with a cream or gel that kills sperm
- intrauterine device (IUD)
• hormonal birth control drugs that prevent pregnancy given by pills, shots or placed on or under the skin.

Lipitor can increase the blood levels of some oral birth control pills by 20-30%. On the other hand, protease inhibitors can make hormonal birth control pills less effective. If you are taking a protease inhibitor, hormonal birth control alone may not be considered adequate.

If you have had your uterus or ovaries removed or if you have had a tubal ligation (tubes tied), or if your partner has had a successful vasectomy, you do not need to use other methods of birth control.

All birth control methods listed above except condoms do not reduce the risk of giving HIV to someone else. HIV-infected individuals should use a birth control method that includes condoms to keep from giving HIV to someone else.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take(s) part in this study, there may be a direct benefit to you/your child, but no guarantee can be made. It is also possible that you/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BEIDES THIS STUDY?

Instead of being in this study you have the choice of:

• treatment with prescription drugs available to you/your child
• treatment with experimental drugs, if you/your child qualify(ies)
• no treatment

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

WHAT ABOUT CONFIDENTIALITY?

To help us protect your/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, 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 records include the **Office for Human Research Protections (OHRP)**, the site IRB (insert name of site IRB), the National Institutes of Health, study staff, study monitors, drug companies supporting the study, 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 you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

**WHAT ARE THE COSTS TO ME/MY CHILD?**

There is no cost to you for your/your child’s study visits, examinations, or blood tests. There is no cost to you for your/your child’s study medicines, Lipitor. Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you/your child is/are taking part in a research study. The study does not pay for you/your child’s anti-HIV medications.

**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. There is no program for compensation either through this institution or the National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.

**WHAT ARE MY/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 participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are 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/MY CHILD HAS QUESTIONS OR PROBLEMS?**
For questions about this study or a research-related injury, contact:

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

For questions about your/your child’s rights as a research 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)</td>
<td>Witness’s Signature and Date (As appropriate)</td>
</tr>
</tbody>
</table>
APPENDIX V

INFORMATION SHEET-(NICHD SITES ONLY)

IMPAACT P1063 Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol In HIV-Infected Children, Adolescents, and Young Adults, Version 2.0, dated May 28, 2010

This information sheet is to tell you about a change that has been made in how the special laboratory called a specimen repository will be managed.

As part of IMPAACT P1063, you agreed to have some of your blood or your child’s blood stored in the repository of the National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH).

NICHD has a repository because although researchers can learn a lot from a study, as time goes by sometimes, the tests that they use get improved or brand new tests are developed, and more can be learned with these better tests. When study volunteers consent, like you did, to put specimens in the repository, and also consent to have the researchers do new tests on the specimens – at some time in the future after their time in the study is ended - researchers might learn new information by being able to use the stored specimens.

We are very grateful for your trust and willingness to help researchers keep learning more from the time you gave to the study.

The change we are making is in the group of people who oversee your stored specimens to make sure that your rights and privacy are protected in any future studies.

Before, the Institutional Review Board (IRB) at Westat, a data and operations center, was responsible for reviewing each future study.

Now we have a new procedure, approved by the NICHD IRB, that will have NICHD program staff review each future study. These NICHD staff members are very knowledgeable of the rules and procedures for oversight of specimen repositories, and they will be responsible for ensuring that your rights and privacy are protected.

If you have any questions about this change, you may contact:

[Add site research staff contact information here.]

NICHD program staff and everyone working on this study thank you for all you have done to make it successful.
APPENDIX VI

FACT SHEET and TEMPLATE CONSENT FORM for
Specimen Storage at Repositories funded by the
National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET (Version 2.0- 29 November 2005)

IMPAACT P1063 Phase I/II Safety and Efficacy Investigation of Atorvastatin for
Treatment of Increased LDL Cholesterol In HIV-Infected Children, Adolescents, and
Young Adults, Version 2.0, dated May 28, 2010

When your child joins this NICHD sponsored Study, you will be asked to give permission
for having some specimens that the doctor or nurse will take from your child’s body saved
in a repository. (A repository is a special laboratory with freezers where specimens like
blood or tissue cells and body fluids that are taken from you during a study are kept. Your
child’s name will not be on these specimens, only a special study number. The people who
run the repository laboratory will not know your child’s name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get
better or brand new tests are developed, and more can be learned with these better or new
tests. When study volunteers consent to put specimens in the repository and consent to the
researchers doing new tests on the specimens at some time in the future after their time in
the study is ended, researchers can learn new information by being able to use the
specimens. Your child’s rights and privacy will be protected in any of these new studies.

How will my child’s privacy be protected?

The only record that your child participated in this NICHD sponsored study is at the clinic
where it is kept separate from your child’s health records and locked away.

Your child’s specimens in the repository will not have your child’s name on them. The
specimens will have a special study code. It will be the same code that is on your child’s
information in the NICHD sponsored Study from your child’s interviews and
examinations. Again, none of this information will have your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in
the future, he or she will write up the idea and it will have to be approved by a committee
to make sure the research is worthwhile. If the idea is approved, then coded specimens and
coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my child’s specimens?

You will not receive the results of research done with your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child’s specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child’s care right now, but they may be helpful to people like your child in the future. Your child’s specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my child’s specimens?

All of the studies to be done in the future on your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD Study has to be reviewed to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my child’s specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.
As part of this study (Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol in HIV-infected Children, Adolescents, and Young Adults), your child is being asked to have some blood and urine taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child’s time in this NICHD sponsored Study.
You do not have to agree to store your child’s specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child’s specimens.

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.

TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child’s DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test.
I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

<table>
<thead>
<tr>
<th>Parent or Legal Guardian Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

<table>
<thead>
<tr>
<th>Participant Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your child’s DNA) either protects them or puts them at greater risk. It may be that researchers use some of your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child’s genetic makeup.
I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________  ___________________________  ___________
Parent or Legal Guardian Signature    Witness Signature    Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________  ___________________________  ___________
Participant Signature    Witness Signature    Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

___________________________  ___________________________  ___________
Parent or Legal Guardian Signature    Witness Signature    Date
APPENDIX VII

FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at the Repository of the National Institute of Child Health and Human Development (NICHD)

IMPAACT P1063 Phase I/II Safety and Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol In HIV-Infected Children, Adolescents and Young Adults, Version 2.0, dated May 28, 2010

YOUTH FACT SHEET

When you join this NICHD sponsored Study, you will be asked to consent to having some specimens that the doctor or nurse will take from your body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during the study are kept. Your name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your rights are being protected.

How will my privacy be protected?

The only record that you participated in this NICHD sponsored Study is at your clinic where it is kept separate from your health records and locked away.

Your specimens in the repository will not have your name on them, only a special study code. It will be the same code that is on your information in the NICHD sponsored Study from your interviews and examinations. Again, none of this information will have your name on it.
How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my specimens?

You will not receive the results of research done with your specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your specimens may not be ready for many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your care right now, but they may be helpful to people like you in the future. Your specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my specimens?

All of the studies to be done in the future on your specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the new study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give consent for the new study.

I gave my consent to testing my specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from you in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.
What type of research will be done with my specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests or drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study you are being asked to have some blood taken from you. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your time in this NICHD sponsored Study.

You do not have to agree to store your specimens for future tests to take part in this study. You will not lose any benefits to which you are entitled if you decide against storing your specimens.

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your DNA).

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test.

I consent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).
What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your DNA) either protects them or puts them at greater risk. It may be that researchers use some of your blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your genetic makeup.

I consent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

___________________________ ___________________________   _________
Participant Signature   Witness Signature   Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone).
If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected for storage in the repository.

___________________________ ___________________________   _________
Participant Signature   Witness Signature   Date