INTENSIVE PHARMACOKINETIC STUDIES OF NEW CLASSES OF ANTIRETROVIRAL DRUG COMBINATIONS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

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

Sponsored by:

The National Institute of Allergy and Infectious Diseases (NIAID)

and

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

IND EXEMPT

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impact.teamp1058A@fstrf.org. Remember to include the subject’s patient identification (PID)
when applicable. The appropriate team member will respond to questions via e-mail with a "cc"
to impact.teamp1058A@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@techres.com or via FAX at (301) 897-1701 or 1-800-418-3544.
- For randomization or enrollment questions, contact the Data Management Center (DMC), Frontier Science & Technology Research Foundation, Inc. (FTSRF) randomization desk at sdac.random.desk@fstrf.org or call (716) 834-0900 x 7301.

Please refer to the IMPAACT website (http://www.impaactgroup.org) and the Protocol Specific
Webpage for all P1058A study-related documents and materials.

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IV. FACT SHEET AND TEMPLATE CONSENT FORM FOR SPECIMEN STORAGE AT THE REPOSITORY OF THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD) - YOUTH FACT SHEET (Version 2.0, dated 11/29/05)
SUMMARY OF CHANGES

P1058A

INTENSIVE PHARMACOKINETIC STUDIES OF NEW CLASSES OF ANTIRETROVIRAL DRUG COMBINATIONS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

All changes in this version appear in boldface type. Major changes are listed below. Editorial changes, corrections of typographical errors, and other changes required to update information that do not affect regulatory issues or subject consent may also be included. Information from Letter of Amendment #1 (October 14, 2009) is included.

1. The Foreword from Version 1.0 has been deleted.

2. The phone number for the DMC randomization desk has been corrected.

3. The Protocol Team Roster has been updated.

4. Schema: The Study Design and Regimens of Interest sections have been updated to add 24-hour intensive pharmacokinetic study for the new regimens of interest that have been added.

5. Schema (Sample Size section) and Section 3.3 have been updated to indicate the target total across all groups, include the definition for evaluable subjects in the context of this study and specify the target total for Version 1.0 and Version 2.0. The section has also been updated to include the Groups for the new regimens of interest and indicate that the Groups in Version 1.0 have been closed as described below.
   • Groups M, N, O, P and Q have been added.
   • Group G has been closed.
   • Group H has been closed.
   • Group I has been closed.
   • Groups J, K and L have been closed due to lack of enrollment.

6. Schema: The Population section has been updated to indicate that subjects are eligible up to the day before their 24th birthday and to add the 24-hour pharmacokinetics.

7. Schema (Population and Regimens of Interest sections), Section 3.0 (sub-sections 3.1 and 3.21) and Section 5.0 have been updated to clarify that subjects must be on a stable regimen of interest for at least 30 days before screening/entry into the study.

8. Schema and Section 5.0: Table 1 has been updated to add the new regimens of interest. The Groups for the regimens of interest in Version 1.0 have been grayed out and a statement that the groups are closed has been added under the table. Additionally,
Group H has been updated to remove the brand names of Viread® and Truvada® as the options for TDF. The footnotes have been updated as described below.

- Footnote 4 was updated to state that it applies to Group H.
- Footnote 5 was added to indicate subjects in Groups P and Q cannot be on H2 blockers and must take RPV with food.
- Footnote 6 was added to provide the medications in Complera™.

9. Schema: The Regimens of Interest section has been updated as described below.
   - The 3rd sentence in the 2nd paragraph has been revised to state that the regimens in Table 1 summarize the entry criteria.
   - The list of regimens of interest has been removed as they are provided in Table 1. The notes about other ARVs have also been removed.
   - The 3rd paragraph has been revised to specify that 12-hr PK was done for Version 1.0, a 24-hr PK will be done in Version 2.0 and the intensive PKs should be performed after the subject has been on ARVs for at least 30 days.

10. Schema (Regimens of Interest section), Section 1.2 3rd paragraph, Section 3.0 (PK Results and Repeat PK sub-section) and Section 8.6 5th paragraph have been updated to remove the formulation information for raltegravir and tenofovir, and to specify the repeat PK guidelines were for Version 1.0, repeat PKs were only performed for certain groups who required dose adjustments after completion of the PK study and repeat PKs for RAL dosing changes were on a case-by-case basis. The repeat PK guidelines for Version 2.0 have also been added.

11. Schema and Section 2.1 have been updated as described below.
   - The primary objectives have been grouped per version.
   - The primary objectives for the maraviroc regimens in Version 1.0 have been updated to indicate that due to lack of enrollment the groups have been closed and analysis will not be done.
   - The primary objectives for the new regimens of interest have been added.
   - The objective “To assess the steady state pharmacokinetics of darunavir/ritonavir administered in older children, adolescents and young adults” was incorrectly listed as a secondary objective in Version 1.0 (Secondary Objective #4 in Schema and Item 2.24). It has been moved to the section for primary objectives for Version 1.0 and as Item 2.15. In addition, the objective has been updated to clarify that the steady state pharmacokinetics that will be assessed is darunavir/ritonavir BID.

12. Section 1.0: Table 2 - Current FDA Labeling for Antiretroviral Drugs in Pediatrics, has been updated as described below.
   - FDA-approved age labeling has been updated for Emtricitabine, Lamivudine, Tenofovir, Nevirapine, and Ritonavir.
   - FDA-approved weight has been updated for Darunavir.
• Addition of Rilpivirine.
• Addition of FPV, which is another abbreviation for Fosamprenavir.
• Removal of Zalcitabine, Delavirdine and Amprenavir, which are no longer manufactured.
• The statement “investigational in children” has been removed for Tenofovir, Etravirine, Indinavir and Raltegravir.

13. Section 1.0: The paragraph about ARVs that have been approved has been deleted as the information is obsolete and the current information is shown in Table 2.

14. Section 1.0: The 2nd paragraph has been updated as described below.
• The 5th sentence has been updated to state that results from P1058 Version 1.0 have been reported and to correct a grammatical error in the author list.
• A 6th sentence was added to state that results from P1058 Version 2.0 were recently reported.

15. Section 1.1: The sub-section “Results from Version 2.0 of P1058” has been updated as described below.
• The title of the sub-section has been changed from “Preliminary Results from Version 2.0 of P1058” to “Results from Version 2.0 of P1058”.
• The 1st paragraph was deleted except for the 1st sentence, which was revised to indicate that P1058 Version 2.0 is no longer a current study.
• The 2nd, 3rd and 4th paragraphs were deleted.
• The summary of the results recently reported for P1058 Version 2.0 has been added.

16. Section 1.1: The sub-section “Rationale for Regimens of Interest for P1058A and Design Changes” has been updated as described below.
• The 5th sentence in the 1st paragraph has been updated to specify that the BSA stratification did not affect the results in P1058 Version 2.0.
• The 7th sentence in the 1st paragraph has been updated to indicate that the upper limit of the age range has been modified to < 24 years of age.
• The 2nd sentence of the 3rd paragraph has been updated to specify that a 12-hr PK was done in P1058A Version 1.0. The phrase about site preference has also been removed.
• A 3rd sentence has been added to the 3rd paragraph to explain the Groups in P1058A Version 1.0 have been closed.
• A 4th sentence has been added to the 3rd paragraph to explain the regimens of interest in P1058A Version 2.0 involve ARVs administered once daily and 24-hr PK analysis will be done.
• The 1st sentence of the 4th paragraph has been updated to specify the evaluation done in P1058 Version 2.0 and clarify that the pharmacokinetics of antiretroviral drug combinations with limited data in the pediatric and
adolescent populations but are used by physicians to treat pediatric and adolescent patients be evaluated in P1058A.

17. Section 1.1 (Sub-sections titled “Rationale for Regimens of Interest for P1058A and Design Changes”, 3rd paragraph and “Withdrawal of the IND for P1058”, 1st sentence of 4th paragraph), Section 4.6 (1st sentence of 1st paragraph), Section 4.4 (3rd sentence of 1st paragraph) and Section 12 have been updated to change Regulatory Compliance Center to Regulatory Support Center, change RCC to RSC and to update the website address to http://rsc.tech-res.com/ as applicable.

18. Section 1.1: Sub-section titled “Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) Regimen of Interest” has been updated as described below.
   - The 1st sentence in the 1st paragraph has been updated to state that etravirine is a recently available NNRTI.
   - The 3rd sentence in the 1st paragraph has been updated to indicate that ETV now has a 200 mg tablet available.
   - The 9th sentence in the 1st paragraph has been updated to clarify that FDA dosing for DRV is by weight band for subjects that weigh at least 20 kg and that the treatment-experienced adult dose is twice daily.
   - The 2nd paragraph has been updated to add DRV 400 and 600 mg tablets and to indicate that DRV will be taken with corresponding ritonavir dosing with liquid, capsules or tablets.

19. Section 1.1: The background and rationale for the Darunavir-based, Unboosted Atazanavir-based and Rilpivirine-based regimens of interest have been added.

20. Section 1.1: Sub-section titled “P1058A” describing logistical concerns with previous versions of P1058 has been removed. New regimens of interest will be added to P1058A via an amendment to the protocol.

21. Section 1.2: The 1st paragraph has been updated as described below.
   - The 1st sentence has been revised from the specific rationale for P1058A Version 1.0 to a more general rationale for the entire P1058A study.
   - The 3rd sentence has been updated to specify that the results of the BSA are from P1058 Version 2.0.
   - The 4th sentence has been updated to state that weight band dosing were followed in P1058A Version 1.0.
   - The 5th sentence has been updated to specify that the sample size described is for P1058A Version 1.0.
   - A sentence was inserted (as the 6th sentence) to state that a summary of the accrual in the Groups in P1058A Version 1.0 are in Section 1.5.
   - A sentence was inserted (as the 7th sentence) to provide the sample size for the Groups in P1058A Version 2.0.
22. Section 1.2 2nd sentence of 1st paragraph, Section 3.0 2nd paragraph and Inclusion Criterion 4.12 have been updated to indicate that subjects are eligible up to < 24 years of age.

23. Section 1.5 has been added to provide a summary of the results of Version 1.0 and the structure of Version 2.0.

24. Section 3.0: 2nd paragraph has been updated to add 24-hour pharmacokinetics and the 24 hours post-dose blood draw. Statements have also been added (as 2nd and 3rd sentences) to specify that 12-hr PK was done for Version 1.0 while a 24-hr PK will be done for Version 2.0.

25. Section 3.0, sub-section titled “PK Results and Repeat PK”, the 1st paragraph has been updated to replace the repeat PK guidelines for the groups that have been closed with the guidelines for Version 2.0. A statement that the subjects must have received the revised dose for at least 14 days before the repeat PK was also added.

26. Section 3.1: This section has been updated as described below.
   - Regimen group has been updated to state that subjects will accrue in all open Groups in Table 1 in the Schema and Section 5.
   - The 2nd paragraph was updated to indicate that all Groups will have either a 12-hr or 24-hour PK and the subject must have been on the regimen of interest at least 30 days before the PK. Additionally, it was clarified that if the treating physician decides to adjust the dose of subjects in specific Groups as previously described and requests another PK, a repeat PK ≥ 14 days post-dosage adjustment will be done with approval of the P1058A team.

27. Section 3.23: The section has been modified to clarify that the intensive PK may be repeated if the provider decides to change the dose and request a repeat PK.

28. Section 3.3: The number of IMPAACT sites within the US has been updated.

29. Section 3.4: The re-enrollment requirement for P1058A has been updated. In addition, the re-enrollment procedure that will be used for P1058A has been added.

30. Section 4.1: Inclusion criterion 4.11 has been updated with the new HIV-1 Infection documentation requirements for enrollment into an IMPAACT Clinical Trial. The last sentence has also been updated to indicate that sites should use an FDA-licensed HIV-1 test kit if possible.

31. Section 4.1: Inclusion criterion 4.13 has been updated as described below.
   - The 1st paragraph has been updated to reference Table 1 in the Schema for the regimens of interest for eligibility, and to clarify that subjects must be stable on
the specified antiretroviral regimen for at least 30 days prior to screening and entry.

- The 1st sentence of the 2nd paragraph has been updated to add “the” before “regimens”.
- The 2nd sentence of the 2nd paragraph has been updated to clarify that the decision to initiate the regimen is not that of the P1058A team.
- Statements about allowing licensed formulations and referencing Section 5 for the allowed formulations have been added to the 2nd paragraph. These were previously the 2nd bullet in this section.
- Bullet #1 has been added to state that all P1058A eligible subjects will need to register to one of the regimen of interest groups.
- Bullet #2, which was previously bullet #1, has been updated with the new guidelines for re-enrolling subjects.
- Bullets #3, #4 and #5 have been deleted.

32. Section 4.2: Exclusion criterion for clinical evidence of pancreatitis has been moved from 4.22c to 4.22. It has also been updated to only include moderate clinical symptoms.

33. Section 4.2: Exclusion criterion for Lipase, AST and ALT has been moved from 4.22b to 4.23.

34. Section 4.2: Exclusion criterion for Total Bilirubin has been moved from 4.22a to 4.24. It has also been simplified to state the exclusion criterion for Total Bilirubin is > Grade 1, except for subjects who are taking ATV it is > Grade 3.

35. Section 4.2: Exclusion criterion 4.28 has been updated to specify that investigational vaccine use within 30 days prior to entry is exclusionary. The 2nd bullet item regarding routine vaccinations has been removed.

36. Section 4.2: Exclusion criterion 4.29 has been updated to remove the bullet regarding maraviroc hypersensitivity or allergy since the maraviroc-based regimens of interest have been closed.

37. Section 4.3: This section has been updated to reference the regimens of interest in Table 1 in the Schema and Section 5.

38. Section 4.4: The 2nd sentence of the 1st paragraph has been updated to remove the reference to the DMC study-specific area for P1058A. Instructions on what to do in the event the ACTG Drug Interactions Database cannot be accessed or is unavailable have also been added as the last paragraph in this section.

39. Sections 4.4 and 4.5: The location of the resource for the Prohibited and Precautionary Medication Tables has been updated to the ACTG Drug Interactions Database, and the
web address for this online searchable database has been added.

40. Section 4.5: Sub-section titled “Precautionary Medications” has been updated as described below.
   - The 1st sentence of the 3rd paragraph has been updated with the new reference numbers for potential exceptions that are in the exclusionary criteria.

41. Section 4.6: The section has been updated as described below.
   - The 1st, 2nd and 3rd sentences of the 1st paragraph have been deleted. The last sentence of the 1st paragraph has been moved as the 5th paragraph.
   - New paragraphs (as the 1st, 2nd, 3rd and 4th paragraphs) have been added to include the updated protocol registration information.
   - The information that the protocol is open to all IMPAACT US sites has been added as the 1st sentence of the 1st paragraph.

42. Section 5.0: The section has been updated as described below.
   - Statements have been added to the 1st paragraph to clarify that regimen groups in Version 1.0 have been closed and provide the regimen groups that have been added in Version 2.0.
   - A statement about the addition of study drugs and regimens by amendment has been added.
   - Formulations that may be used for Version 1.0 have been specified.
   - The generic name for Prezista®, which is Darunavir, has been added in all places where Prezista® is mentioned in the note regarding recommended oral dose for pediatric patients.
   - Formulations that may be used for Version 2.0 have been added.

43. Section 6.0: The sub-section EAE reporting has been updated to clarify the procedure for providing the P1058A Medical Officers and Chairs with a listing of all new SAEs.

44. Section 6.3: The 1st bullet has been updated to include PK evaluations and repeat PK evaluations if the initial PK could not be adequately evaluated.

45. Section 7.1: This section has been updated as described below.
   - The 3rd sentence has been modified to replace the list of Groups with Version 1.0 and clarify that the PK was scheduled after at least 30 days on the combination of interest.
   - A 4th sentence has been inserted to provide the intensive PK and requirement for scheduling for Version 2.0.
   - The 5th sentence has been updated to clarify that the intensive PK should be performed within 5 weeks of screening/entry evaluations.
   - A 6th sentence has been inserted to explain that individuals in Groups N and O will receive one of two possible dosing schedules, 200 mg BID or 400 mg QD or
ETV and 400 mg QD or 600 mg QD of Unboosted ATV respectively.

- A 7\textsuperscript{th} sentence has been inserted to explain how the two possible dosing schedules of ETV in Group N and Unboosted ATV in Group O will be analyzed.
- The 9\textsuperscript{th} sentence has been modified to clarify that the primary objectives will focus on the steady state PK of the regimens of interest.
- A 2\textsuperscript{nd} paragraph has been added to explain that the study will not be able to identify inadequate PK or toxicity within the first 30 days after starting the regimen.

46. Section 7.2: The pre-dosage concentration has been updated to specify that $C_{12}$ is for Version 1.0 and to add $C_{24}$ for Version 2.0.

47. Section 7.4: This section has been updated to add the accrual for the new groups and the target total for all the Groups. It has also been updated to indicate that the target accrual for each group is of evaluable subjects and the definition of evaluable in the context of this study has been added.

48. Section 7.5: This section has been updated to add the information for the new groups.

49. Section 7.6: This section has been updated to clarify that more specific monitoring of accrual in the RPV containing arms P and Q will be done since the use of RPV may be limited in pediatrics.

50. Section 7.7: This section has been updated as described below.
   - The 2\textsuperscript{nd} sentence of the 1\textsuperscript{st} paragraph has been updated to add DRV and the corresponding new groups.
   - The 3\textsuperscript{rd} sentence of the 1\textsuperscript{st} paragraph has been updated to add DRV.
   - Sentences have been added at the end of the 1\textsuperscript{st} paragraph to state that the analysis presented is provisional based on the information available at the time of protocol development, and at the time of analysis the most relevant available comparison data will be used for interpretation of the findings in addition to those described in the plan.

51. Section 8.1: This section has been updated to indicate that the maraviroc regimen groups have been closed due to lack of enrollment and the analysis will not be done. The combinations for the new groups have also been added.

52. Section 8.2: The 1\textsuperscript{st} bullet under the 1\textsuperscript{st} paragraph has been updated to indicate that a 1-week dosing recall history will be taken.

53. Section 8.3: This section has been updated as described below.
   - The 1\textsuperscript{st} paragraph has been updated to clarify that witnessed dosing of 12 hours is for twice daily regimens and to add 24 hours for once daily regimens.
• Item #4 has been modified to add peripheral venipuncture. An additional blood sample drawn 24 hours post-dosing for Version 2.0, and the corresponding total number of blood draws and volume, have also been added.
• The last paragraph has been modified to state that all PK assays will be done either in the IMPAACT Pharmacology Laboratory in the University of Nebraska or University of Alabama-Birmingham.

54. Section 8.4: This section has been updated as described below.
• The 1st sentence of the 1st paragraph has been updated to specify the concentration results that were examined for Version 1.0.
• A statement that maraviroc regimens will not be studied due to lack of enrollment has been added.
• Concentration results to be examined for Version 2.0 have been added.

55. Section 8.5: This section has been updated to correctly cite WinNonlin version 3.2 in the section so it will be included in the Reference List.

56. Section 8.6: This section has been updated as described below.
• The 1st paragraph has been updated to specify the anticipated outcomes that were examined for Version 1.0 and to clarify that the new ARVs of interest were fixed doses.
• The last sentence of the 1st paragraph about ARV of interest and relationship between Tanner stage and antiretroviral pharmacokinetics has been moved to be the 3rd paragraph in this section.
• A new paragraph (as 2nd paragraph) has been added for the anticipated outcomes for Version 2.0.
• The last paragraph regarding potential exploratory analysis of the effects of the combination of TDF and ATV/r on the PK of RAL has been updated to specify analysis was for Version 1.0 if enough subjects enroll. A sentence was added to explain that the analysis will no longer be done.

57. Section 12: The reference list has been updated to include new references.

58. The following changes have been made to Appendix I, the Schedule of Evaluations:
• The heading section of the 4th column has been updated to remove the following: “(ATV/r, LPV/r, DRV/r only if dose changes; RAL case by case basis)” as the repeat PK guidelines are different for Version 1.0 and Version 2.0.
• The web address for the P1058A webpage in the table and in footnote 3 has been updated.
• 24-hour intensive PK has been added.
• The PK blood volumes in the table for the intensive PK and repeat PK visits have been updated to 28 – 32 ml.
The total blood volume in the table at the screen/entry visit has been updated to 2 – 3 ml.
The total blood volume in the table at the intensive PK visit has been updated to 43 – 48 ml.
The total blood volume in the table at the repeat PK visit has been updated to 29 – 34 ml.
The NIH Clinical Center guidelines for blood volume in research trials below the table and in the specific instructions for the PK visit below footnote #9 has been updated as described below.
− The blood drawing limits for research purposes has been updated to 5 mL/kg in a single day and 9.5 mL/kg in an eight-week period.
− The 2nd sentence was updated to clarify that further limits in blood volume should be considered in patients with significant anemia or compromised cardiac output.
− A 3rd sentence has been added to explain that in instances of clinical need, it is the responsibility of the patient’s attending physician to determine if phlebotomy in excess of the stated limits may be permitted.
Specific instructions for the PK visit were moved from below footnote #1 to below footnote #9.
Footnote 3 has been updated to correct the location of the Tanner Stage tool to the Current Study Implementation Materials in the P1058A web page.
Footnotes 4 and 5 have been updated to indicate that the tests will be done in real-time at the clinic’s local CLIA-certified laboratory.
Footnotes 6 and 8 have been updated to indicate that the tests will be done in real-time.
Footnote 7 has been updated to add a statement that the sample may also be drawn 24 hours post dose.
Footnote 9 has been updated to add 24 hours in the post-dose blood drawing timepoints for the intensive PK. The total number of blood draws has been updated to 7 – 8, and the total blood volume has been updated to 28 – 32 ml and 6 – 7 teaspoons. Clarification that 12-hour PK was done for Version 1.0 and 24-hour PK will be done for Version 2.0 has been added. It was also updated to clarify that the PK specimens will be processed and shipped in real-time and that subjects must be on the revised dose for at least 14 days before the PK study can be repeated.

59. The following changes have been made to the Sample Informed Consent:
− In the title section, the web address for location of the standard template for the sample informed consent has been updated.
− In the Introduction section, the 1st sentence of the 2nd paragraph has been updated to clarify that subjects have been taking the combination of newer anti-HIV medications for at least 30 days, which is why they are being asked to take part in the study.
• In the Introduction section, a statement explaining that this is an on-going study of different combinations of newer anti-HIV medications to evaluate doses of the medications in children, adolescents and young adults has been added.
• In the Introduction section, the 2nd paragraph has been updated to remove the anti-HIV medications of the groups that have been closed and add the anti-HIV medications of the new groups. It has also been updated to remove the other allowed anti-HIV medications for the groups that have been closed and add the other allowed anti-HIV medications for the new groups.
• In the Introduction section, the 3rd paragraph has been modified to clarify that the regimens of interest are for the new version of the study and replace the groups that have been closed with the new groups. A statement that other combinations of anti-HIV medications were evaluated in a previous version of the study has been added.
• In the Why is this study being done section, a sentence has been added to the 1st paragraph to explain that some of the medications being studied may not yet be approved for older children and adolescents less than 18 years old.
• In the Why is this study being done section, the 5th sentence of the 1st paragraph (which was previously the 4th sentence) has been updated to remove the anti-HIV medications of the groups that have been closed and add the anti-HIV medications of the new groups.
• In the Why is this study being done section, list of regimen groups has been updated to remove the groups that have been closed and add the new groups.
• In the What do I have to do if I am in this study section, item #2 1st sentence has been updated to clarify that the study required PK will be done after the participant has been on the HIV medications for at least 30 days. The 2nd sentence has been updated to indicate that the PK study visit will take about 24 hours to complete.
• In the What do I have to do if I am in this study section, sub-section titled “Screening and Entry” has been modified to replace 12-hour PK study with 24-hour PK study in the last sentence of the 1st bullet.
• The What do I have to do if I am in this study section, sub-section titled “PK Study Visits” has been updated as described below.
  – A paragraph has been added (as the 2nd paragraph) to include the criteria for re-scheduling the PK visit which are unavailability on the scheduled day of the visit, use of a medication that is not allowed within 14 days before the visit, missing any of the 2 doses of the ARVs of interest before the visit, missing at least 2 doses of the ARVs of interest within 7 days before the visit or not switching once-a-day ARVs of interest to be taken in the morning during the 3 days before the visit.
  – The 3rd sentence of the 3rd paragraph has been updated to add routine laboratory tests to the blood tests that will be done at the PK visit.
  – The 2nd sentence of the 4th paragraph has been modified to state that about 1 teaspoon of blood will be taken before the anti-HIV medications
are taken.
- The 3rd sentence of the 4th paragraph has been updated to add 24 hours in the post-dose blood drawing timepoints for the intensive PK.
- A 4th sentence was inserted in the 4th paragraph to clarify that about 1 teaspoon of blood will be taken at each blood draw timepoint of the intensive PK.
- A 5th sentence was inserted in the 4th paragraph to clarify that the blood samples will be used to measure the participant’s blood levels of anti-HIV medications.
- The 10th sentence of the 4th paragraph has been updated to state that about 7 teaspoons of blood will be collected for the PK study.
- The 1st sentence of the 5th paragraph was modified to replace 12-hour with 24-hour.
- The 7th paragraph was modified to replace 12-hour PK with 24-hour PK and to clarify that a repeat PK may be done as part of the study if the results of the first PK study could not be measured or the participant’s doctor decides to change the dose for certain anti-HIV medications and requests for another PK.
- In the Storage of blood samples for future testing section, the 1st sentence of the 1st paragraph has been modified to indicate that the 1 teaspoon of blood will be taken during the PK study visit.
- The How many people will take part in this study section has been updated to indicate that about 165 children, adolescents and young adults in total will take part in the study. The number of participants that took part in the previous version and the number that will take part in the new version have also been added. A clarification that only the participants with PK study results that could be measured will be counted as taking part in this study has been added.
- The Why would the doctor take me off this study early section has been updated to add unable to do the PK study or a repeat PK study if it is needed because the results of the first PK study could not be measured to the criteria for discontinuation.
- The information in the What happens if I am injured section has been replaced with the following: If you are injured as a result of being in this study, you 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.
- In the What are my rights as a research subject section, the following sentence has been added as the 3rd sentence in the first paragraph: You will be treated the same no matter what you decide.
INTENSIVE PHARMACOKINETIC STUDIES OF NEW CLASSES OF ANTIRETROVIRAL DRUG COMBINATIONS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

**DESIGN:** An intensive 12-hour or 24-hour pharmacokinetic (PK) study

**SAMPLE SIZE:** Target total is up to 200 evaluable subjects across all Groups. Evaluable subjects are those subjects whose PK results can be adequately evaluated.

The target total for Version 1.0 was 115 and sample sizes for each regimen of interest were:
- Group G: 15 evaluable subjects. This Group is closed.
- Group H: 15 evaluable subjects. This Group is closed.
- Group I: 40 evaluable subjects. This Group is closed.
- Group J: 15 evaluable subjects. This Group is closed.
- Group K: 15 evaluable subjects. This Group is closed.
- Group L: 15 evaluable subjects. This Group is closed.

The target total for Version 2.0 is 85 and sample sizes for each regimen of interest are:
- Group M: 15 evaluable subjects.
- Group N: 15 evaluable subjects.
- Group O: 25 evaluable subjects.
- Group P: 15 evaluable subjects.
- Group Q: 15 evaluable subjects.

**POPULATION:** HIV-infected children, adolescents and young adults who are receiving a regimen of antiretroviral drugs prescribed by their physician that includes one of the combinations described below.

For all regimens:
- Body Surface Area (BSA) ≥ 0.85 m²
- Age: ≥ 6 and < 24 years of age
- Stable on the regimen of interest for at least 30 days prior to the intensive 12-hr or 24-hr PK study day
### REGIMENS OF INTEREST: Table 1. If “Optional” the NRTI, NNRTI dose is not defined; fixed doses, as indicated

<table>
<thead>
<tr>
<th>Group</th>
<th>Regimens of Interest (ROI)</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry Inhibitor</th>
<th>CCR5 Antagonist</th>
<th>Integrase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>RAL 400 mg BID + ATV/r 300/100 mg QD</td>
<td>YES³</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>H</td>
<td>RAL 400 mg BID + TDF 300mg QD</td>
<td>YES</td>
<td>ETV⁴</td>
<td>EFV</td>
<td>NVP</td>
<td>DRV/r³</td>
<td>YES</td>
</tr>
<tr>
<td>I</td>
<td>ETV 200 mg BID + DRV/r, per weight, BID</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>MVC 150 mg BID + ATV/r 300/100 mg QD</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>MVC 150 mg BID + LPV/r 400/100 mg BID</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>MVC 600 mg BID + RAL 400 mg BID + ETV 200 mg BID</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>DRV/r 800/100 mg QD</td>
<td>YES</td>
<td>NO ETV, RPV</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>DRV/r 800/100 mg QD + ETV 200 mg BID or 400 mg QD</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Unboosted (without ritonavir) ATV 400mg QD or 600 mg QD</td>
<td>NO TDF</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>RPV 25 mg QD or Complera™ QD³ + DRV/r 800/100 mg QD or ATV/r 300/100 mg QD</td>
<td>YES</td>
<td>NO</td>
<td>NO LPV, TPV, IDV, SQV, FPV, NFV</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td>RPV 25 mg QD or Complera™ QD³</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
</tbody>
</table>

Groups G, H, I, J, K and L which have been grayed out were the regimens of interest in Version 1.0. These groups have been closed.

Questions on specific ARV regimens, if not addressed here, please send to impaact.teamp1058A@fsrif.org

1 Enfuvirtide, ENF, T-20 (Fuzeon®) a Fusion Inhibitor, is allowed in all groups.
2 MVC 600 mg BID, if given with ETV is recommended (Group H and I).
3 TDF preferred (Group G).
4 DRV+ETV not allowed in Group H. In Group H, if ETV is the optional NNRTI, then DRV/r cannot be the optional PI.
5 Subject cannot be on H2 blockers and must take RPV with food.
6 Complera™ (Emtricitabine [FTC] 200 mg + Rilpivirine [RPV] 27.5 mg + Tenofovir [TDF] 300 mg)

On February 10, 2009 the Food and Drug Administration (FDA) determined that the IND # 73,379, assigned to IMPAACT P1058, Version 2.0, dated November 8, 2007, “Intensive Pharmacokinetic Studies of Antiretroviral Drug Combinations in Children,” should be exempt from the requirements of the IND regulations.
SCHEMA (Cont.)

IMPAACT P1058A will make observations in subjects who have been prescribed certain medications, in some cases outside of product labeling for more recently approved antiretrovirals (ARVs). The protocol does not prescribe therapy, provide medications or dictate subject management. The regimens in Table 1 summarize entry criteria for P1058A.

The subject should be on the regimen of interest for at least 30 days prior to screening/entry. All Groups in Version 1.0 had an intensive 12-hour PK study and all Groups in Version 2.0 will have an intensive 24-hour PK study. The intensive PK should be performed only after the subject has been on the ARVs for at least 30 days, and within 35 days (5 weeks) of screening/entry evaluations.

P1058A Version 1.0 only performed repeat PKs for subjects in Groups G, I, J, K and L at the discretion of the treating physician, who required dose adjustments for ATV, ETV, DRV, MVC or LPV respectively, after completion of the PK study. Repeat PKs for RAL were done on a case-by-case basis, if needed, per the treating clinician and protocol chairs.

In P1058A Version 2.0, if the treating physician decides to adjust the dose of DRV QD, ETV, unboosted (without ritonavir) ATV or RPV after completion of the PK study, and requests a repeat PK, it can be performed with approval of the P1058A team.

STUDY DURATION:

Minimum: 1 week
Maximum: 7 weeks

PRIMARY OBJECTIVES (Version 1.0):

1. To assess the steady state pharmacokinetics of raltegravir administered in combination with atazanavir/ritonavir or tenofovir or maraviroc/etravirine to older children, adolescents and young adults. Due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.

2. To assess the steady state pharmacokinetics of etravirine administered to older children, adolescents and young adults.

3. To assess the steady state pharmacokinetics of maraviroc administered in combination with atazanavir/ritonavir or lopinavir/ritonavir to older children, adolescents and young adults. Due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.

4. To assess the steady state pharmacokinetics of maraviroc (600 mg BID) given in combination with raltegravir and etravirine (a PI sparing regimen) to older children, adolescents and young adults. Due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.
5. To assess the steady state pharmacokinetics of darunavir/ritonavir BID administered to older children, adolescents and young adults.

**PRIMARY OBJECTIVES (Version 2.0):**

1. To assess the steady state pharmacokinetics of darunavir QD with or without etravirine administered to older children, adolescents and young adults.

2. To assess the steady state pharmacokinetics of unboosted (without ritonavir) atazanavir administered to older children, adolescents and young adults.

3. To assess the steady state pharmacokinetics of rilpivirine 25 mg QD with and without the protease inhibitors darunavir/ritonavir or atazanavir/ritonavir.

**SECONDARY OBJECTIVES:**

1. To describe the relationship between Tanner stage and the pharmacokinetics of the regimens of interest in children and adolescents.

2. To describe the relationships between the pharmacokinetic parameters and polymorphisms that may affect the antiretrovirals of interest in older children, adolescents and young adults.

3. To record adverse events associated with the antiretrovirals of interest.
1.0 BACKGROUND AND RATIONALE

Antiretroviral therapy for HIV-infected children, adolescents and young adults has become highly complex and individualized due to extensive antiretroviral treatment experience, the availability of new classes of antiretroviral drugs, and the ability to define complex resistance patterns by genotypic and phenotypic testing. Rather than using a small number of tested fixed drug combinations, clinicians are basing treatment decisions on factors such as palatability, tolerability, safety, convenience, and most prominently, resistance patterns. Because of the urgent need to find suppressive regimens in heavily treated children, adolescents and young adults, clinicians often begin using drugs prior to industry-sponsored pediatric and/or adolescent studies. A major first step in rationalizing this practice and designing subsequent studies is to assess the pharmacokinetics in these populations.

Table 2. Current* FDA Labeling for Antiretroviral Drugs in Pediatrics [1]

<table>
<thead>
<tr>
<th>ARV</th>
<th>Age-FDA-approved labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRTIs</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>≥ 3 months</td>
</tr>
<tr>
<td>Didanosine (dDI)</td>
<td>≥ 2 weeks</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Birth and up</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Birth and up</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Birth and up</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>≥ 12 years, &gt; 35 kg</td>
</tr>
<tr>
<td>Zidovudine (ZDV or AZT)</td>
<td>Premature infants and up</td>
</tr>
<tr>
<td></td>
<td>NNRTIs</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>≥ 3 years, ≥ 10 kg</td>
</tr>
<tr>
<td>Etravirine (ETV or ETR)</td>
<td>≥ 18 years</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>≥ 15 days</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>≥ 18 years</td>
</tr>
<tr>
<td></td>
<td>PIs</td>
</tr>
<tr>
<td>Atazanavir (ATV)</td>
<td>≥ 6 years (with ritonavir recommended)</td>
</tr>
<tr>
<td>Darunavir (DRV)</td>
<td>≥ 6 years, ≥ 20 kg (with ritonavir)</td>
</tr>
<tr>
<td>Fosamprenavir (f-APV or FPV)</td>
<td>≥ 2 years</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>&gt; 18 years</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>≥ 14 days</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>≥ 2 years</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>≥ 14 days</td>
</tr>
<tr>
<td>Saquinavir (SQV)</td>
<td>&gt; 16 years</td>
</tr>
<tr>
<td>Tipranavir (TPV)</td>
<td>≥ 2 years (with ritonavir)</td>
</tr>
<tr>
<td></td>
<td>New Entry and Fusion Inhibitors and Integrase Inhibitors</td>
</tr>
<tr>
<td>Enfuvirtide (T-20)</td>
<td>≥ 6 years</td>
</tr>
<tr>
<td>Maraviroc (MVC)</td>
<td>≥ 16 years</td>
</tr>
<tr>
<td>Raltegravir (RGV or RAL)</td>
<td>≥ 16 years</td>
</tr>
</tbody>
</table>

*Ref: List of FDA Approved Drug Products, [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), and package inserts [2-7].
Despite the absence of labeling for the full pediatric age range, current guidelines for antiretroviral therapy of children state that, where appropriate, this deficit should not limit antiretroviral options. The use of new drugs that have been evaluated in adults but have not been fully evaluated in children might be justified and is ideally done in the framework of a clinical trial [1,8,9]. Uncertainty regarding dosing, as may occur when used in interacting combinations, threatens to produce either toxicity or incomplete viral suppression, which in turn can threaten adherence or select for resistance. In order to design prospective studies to test treatment strategies and to examine determinants of treatment outcome, pharmacokinetic information upon which rational dosing can be based, is needed. Results from P1058, Version 1.0 for Groups A, B and C have been reported by King et al. in "Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in HIV-infected pediatric patients" [10]. Additionally, results from P1058 Version 2.0 for Groups D (TDF 300 mg q.d. ± 1 NNRTI [EFV q.d. or NVP b.i.d]), E (TDF 300 mg q.d. + DRV/r 300/50 mg or 600/100 mg b.i.d. ± EFV) and F (TDF 300 mg q.d. + ATV 200 – 400 mg/RTV 50 – 100 mg q.d. ± EFV) were recently published [11].

Data obtained from this protocol must be interpreted in the context of data from other studies demonstrating safety and efficacy [12]. These studies are reviewed for correlation with safety and virologic efficacy in the same or similar population, ages of subjects, validity of analytic methods, sample size and precision of PK estimates. Selection of comparator data must be based on therapeutic goals, which may differ for children with wild-type versus resistant virus, and should be from regimens with similar virologic and pharmacokinetic goals as the regimen to be studied. In general, these will be regimens designed to overcome low to moderate levels of resistance, within the limits of tolerability, feasibility, and safety.

1.1 Rationale for IMPAACT P1058A

Results from Version 2.0 of P1058

P1058, Version 2.0 (11/8/07, IND# 73,379) was a multi-center study evaluating the steady-state pharmacokinetics (PK) of antiretroviral combinations in HIV-infected children.

HIV-infected children were treated with tenofovir in combination with other, potentially interacting, antiretroviral agents. The team reported the pharmacokinetic parameters of tenofovir in combination with efavirenz, darunavir-ritonavir, or atazanavir-ritonavir in HIV-infected children [11]. HIV-infected patients 8 to 18 years of age receiving a tenofovir-based regimen containing efavirenz once daily (TDF 300 mg q.d. ± 1 NNRTI [EFV q.d. or NVP b.i.d]; Group D), darunavir-ritonavir twice daily (TDF 300 mg q.d. + DRV/r 300/50 mg or 600/100 mg b.i.d. ± EFV; Group E), or atazanavir-ritonavir once daily (TDF 300 mg q.d. + ATV 200 – 400 mg/RTV 50 – 100 mg q.d. ± EFV) were recently published [11].
mg q.d. ± EFV; Group F) were enrolled. Plasma samples were collected over a 24-h time interval. The 90% confidence intervals (90% CI) of the geometric means for the area under the plasma concentration-time curve (AUC) and the minimum concentration of drug in serum (Cmin) of each antiretroviral were computed and checked for overlap with intervals bracketing published values obtained in adult or pediatric studies demonstrating safety and/or efficacy. Group D efavirenz plasma concentrations were observed to be higher in patients receiving fixed-dose combination tablets compared with subjects receiving the individual formulation. In Group E, tenofovir and darunavir exposure was observed to be lower than expected. In Group F, tenofovir and atazanavir administered concomitantly produced exposures similar to those published for adult patients. The 90% CI of AUC and Cmin for tenofovir overlapped the target range for all combinations. Informal comparisons of treatment groups did not indicate any advantage to any combination with respect to tenofovir exposure. In other words, tenofovir exposure was not compromised in any of the 3 groups studied. Further study of exposures achieved with antiretrovirals administered in combination is warranted.

Rationale for Regimens of Interest for P1058A and Design Changes

P1058A is designed as a follow-on protocol to P1058 Version 2.0, and will remain “opportunistic” in approach, enrolling subjects who have already been prescribed the drug of interest. In June 2008, investigators were surveyed for newer ARV combinations to evaluate, based on recent FDA approvals of integrase inhibitors and entry inhibitors, and new formulations of existing ARVs. These results were used to determine the new Groups for P1058A. A withdrawal request for IND# 73, 379 was submitted on 9/12/08 along with a proposal to add new arms, with a change from 24-hour intensive PK to 12-hour intensive PK. The BSA stratification will not be used, in P1058A, as it did not really affect the PK results, in P1058 Version 2.0. A minimum BSA will remain for inclusion and Tanner stage comparisons will be done. The age range was modified to ≥ 6 to <21 years of age, and more recently to < 24 years of age. Another regimen of interest, Regimen L, which contains maraviroc, raltegravir and etravirine and does not contain RTV, was proposed based on discussions with DAIDS Medical Officers and other clinicians, that this is a reasonable approach, especially for adolescents or others who will not take ritonavir at all because of the taste/smell and gastrointestinal toxicity; very elevated lipids and/or significant lipodystrophy associated with it. With the new therapies, this becomes a real option and should be potent in most cases.

The resultant regimens for study in P1058A were selected based on input from the Primary Therapy Scientific Committee and recent results within IMPAACT such as the withdrawal of IMPAACT P1075, “An Open Label Multicenter Phase I/II 48
Week Trial of Maraviroc in Combination with Optimized Background Therapy for the Treatment of Antiretroviral Experienced HIV-1 Infected Children and Adolescents”; and current information from IMPAACT P1066, Version 2.0 dated 4/24/08, “A Phase I/II, Multicenter, Open-Label, Noncomparative Study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress®, MK-0518) in HIV-1 Infected Children and Adolescents,” IND # 77,787. In addition, combinations not allowed in IMPAACT P1071, Version 1.0, dated 9/8/08, “Phase I/II Open-Label Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Antiviral Activity of Vicriviroc (SCH-417690) a Novel CCR5 Antagonist in Combination Regimens in HIV-infected Antiretroviral Therapy Experienced Children and Adolescents”, IND#69,661 will be investigated.

Updated Package Inserts for raltegravir, efavirenz, darunavir and other ARVs, available on the Regulatory Support Center (RSC) website http://rsc.tech-res.com/; and updated treatment guidelines such as Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection [1] and Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [9] were also consulted. The new regimens of interest in P1058A Version 1.0 involved ARVs that are administered twice daily, so a 12-hour PK analysis was done. The Groups in Version 1.0 have been closed. In P1058A Version 2.0, the new regimens of interest involve ARVs that are administered once daily, so a 24-hour PK analysis will be done.

Whereas P1058 Version 2.0 evaluated the pharmacokinetics of TDF-based regimens in HIV-infected children, P1058A will evaluate the pharmacokinetics of antiretroviral drug combinations with limited data in the pediatric and adolescent populations but are used by physicians to treat pediatric and adolescent patients. The regimens and doses to be evaluated were chosen based upon the following information collected in HIV-negative and HIV-infected adults. The goal of this version is to evaluate the pharmacokinetics of these drugs in combination administered to HIV-infected children, adolescents and young adults and to ascertain whether the degree of interaction between these antiretroviral agents are similar to or different than, those seen in adults.

**Raltegravir based Regimens of Interest**

| RAL + ATV/r |
| RAL + TDF |

Raltegravir (RAL, Isentress®) is a potent and selective inhibitor of HIV-1 integrase catalyzed strand transfer. The current FDA approved adult dose is 400 mg twice daily and the drug is available as a 400 mg tablet [6]. Merck data [13] suggest that raltegravir can be dosed without regard to food. The potential for
drug-drug interaction has been investigated in a series of clinical studies in uninfected subjects. Comparison of raltegravir pharmacokinetics in the absence and presence of ritonavir or efavirenz indicated little to no effect on raltegravir C\textsubscript{12 hr}.\[14\]. Co-dosing of raltegravir with atazanavir resulted in an increase in raltegravir pharmacokinetic parameters by ~50 to 100% (AUC, C\text{max}, and C\text{12 hr}), and plasma levels of raltegravir were modestly increased by co-dosing with atazanavir and ritonavir, although the effect was somewhat less than that observed for atazanavir alone [15]. Co-dosing of raltegravir with tenofovir disoproxil fumarate indicates that raltegravir C\text{12 hr} was similar in the presence and absence of tenofovir while raltegravir AUC\text{0-12 hr} and C\text{max} increased approximately 49% and 64%, respectively[16,17]. Co-administration of raltegravir with tenofovir resulted in little change in tenofovir pharmacokinetics. In contrast, when this combination was used in HIV-infected adults, raltegravir AUC\text{0-12 hr}, C\text{max} and C\text{min} increased 78%, 90% and 69%, respectively.

In the P1066 poster presented at ICAAC [18] the mean RAL AUC\text{12} was 23.56 µM*h. The PK parameters reported in P1058 are in mg*h/L. If the AUC\text{12} in the poster is converted to mg*h/L, the mean (SD) RAL AUC\text{12} is 10.5 (10) mg*h/L. The median (range) RAL AUC\text{12} is 7.4 (2.0-35) mgxh/L. This poster reported data on the 11 additional subjects enrolled into Cohort 1 for fasting PK. The data used to determine RAL target ranges was from an earlier P1066 poster [12] with data from non-fasting children. In the ICAAC poster (fasting PK), the mean RAL AUC\text{12} is higher (10.5 vs. 5.5 mgxh/L) as is the variability in this cohort of children compared with the non-fasting children. In P1058, the protocol team does not dictate what the children and adolescents eat. Instead, the protocol team asks sites to record the food content when RAL is taken. The original data used to determine RAL ranges seems more appropriate. The below is from P1066.[12,18,19]
Maraviroc (MVC, Selzentry®) is a small molecule antagonist of the interaction between human CCR5 and HIV-1 gp120, blocking CCR5-tropic HIV-1 entry into cells. The current FDA approved adult dose is 300 mg twice daily and the drug is available as either a 150 or 300 mg tablet. Maraviroc can be dosed without regard to food. When maraviroc is administered with a CYP3A inhibitor such as a protease inhibitor, the recommended dose is 150 mg twice daily and when administered with CYP3A inducers, the recommended adult dose is 600 mg twice daily. Co-administration of maraviroc with a lopinavir/ritonavir-based regimen in HIV-infected adults resulted in a 2.6-fold higher AUC12, which is consistent with drug interaction studies in healthy volunteers [20]. The effect of atazanavir alone (400 mg once daily) or atazanavir/ritonavir (300/100 mg once daily) on the pharmacokinetics of maraviroc (300 mg twice daily) was studied in 12 HIV-subjects [21,22]. Atazanavir alone increased maraviroc AUC by 3.6-fold and Cmax by 2.1-fold; atazanavir/ritonavir further increased maraviroc AUC (4.9-fold) and Cmax (2.7-fold). Thus, the suggested maraviroc dose when given with atazanavir or atazanavir/ritonavir is 150 mg twice daily. Co-administration of maraviroc and raltegravir to healthy volunteers resulted in a slight reduction of maraviroc pharmacokinetic parameters (10-20%). However, raltegravir concentrations were reduced. Mean C12 was reduced by 28%, while AUC was
reduced by 37% [23]. ETV decreases MVC AUC 53% and \(C_{\text{max}}\) 60%; the recommendation in the November 2008 guidelines is to dose MVC at 600 mg BID with ETV.

**Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) Regimen of Interest**

**ETV + DRV/r**

Etravirine (ETV, Intenence®) is a recently available NNRTI for the treatment of HIV. The FDA approved dose is 200 mg taken twice daily following a meal. It is available as 100 mg and 200 mg tablets. The pharmacokinetics of ETV in combination with darunavir/ritonavir (DRV/r) have been evaluated in healthy volunteers [24]. ETV AUC\(_{12}\) administered as 100 mg twice daily with DRV/r was decreased by 37%; while \(C_{\text{max}}\) and \(C_{\text{min}}\) were decreased by 32% and 49%, respectively. For ETV 200 mg twice daily co-administered with DRV/r, AUC\(_{12h}\), \(C_{\text{max}}\) and \(C_{\text{min}}\) of ETV were 80%, 81% and 67% greater, respectively, versus ETV 100 mg twice daily alone. DRV pharmacokinetics were unchanged except a 15% increase in AUC\(_{12h}\) when given with ETV 200 mg twice daily. No clinically relevant changes in DRV pharmacokinetics were observed when combined with ETV; therefore DRV dose adjustment is not required. For pediatric patients age 6 to <18 years, the FDA approved dosing is by weight band for patients that weigh at least 20 kg and should not exceed the treatment-experienced adult dose of DRV/r (which is 600/100 mg twice daily). Co-administration of ETV (100 mg twice daily) with DRV/r decreased ETV exposure by 37%. However, ETV exposure was increased by 80% when given as 200 mg twice daily. This appears to reflect the higher ETV dose and not the interaction with DRV/r. Thus, no dose adjustment of ETV is needed when combined with DRV/r.

DRV will be weight based dosing in accordance with the package insert [http://www.prezista.com/prezista/documents/us_package_insert.pdf](http://www.prezista.com/prezista/documents/us_package insert.pdf), using the 75 mg, 150 mg, 400 mg, and 600 mg tablets with corresponding ritonavir dosing with liquid, capsules or tablets.

**Darunavir based Regimens of Interest**

**DRV/r**

**DRV/r + ETV**

Darunavir (DRV, Prezista®) is a nonpeptidic inhibitor of HIV-1 and HIV-2 protease, and similar to other protease inhibitors, it prevents cleavage of the HIV polyprotein encoded by the *gag-pol* region. It must be co-administered with ritonavir to exert its therapeutic effect [25]. The protein-binding corrected IC\(_{95}\) for darunavir against wild-type virus is 0.022 mg/L. The FDA-approved dose in combination with ritonavir for treatment-naïve adults and for treatment-experienced adults without DRV resistance mutations is 800/100 mg once daily and for treatment-experienced adults with at least one
DRV resistance mutation is 600/100 twice daily. The dose is recommended to be taken with food. In children and adolescents, the FDA approved dose is darunavir/ritonavir 375/50 mg twice daily for children 20 to < 30 kg, 450/60 mg twice daily for children 30 to < 40 kg and 600/100 mg twice daily for children ≥ 40 kg. The drug is available as 75, 150, 400 and 600 mg tablets.

The majority of pharmacokinetic evaluations for darunavir have been conducted in adults. The first open-label evaluation of the pharmacokinetics, safety and efficacy of darunavir in children and adolescents was conducted through the DELPHI (A Pediatric Trial to Provide Dose Recommendation of TMC114/Rtv in HIV-1 Infected Children and Adolescents) study. Darunavir plasma concentrations were measured after 2 weeks of weight-based dosing recommendations as those included in the FDA-approved package insert. The median (range) AUC_{24} was 127.3 (67.1-230.7) mgxh/mL and C_{0h} was 3.9 (1.8-7.8) mg/L. These results were similar to the median (range) AUC_{24} of 123.3 (67.7-213.0) mgxh/L and C_{0h} of 3.5 (1.3-7.4) mg/L reported in adults after twice daily dosing of 600/100 mg twice daily. An earlier version of P1058 examined the pharmacokinetics of weight-based dosing of darunavir/rtv twice daily in combination with tenofovir. Median (range) darunavir AUC and C_{12h} for 9 children 8-18 years of age were 55.5 (27.7-122.7) mgxh/L and 2.0 (1.2-7.5) mg/L, respectively. Darunavir exposure given on a BID basis was lower than expected in our patient population than published adult data.

Once daily dosing of darunavir is not recommended for use in children but is approved for patients who are ≥ 18 years of age who are treatment naïve. However, the convenience and patient preference and or insistence for QD regimens and difficulties with adherence in adolescents and young adults have led to QD darunavir use by clinicians. Simplifying the treatment regimen is believed to improve adherence in this patient population and thereby improving clinical outcomes. Therefore, pharmacokinetic data on once daily dosing of darunavir/ritonavir in this patient population is warranted.

Pharmacokinetic data supporting once daily use in children and adolescents are limited [26]. However, during the clinical development of darunavir, pharmacokinetics of once-daily dosing were evaluated in healthy volunteers [27]. The results are reported in Table 3.
Table 3

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>DRV/rtv 400/100 mg QD</th>
<th>DRV/rtv 800/100 mg QD</th>
<th>DRV/rtv 1200/100 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>C_{min} (mg/L)</td>
<td>0.64 ± 0.46</td>
<td>1.1 ± 0.36</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>C_{max} (mg/L)</td>
<td>3.8 ± 0.94</td>
<td>5.3 ± 1.6</td>
<td>7.3 ± 0.7</td>
</tr>
<tr>
<td>AUC_{24h} (mgxh/L)</td>
<td>38.6 ± 14.8</td>
<td>61.1 ± 22.5</td>
<td>89.3 ± 11.9</td>
</tr>
</tbody>
</table>

P1058A version 1.0 evaluated DRV/RTV twice daily with ETV twice daily in this patient population. For DRV, 13 of 41 (32%) patients and 8 of 41 (20%) patients had a DRV AUC and C_{min} ABOVE the target value of 80 mgxh/L and 4.9 mg/L, respectively. In contrast, 12 of 41 (30%) patients and 17 of 41 (42%) patients had a DRV AUC and C_{min} BELOW the target value of 51 mgxh/L and 3.1 mg/L, respectively. For ETV, 7 of 41 (17%) patients and 4 of 41 (10%) patients had an ETV AUC and C_{min} ABOVE the target value of 6.9 mgxh/L and 0.5 mg/L, respectively. In contrast, 23 of 41 (56%) patients and 21 of 41 (51%) patients had an ETV AUC and C_{min} BELOW the target value of 4.4 mgxh/L and 0.3 mg/L, respectively. Furthermore, pharmacokinetic parameters in participants receiving DRV/rtv and ETV in version 1.0 exhibited extreme between-patient variability. As a result, those participants receiving DRV/rtv and ETV will be enrolled into a separate group (Regimen N) in Version 2.0.

Unboosted (without ritonavir) Atazanavir based Regimen of Interest

Early studies in adults with unboosted atazanavir (ATV, Reyataz®) have shown that 94% of the patients had levels of > 60 ng/mL at 24 hours post-steady-state dose (a level that seems to correlate better with efficacy) [28]. In addition, the administration of unboosted ATV with food results in no change in C_{max} but an increase in AUC, therefore patients need to take unboosted ATV with food. When ATV was given with meals, the variability in AUCs was significantly reduced, from 69% in the fasted state to 37% with a light meal and 43% with a high-fat meal [28]. Subsequent studies in healthy subjects showed improvement in both the exposure (increased) and variability (decreased) with the co-administration of food. Of 29 trough values in the fasted patients, 11 were below 59 ng/mL threshold, whereas in the fed state, 33 of 35 trough values were > 60 ng/mL [29].

A phase II study of the antiviral efficacy and clinical safety of unboosted ATV in HIV-infected adults indicated that the antiviral efficacy of this drug is comparable to that of other PIs, with median viral load reduction of 1.5 log_{10} after 2-week monotherapy and 2.5 log_{10} decrease in viral load through 16 weeks after the start of two nucleosides [30]. In this study, 88 subjects were evaluable at 2 weeks, and 70 were evaluable at Week 16. The proportion of subjects with viral loads ≤ 400 c/mL was 60%, and the
proportion with viral loads less \( \leq 50 \text{ c/mL} \) was 40%. Of note, the subjects in this study were treatment-naïve adults (with less than 4 weeks of prior NRTI treatment or less than 1 week of prior NNRTI or PI treatment) with baseline HIV RNA levels across all arms of 4.8 \( \log_{10} \) (all subjects has baseline viral loads > 30,000 c/mL) and a median CD4 cell count of 386 cells/mL [28,30]. Although several studies have shown the benefit of the synergistic effect of combining ATV with low dose ritonavir, this combination is hindered by patients’ non-adherence. While decisions about dosing levels and drug combinations are based on the assumption that subjects will take the drug(s) as prescribed, this assumption is not founded, as there is evidence to suggest that 50% to 80% of pediatric subjects with a chronic illness are non-adherent to varying degrees [31]. Further, as the complexity of drug regimens increases, so does the probability that non-adherence will occur [31,32]. Thus, it is critical to the integrity of treatment outcomes to improve patients’ compliance. As the perinatally HIV-infected population is getting older, more patients refuse (or don’t take) ritonavir because of palatability, toxicity or repulsion. Thus, physicians are discontinuing this drug and treating their patients with unboosted ATV.

Data from IMPAACT Protocol P1020A (Phase I/II, Open-Label, Pharmacokinetic and Safety Study of a Novel Protease Inhibitor (BMS-232632, Atazanavir, ATV, Reyataz™) in Combination Regimens in Antiretroviral Therapy (ART)-Naïve and Experienced HIV-Infected Infants, Children, and Adolescents) suggest that using a high dose ATV (median 584-587 ng/m\(^2\)) achieved a Cmin \( \geq 60 \text{ ng/mL} \) in 90% (9/10) of children (3 months to 13 years of age) [33]. But when lower doses (median 369 mg/m\(^2\)) were used in adolescents (13 to 21 years of age) only a few achieved this level. Thus, there is some hesitation in using unboosted ATV. Yet, unboosted ATV was found to have similar efficacy to efavirenz or nelfinavir [34-36]. In addition, switching subjects with previously undetectable viral loads to boosted or unboosted ATV, patients receiving unboosted ATV had a similar or better virological suppression compared with other PIs (including lopinavir/ritonavir) [37,38]. A recent study that evaluated the long term (mean observational time of 23.9 months) efficacy and safety of boosted and unboosted ATV-containing ARV regimens in real life concluded that “in unselected clinical settings, ATV-containing ARV therapy is durable and safe in both formulations” [39]. Of note, 86.9% (113/130) of the patients in the unboosted ATV cohort were pretreated with another PI (i.e. they were treatment-experienced subjects) for a mean of 87 (± 51) months. The only statistically different outcome between the boosted and unboosted regimens was lower cholesterol in the unboosted group (167 ± 44) vs. 188 (± 48); \( P=0.005 \). Of interest, Gupta et al. reported on six treatment-experienced subjects treated with raltegravir and unboosted ATV who had a good virologic and immunologic outcome (after 26 to 82 week follow-up) [40].
Three subjects received only RAL and unboosted ATV and a 4th one was treated with this combination + 3TC only. While this case series is small, some physicians may choose to use this simplified combination for patients who cannot tolerate ritonavir, refuse to take “too many pills”, or in an effort to reduce changes in body composition.

Rilpivirine based Regimen of Interest
RPV
RPV + DRV/r or ATV/r

Rilpivirine (TMC278, RPV, Edurant™, Complera™) is a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI) that was approved in May 2011 for use in antiretroviral naïve individuals. Like etravirine, it is a diarylpyrimidine (DAPY) which has greater structural flexibility which, in theory, affords a greater barrier to developing or overcoming NNRTI associated mutations. The licensed dose of rilpivirine is 25 mg/day and the tablet is small, relative to other ARVs [41]. A fixed dose combination (Complera™) consisting of rilpivirine plus tenofovir and emtricitabine (Truvada®) was FDA approved on August 11, 2011. Rilpivirine has a long half (45 hours), the Cmax is obtained 3-4 hrs post dose, AUC is increased by about 60% when administered with food (licensed to be administered with food), exhibits linear pharmacokinetics for Cmax and AUC and is 99.7% protein bound, in vitro. Phase I metabolism is primarily via the cytochrome P450 enzyme CYP3A4/5 and is predominantly excreted in feces. The mean area under the plasma concentration-time curve from time of administration up to 24 hours (AUC24h) was 2397 ± 1032 ng(h)/mL and there was a mean pre-dose plasma concentration (C0h) of 80 ± 37 ng/mL.

TMC278-C204 (TMC278 in Treatment Naive HIV-1 Infected Subjects) evaluated EFV or TMC278 + 2 NRTI in ARV naïve individuals at a dose of 25 mg, 75 mg and 150 mg QD. Similar (approximately -2.60 log10) viral load decreases and virologic suppression (80%) were seen in each group at 48 weeks which was sustained but concerns about a dose and concentration dependent increase in QTc was observed and the 25 mg dose was chosen for phase II evaluation. Two pivotal non-inferiority randomized double blind phase III studies, ECHO (A Clinical Trial in Treatment Naive HIV-1 Patients Comparing TMC278 to Efavirenz in Combination With Tenofovir + Emtricitabine) [42] and THRIVE (A Clinical Trial in Treatment Naive HIV-subjects Patients Comparing TMC278 to Efavirenz in Combination With 2 Nucleoside/Nucleotide Reverse Transcriptase Inhibitors) [43], were conducted in adults treated with EFV or TMC278 + 2NRTI. Overall, both arms showed high response rates (82-84% <50 copies/ml) at 48 weeks. Further analysis demonstrated that TMC 278 had a significant advantage over efavirenz with respect to > grade 2 toxicity, predominantly rash and
dizziness and abnormal dreams, leading to study drug discontinuation. However, the rate of virologic failure (VF) was significantly higher in the TMC 278 treatment arm (9%) than the EFV arm (4.8%), with VF being associated with baseline VL > 100,000 and sub-optimal adherence. TMC278 failure was associated with E138K/G/R, K101E/P, H221Y and Y181C/I/V, was associated with high levels of EFV, etravirine and nevirapine resistance and resulted in a greater likelihood of developing NRTI mutations. These results led to the licensing of TMC278 for ARV naïve adults with HIV RNA viral loads < 100,000.

As rilpivirine is primarily metabolized by cytochrome P450 (CYP) 3A, drugs that induce CYP3A decrease rilpivirine concentrations whereas drugs that inhibit CYP3A may increase rilpivirine concentrations, which may affect virologic responses, development of drug resistance and observed toxicity. Additionally, rilpivirine was studied in ARV naïve individuals receiving concomitant NRTI therapy and there is limited data when combined with many other ARVs. It is not recommended to be used with many anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), several antimycobacterials (rifabutin, rifampin, rifapentine), proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole), multiple doses of dexamethasone, St John’s wort and other NNRTI therapy [44]. Drugs that may have potentially significant drug interactions include ddI, darunavir/r, lopinavir/r and other boosted and unboosted PIs may increase rilpivirine levels but are not expected to affect PI levels, azole antifungals may increase rilpivirine concentrations while not be affected by rilpivirine and macrolide antibiotics (i.e. clarithromycin) many increase rilpivirine concentrations. Concomitant antacid therapy may decrease rilpivirine concentrations and should be administered 2 hours before or 4 hours after rilpivirine administration. There is limited information available about these drug:drug interactions and observed QTc intervals.

It is likely that rilpivirine will be an attractive agent for prescription for HIV infected adolescents and young adults. Rilpivirine is a small tablet administered once a day, has less CNS and rash toxicity than efavirenz and does not share the same safety concerns during pregnancy or women of child bearing age that accompany efavirenz. Importantly, many of these characteristics are more consistent with an adolescent lifestyle relative to efavirenz treatment. The recent approval of Complera™, a fixed dose preparation considering of rilpivirine plus Truvada®, may serve as a substitute for the efavirenz containing Atripla®. Despite rilpilvirine being approved for use in ARV naïve individuals and concerns remain about its use in the presence of high viral loads, this agent may be prescribed by
clinicians treating both ARV experienced individuals or in a switch strategy.

Withdrawal of the IND for P1058:

The P1058 Protocol Team requested the withdrawal of IND 73,379 for the next version of this study because the new ARV drugs in the regimens of interest that the protocol team wishes to collect pharmacokinetic information about are prescribed by the subjects' providers for clinical reasons and are not part by the protocol. In addition, these ARVs are not supplied by the study. P1058A only specifies the ARV drugs in the combinations of interest and doses already used in clinical practice; therefore, they are not designated as "study drugs". This request was submitted to the FDA with the annual report for the IND for Version 2.0, on 11/14/08.

On February 10, 2009, the Protocol Team was informed on behalf of the Regulatory Affairs Branch, Division of Acquired Immunodeficiency Syndrome, that the Food and Drug Administration has determined that the IND 73,379, Protocol P1058, Version 2.0, dated November 8, 2007, "Intensive Pharmacokinetic Studies of Antiretroviral Drug Combinations in Children," should be exempt from the requirements of the IND regulations. The FDA concluded that the study met all the requirements for exemption from the IND regulations and therefore an IND is not required to conduct our investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA has exempted the application.

In P1058A, the responsibility for safety monitoring will remain the responsibility of the prescribing physician. P1058A will continue, however, to record basic information on safety at the time of screening/enrollment and the PK study. Specifically, any adverse events greater than grade 2 occurring from the time of screening up to the time the subject is off study will be reported to the protocol team. The form used to collect hematomas, chemistries, fasting lipids, diagnosis, signs and symptoms is the same form used in the earlier versions of the protocol. A report based on these results will be generated and sent to the protocol team. References to ARVs are current as of the time of finalization of this version of the protocol. Study drug risk lists will not be listed in the Informed Consent, since they are not being supplied by the study, and P1058A is exempt from IND reporting. The doses are based on current manufacturer recommendations as listed in the Investigators Brochure and/or Package Insert.

Please access the Regulatory Support Center's (RSC) home page: http://rsc.tech-res.com/. Please access the Package Insert (PI) link on the right and then select the PI to review by clicking on the appropriate PI dates. The protocol team will forward notices from the FDA and other relevant information, to sites, if indicated. The listed principal investigator for each site registered, is
responsible for maintaining and sharing RSC Safety messages with the respective site IRB.

1.2 Rationale for Subject Selection, Stratification and Management

Given that some antiretroviral drugs are not always approved for children and adolescents yet they are used by physicians and the relative safety in adults, the study of the available dosage formulation in larger children, adolescents and young adults is of interest. P1058A will enroll children six years of age and older, as well as adolescents and young adults who have not reached their 24th birthday. Results from P1058 Version 2.0 showed that BSA was not that important, therefore, it has been deleted as a stratification factor in P1058A. Weight based dosing, if specified per manufacturer guidelines, were followed in P1058A Version 1.0. In P1058A Version 1.0, the target sample size for Group G, H, J, K and L was 15; for Group I it was 40. A summary of the accrual in the Groups in Version 1.0 is provided in Section 1.5. In P1058A Version 2.0, the target sample size for Group M, N, P and Q is 15; for Group O it is 25. Please see the Statistics section for justification.

The primary objective of this protocol is to compare pharmacokinetic parameters achieved on fixed dosages of interacting drugs. It is possible that some subjects may be found to have extreme outlying PK values, and, in the context of their clinical circumstances, a dosage or regimen adjustment may be indicated. Therefore, results of PK studies will be communicated to local investigators. Decisions regarding changes in treatment will be solely at the discretion of the treating physician. This approach is similar to IMPAACT/PACTG P1026s, except that P1026s provides more rapid results in the setting of pregnancy. In order to aid the clinician in making dosage adjustments, P1058A will allow for a second PK after adjustment of the dosage of drugs of interest for which available formulations may reasonably allow dosage adjustment. The Protocol Chair(s) must approve any repeat PK study. A third PK, for the same subject, will not be done.

P1058A Version 1.0 only performed repeat PKs for subjects in Groups G, I, J, K and L at the discretion of the treating physician (with approval of the P1058A team), who required dose adjustments for ATV, ETV, DRV, MVC or LPV respectively, after completion of the PK study. For RAL PK results, if the variability in AUC is suspected of being due to a food effect, the treating physician may discuss this on a case-by-case basis with the Protocol Chairs, and a repeat PK may be allowed, if indicated. In P1058A Version 2.0, if the treating physician decides to adjust the dose of DRV QD, ETV, unboosted (without ritonavir) ATV or RPV after completion of the PK study, and requests a repeat PK, it can be performed with approval of the P1058A team.
1.3 Rationale for Pharmacogenetics

This study provides an opportunity to complement the pharmacokinetic studies to be performed with pharmacogenetic information that can be obtained from a single blood sample. A secondary objective of P1058A is to describe relationships between PK parameters and polymorphisms that may affect the ARVs of interest in the P1058A target population. The pharmacogenetic data collected may have the potential to help explain inter-patient pharmacokinetic variability and provide insights on how to optimize treatment for individual patients. Inter-individual pharmacokinetic variability can be a substantial confounding factor when patients are treated with standard, fixed dose regimens of antiretroviral agents. Moreover, pharmacokinetic differences between children and adults are well established and simple extrapolation of dose regimens on the basis of body size is not sufficient to provide similar systemic exposures and therapeutic outcomes. Evaluating pharmacogenetic differences among patients who demonstrate a substantially different pharmacological phenotype (e.g., systemic clearance, AUC offers the potential to identify reasons for inter-individual and age related pharmacokinetic variability.

The pharmacogenetic data from this study will also be combined with similar data from other IMPAACT and former PACTG studies to establish a larger assessment of relationships between a pharmacological phenotype, drug disposition genotype, and patient characteristics. The pharmacogenetic information will not be used in any fashion for making therapeutic decisions and has no known relevance to a specific subject’s general health, treatment, or response to therapy. The overall aim for the pharmacogenetic-pharmacokinetic data collected is to contribute to a large database with the potential to identify groups of subjects that may benefit from different treatment regimens across IMPAACT protocols.

The initial pharmacogenetic evaluations will focus on the \textit{ABCB1}(\textit{mdr1}) gene product P-glycoprotein, a transporter that affects absorption, metabolism, and distribution of several antiretroviral agents. Depending on the antiretrovirals used, genes affecting expression of \textit{CYP2B6} and \textit{CYP3A4} will also be assessed. These initial targets have been selected because of known genetic polymorphisms with substantial differences in allele frequency that may explain pharmacokinetic differences. P1058A will perform three single nucleotide polymorphism (SNP) analyses for each subject (\textit{CYP2B6-516-G/T}, \textit{CYP2B6-785-A/G}, \textit{CYP3A4*1B A-290G} and \textit{ABCB1}-3435-C/T). As further information is forthcoming regarding genetic polymorphisms or other genetically determined characteristics relevant to drug disposition, the samples will be available for subsequent analysis.

1.4 Rationale for Plasma Storage

Storage of plasma will permit future studies examining the relationships between
pharmacokinetics, drug sensitivity, other virologic characteristics, and virologic response in subjects of this study, or combined with data from other IMPAACT/PACTG or other network protocols. (Priority storage at BRI for NIAID sites was approved on 3/24/09 by the IMPAACT Laboratory Committee).

1.5 Results of Version 1.0 and Structure of Version 2.0

Version 1.0 had the following regimen groups: RAL + ATV/r, RAL + TDF, MVC + ATV/r, MVC + LPV/r, MVC + RAL + ETV, and ETV+ DRV/r.

Table 4 presents total enrollment in each P1058A Version 1.0 group as of October 21, 2011. A total of 80 subjects were enrolled in Version 1.0.

Table 4.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>G – RAL + ATV/r</td>
<td>15</td>
</tr>
<tr>
<td>H – RAL + TDF</td>
<td>19</td>
</tr>
<tr>
<td>I – ETV + DRV/r</td>
<td>44</td>
</tr>
<tr>
<td>J – MVC + ATV/r</td>
<td>1</td>
</tr>
<tr>
<td>K – MVC + LPV/r</td>
<td>0</td>
</tr>
<tr>
<td>L – MVC + RAL+ ETV</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
</tr>
</tbody>
</table>

In Version 2.0 the following changes will be made:
- Group G had 15 evaluable subjects and thus has met the target accrual. This group has been closed.
- Group H had 16 evaluable subjects and thus has met the target accrual. This group has been closed.
- Group I had 40 evaluable subjects and thus has met the target accrual. This group has been closed.
- Groups J, K and L will not be continued due to lack of enrollment. They will be closed.
- New groups will be opened for DRV/r, DRV/r with ETV, unboosted (without ritonavir) ATV, RPV, and RPV with DRV/r or ATV/r.

NOTE: Evaluable subjects are those subjects whose PK results could be adequately evaluated.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives (Version 1.0)

2.11 To assess the steady state pharmacokinetics of raltegravir administered in combination with atazanavir/ritonavir or tenofovir or maraviroc/etravirine
to older children, adolescents and young adults. **Due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.**

2.12 To assess the steady state pharmacokinetics of etravirine administered to older children, adolescents and young adults.

2.13 To assess the steady state pharmacokinetics of maraviroc administered in combination with atazanavir/ritonavir or lopinavir/ritonavir to older children, adolescents and young adults. **Due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.**

2.14 To assess the steady state pharmacokinetics of maraviroc (600 mg BID) given in combination with raltegravir and etravirine (a PI sparing regimen) to older children, adolescents and young adults. **Due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.**

2.15 To assess the steady state pharmacokinetics of darunavir/ritonavir BID administered to older children, adolescents and young adults.

2.2 Primary Objectives (Version 2.0)

2.21 To assess the steady state pharmacokinetics of darunavir QD with or without etravirine administered to older children, adolescents and young adults.

2.22 To assess the steady state pharmacokinetics of unboosted (without ritonavir) atazanavir administered to older children, adolescents and young adults.

2.23 To assess the steady state pharmacokinetics of rilpivirine 25 mg QD with and without the protease inhibitors darunavir/ritonavir or atazanavir/ritonavir.

2.3 Secondary Objectives

2.21 To describe the relationship between Tanner stage and the pharmacokinetics of the regimens of interest in children and adolescents.

2.22 To describe the relationships between the pharmacokinetic parameters and polymorphisms that may affect the antiretrovirals of interest in older children, adolescents and young adults.
2.23 To record adverse events associated with the antiretrovirals of interest.

3.0 STUDY DESIGN

P1058A includes drugs that may not be approved by the FDA for marketing for use in subjects within the inclusion age range. P1058A is not an FDA-regulated drug study and does not prescribe subject treatment. The decision to prescribe one of the regimens of interest and the responsibility for monitoring treatment safety and efficacy is solely that of the treating clinician.

P1058A is an intensive 12-hour or 24-hour pharmacokinetic study of selected antiretroviral drugs in HIV-infected children, adolescents and young adults age ≥ 6 to < 24 years who are receiving (minimum of 14 days prior to the PK study) a regimen of antiretrovirals that includes one of the drugs or drug combinations of interest. A 12-hr PK was done for P1058A Version 1.0. In P1058A Version 2.0, a 24-hr PK will be done. Blood samples will be drawn at 0, 1, 2, 4, 6, 8, and 12 or 24 hours post dosing. Viral load, CD4, Tanner stage and clinical staging data will be collected in order to characterize the population under study. Samples for potential genetic polymorphisms affecting ABCB1 and CYP genetic variants will be obtained.

PK Results and Repeat PK

Results will be communicated to the local investigator, but there are no protocol-mandated dosage adjustments, and PKs will not be repeated after any change in regimen, except as noted. P1058A Version 1.0 only performed repeat PKs for subjects in Groups G, I, J, K and L at the discretion of the treating physician (with approval of the P1058A team), who required dose adjustments for ATV/r, ETV, DRV/r, MVC or LPV/r respectively, after completion of the PK study. Repeat PK for changes in RAL dosing were on a case-by-case basis (See Section 8.0). In P1058A Version 2.0, if the treating physician decides to adjust the dose of DRV QD, ETV, unboosted (without ritonavir) ATV or RPV after completion of the PK study, and requests a repeat PK, it can be performed with approval of the P1058A team. Subjects must have received the revised dose for at least 14 days before the PK study can be repeated.

The schedule of laboratory and clinical evaluations for P1058A is outlined in Appendix I, Schedule of Evaluations.

For entry eligibility, historical laboratory results obtained up to 28 days before entry may be used, but the PK study must be completed within 35 days of these tests. The subject must be on the ARV combination of interest a minimum of 30 days, prior to the PK study date. The PK study must be completed within 5 weeks (35 days) of the date of screening/entry evaluations or laboratory test results used for eligibility.
All IMPAACT laboratory processing and shipping instructions will be contained in a separate Laboratory Processing Chart for P1058A. A separate Tanner Scale document will be available on the P1058A specific webpage, current documents (it is identical to Appendix II of P1058, Version 2.0).

3.1 Definitions

**Regimen group**
Subjects will accrue into **open regimen groups in Table 1 in the SCHEMA and Section 5.0** according to which antiretroviral regimen inclusion criteria they satisfy for entry: (See SCHEMA, Section 4.0 and Section 5.0 for specific details.)

For **all Groups**, the intensive 12-hour or **24-hour PK study** should be performed only if the subject has been on the regimen of interest for **at least 30** days. Subjects starting a combination of interest must be stable on that regimen for a minimum of **30** days prior to the scheduled PK study date. **If the treating physician decides to adjust the dose of subjects in specific Groups as previously described and requests another PK, a repeat PK ≥ 14 days post-dosage adjustment will be done with approval of the P1058A team.**

3.2 Timing of PK Study Visits

Screening and entry procedures and the PK visit may be combined in a single visit, if the required time on the ARV combination of interest is met, and the results of the requested tests that satisfy screening and eligibility criteria are available. The PK study visit should be completed no later than **5 weeks** (35 days) of the date of the screen/entry results. At the entry visit, the history and current or planned antiretroviral treatment and other medications are reviewed to ensure eligibility, informed consent and screening labs are obtained, and details of the medication regimen and adherence are reviewed in preparation for the intensive PK study.

Once the PK visit is scheduled, a reminder call regarding the intensive PK study visit and reinforcing adherence will be made about 3 days prior to the PK visit. Study visit windows are ± 4 days, to allow for weekends or extended holidays. Subjects receiving QD ARV doses, should take them in the **morning** (beginning at least 3 days prior to the PK study day).

3.2.1 Intensive PK Scheduling

The intensive PK study must be scheduled according to the following timing:

a.) Stable on the regimen of interest for at least **30** days
b.) No more than 35 days after the date of the screening/enrollment results used for eligibility.

c.) Direct Observation of Therapy (DOT)
Witnessed dosing on the day of the intensive PK study should be as close as possible to 12 hours for doses given BID and 24 hours for doses given QD after the most recent home dosing of the ARV of interest as reported by the participant. (See Section 8.3 for details.)

3.22 Rescheduling Intensive PK

The intensive PK study may be rescheduled because of logistical reasons (e.g. subject cannot attend visit), use of disallowed or other interacting drug in the 14 days prior to the intensive PK, or non-adherence to the prescribed regimen, e.g. taking the QD dose in the evening, as defined below.

The 35 days limits specified in Section 3.21 may be extended to 42 days in the event of a rescheduled intensive PK with permission from the Protocol Chair(s). The following criteria for non-adherence will result in the intensive PK study being postponed:

- Missing either of the 2 previous doses of any of the ARVs of interest.
- Missing any 2 doses of any of the ARVs of interest in the past 7 days.
- Not switching QD ARVs of interest to be taken in the morning for 3 days prior to the scheduled PK study day.

3.23 Repeat intensive PK (non-evaluability)

The intensive PK may be repeated once within 6 weeks of the date results of the initial PK are reported to the site if results from the initial PK cannot be evaluated or the provider has decided to change the dose and request a repeat PK.

3.3 Subject Cohorts and Accrual

Target total is up to 200 evaluable subjects across all Groups. Evaluable subjects are those subjects whose PK results can be adequately evaluated.

The target total for Version 1.0 was 115 and sample sizes for each regimen of interest were:
- Group G: 15 evaluable subjects. This Group is closed.
- Group H: 15 evaluable subjects. This Group is closed.
- Group I: 40 evaluable subjects. This Group is closed.
- Group J: 15 evaluable subjects. This Group is closed.
- Group K: 15 evaluable subjects. This Group is closed.
- Group L: 15 evaluable subjects. This Group is closed.

The target total for Version 2.0 is 85 and sample sizes for each regimen of interest are:
- Group M: 15 evaluable subjects.
- Group N: 15 evaluable subjects.
- Group O: 25 evaluable subjects.
- Group P: 15 evaluable subjects.
- Group Q: 15 evaluable subjects.

If a particular Group has not accrued about 50% of the target by 12 months after opening of the protocol to enrollment and after 50% of eligible IMPAACT sites in the U.S. have protocol registered, that regimen Group will be re-evaluated. There are 43 IMPAACT sites within the US (13 NIAID-supported; 30 NICHD-supported); this number may change in the future.

The progress of and prospect for accrual will be reviewed by the protocol team, during monthly calls. A report to the parent Scientific Committee (Primary Therapy) will be done every 6 months. IMPAACT review and evaluation will be as directed by the Performance and Evaluation Resource Committee (PERC). Site credit for enrollment is contingent upon completion of the PK study.

Consideration will be given as to whether sufficient accrual to yield evaluable data can be achieved in a reasonable time. Groups for which sufficient accrual is not expected may be closed or a review may be scheduled earlier at the IMPAACT Leadership and/or Primary Therapy Scientific Committee’s discretion.

3.4 Re-enrollment

Re-enrollment is an option for P1058A because subjects completing the PK who subsequently change therapy to another qualifying regimen may re-enroll in the other Group for which they then qualify. Subjects changing from one P1058A specified regimen of interest to another P1058A specified regimen of interest may re-enroll in P1058A. P1058 Version 1.0 and Version 2.0 treatment-experienced subjects who have subsequently switched to a P1058A specified regimen of interest may also enroll in P1058A. The subject must be re-consented and must meet the entry criteria in Section 4.0 for each re-enrollment in P1058A. A new eligibility checklist must also be completed.

The subject will be re-registered to the protocol using a new Case Identification (CID) Number. The site will use the next available Patient Identification (PID) Number as the new CID to re-enroll a subject. The site will then use this new CID when filling out the eligibility checklist for the
new (i.e. second, third, etc.) regimen group. The subject’s previous PID/PIDs will be collected in the eligibility checklist and the DMC Randomization Desk will map the PIDs together. The new CID will also be used to complete the forms for the new regimen group. For other questions, contact the Protocol Team (impaact.teamp1058A@fstrf.org), on a case-by-case basis.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

Screening and entry visits may be combined into a single visit. However, enrollment using the DMC Subject Enrollment System (SES) should be performed at the entry visit. Inclusion and exclusion criteria must be met before enrollment.

The PK study must be completed within 5 weeks of the date of the screening/entry evaluations or laboratory test results used for eligibility.

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.

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 PCR (quantitative >5,000 copies/mL or qualitative)
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

If the first test is positive, a second sample must be 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).

Sites should use an FDA-licensed HIV-1 test kit, if possible.
4.12 Ages ≥ 6 to < 24 years (from the 6th birthday up to but not including the 24th birthday).

4.13 Subjects must be receiving and be stable on the specified antiretroviral regimen as described in Table 1 in the SCHEMA, for at least 30 days prior to screening/entry, in order to enroll and schedule the PK study. Antiretrovirals will NOT be provided through this protocol.

Subjects must have been prescribed one of the regimens described in the SCHEMA by their clinician on the basis of clinical need (although the availability of drug levels may have been a factor in clinical decision-making). The decision to initiate the regimen was that of the prescribing physician and not that of the P1058A team. Any licensed formulation that achieves these dosages, but without including a disallowed drug, may be used. Please see Section 5.0 for allowed formulations for each specific regimen of interest.

- All P1058A eligible subjects will need to register to one of the regimen of interest groups.
- P1058 Version 1.0 or 2.0 and P1058A subjects who have switched to another regimen of interest specified in the SCHEMA are eligible to enroll to the new groups of P1058A. See Section 3.4 for the re-enrollment procedures.

4.14 Body surface area (BSA) ≥ 0.85 m².

4.15 Participant/parent/primary caregiver (as applicable) must be able and willing to provide signed informed consent.

4.16 Negative pregnancy test

Female study volunteers of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before enrollment, and 48 hours prior to the performance of the PK component of the study.

NOTE: “Female study volunteers of reproductive potential” is defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months), or have not undergone a sterilization procedure (e.g., hysterectomy, bilateral oophorectomy or salpingotomy).
4.17 Birth control

Female study volunteers who are participating in sexual activity that could lead to pregnancy must agree to use two reliable methods of contraception, one of which must be a barrier method. A barrier method of contraception (condoms, diaphragm or cervical cap) together with another reliable form of contraception (condoms, with a spermicidal agent; a diaphragm or cervical cap with spermicide; an IUD; or hormonal-based contraception) must be used while receiving study drugs and for 6 weeks after performance of the PK testing (or repeat PK testing, as applicable). Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission. All study participants must agree not to participate in a conception process (e.g. active attempt to become pregnant or to impregnate, sperm donation, or in vitro fertilization).

4.2 Exclusion criteria

4.21 Hemoglobin < 8.5 g/dL

4.22 Clinical evidence of pancreatitis (i.e. moderate clinical symptoms)

4.23 Lipase, AST and ALT ≥ Grade 2

4.24 Total bilirubin > Grade 1; except for subjects taking ATV, total bilirubin > Grade 3.

4.25 Pregnancy

4.26 Subjects who are breastfeeding

4.27 Treatment in the 14 days prior to performing the intensive PK with any antiretroviral or non-antiretroviral drug that may significantly affect the pharmacokinetics of the studied drugs. This includes but is not limited to the disallowed medications as referenced in Section 4.5.

- If a potential subject is receiving one of these drugs, or other drug that might interact with the pharmacokinetics of the drugs of interest, the site is encouraged to query the Protocol Co-Chairs.
- Available information will be reviewed and if a significant effect of the co-administered drug on the metabolism of the prescribed antiretrovirals is unlikely, enrollment may be permitted. The prescribing physician remains responsible for ensuring that there is no
significant adverse effect due to the interaction of prescribed antiretrovirals and co-administered drugs.

4.28 Use of any immunomodulator (interferons, interleukins, systemic corticosteroids, cyclosporine), or investigational vaccine or therapy within 30 days prior to entry.

- Use of systemic or inhaled corticosteroids for acute therapy for PCP or asthma exacerbation and prednisone $\leq 10$ mg (or equivalent) is permitted as a stable or tapering dose.

4.29 Known allergy/sensitivity or any hypersensitivity to components of two or more study-specified drugs or their formulation.

4.3 Allowed Medications

The ARVs as indicated in the Regimens of Interest in Table 1 in the Schema and Section 5 consisting of ARVs prescribed by the subject’s provider, study-required boosting agents, and the additional NRTI, NNRTI, PI, Entry or Integrase Inhibitor, if indicated in Table 1.

4.4 Concomitant Medications

Tables of prohibited and precautionary concomitant medications are similar to those used by the AIDS Clinical Trials Group (ACTG). Links will be provided in the P1058A protocol specific web page. In order to avoid adverse events caused by drug interactions, whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent’s most recent package inserts, investigator's brochure (IB), or updated information from the RSC or DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

The ACTG Pharmacology Committee table of prohibited and precautionary concomitant medications has been converted into an online searchable database entitled ACTG Drug Interactions Database accessed through the following website address:

If the ACTG Drug Interactions Database cannot be accessed or is unavailable, sites should contact the team at impaact.teamp1058A@fstrf.org for any questions about prohibited and precautionary concomitant medications for potential subjects and subjects enrolled in the study.
4.5 Disallowed Medications

Prohibited Medications

Refer to the ACTG Drug Interactions Database (http://tdm.pharm.buffalo.edu/home/di_search/node/8) for Prohibited and Precautionary Medication guidance.

Subjects should discontinue prohibited medications at least 30 days prior to entry.

Precautionary Medications

Refer to the ACTG Drug Interactions Database (http://tdm.pharm.buffalo.edu/home/di_search/node/8) for Prohibited and Precautionary Medication guidance.

Package inserts of ARV drugs and concomitant agents should be referred to whenever a concomitant medication is initiated or dose changed, to avoid drug interactions AEs.

Sites are encouraged to query the Protocol Team for potential exceptions (See Sections 4.27 and 4.28). The treating clinician has sole responsibility for ensuring that there are no dangerous interactions between the drugs of interest and co-administered drugs. Subjects may not be taking concomitant medications that may significantly affect disposition of the drugs of interest. These include but are not necessarily limited to the following drugs. Site investigators are encouraged to contact the protocol team regarding potential drug interactions.

- Group G: Drugs affecting P450 or glucuronidation
- Group H: Drugs affecting glucuronidation
- Group I: Drugs affecting P450
- Group J, K and L: Drugs affecting P450 or drugs interacting with maraviroc

A complete list of current medications, including over-the-counter medications will be taken at the screening/entry visit as part of the HISTORY and reviewed prior to performing the intensive PK (see Schedule of Evaluations-Appendix I).

4.6 Enrollment Procedures

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

Site-specific informed consent forms (ICFs) *WILL* 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 RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

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

Subject enrollment is done through the DMC Subject Enrollment System (SES).

Re-enrollment of subjects, who have completed the PK study in a specific Group and then switch regimens, is an option in P1058A (see Section 3.4). Subjects that participated in P1058 Version 1.0 or 2.0 are eligible, if they meet entry criteria. (See note in Section 4.1) For other questions, contact the Protocol Team, on a case-by-case basis (impaaact.teamp1058A@fstrf.org).

4.7 Co-Enrollment

Co-enrollment in other treatment trials is permitted, as long as treatment does not violate exclusion criteria. Co-enrollment in IMPAACT P1074 or other network long-term follow-up study is encouraged, and will be granted if the IMPAACT P1058A protocol chairs and other IMPAACT study/ or other network study chair(s) agree. Co-enrollment of P1058, P1058A and P1074 was approved by the IMPAACT Leadership on 2/25/09. Data sharing collaborations may also be
possible on a case-by-case basis. Please contact the protocol Chairs for co-enrollment related questions.

4.8 Replacement of Subjects

Subjects will be replaced if PK results cannot be evaluated (e.g. samples mistimed, missing, contaminated, mislabeled, insufficient quality, etc.), and if a repeat PK (see Section 3.23) at the entry criteria dosage is not feasible, or has already been done and the results also cannot be evaluated.

5.0 STUDY REGIMENS OF INTEREST

P1058A investigates the pharmacokinetics of certain antiretroviral agents that have been prescribed by the treating clinician. P1058A does not provide for study treatment, and does not prescribe or dispense medication. P1058A will evaluate PK parameters of interest in study subjects after they are stable (at least 30 days) on a combination of antiretroviral drugs, prescribed by their physician that includes one of the regimens of interest as described previously in the SCHEMA, Table 1 (below), and previous sections.

**The regimen groups in Version 1.0 (G, H, I, J, K and L) have been closed. The regimen Groups that have been added in Version 2.0 are M, N, O, P and Q.**

**Additional study drugs and regimens will be added by amendment.** The subject should take the indicated ARVs according to the label, with food or without, as indicated (QD-once daily; BID-twice daily) and as detailed in Section 3.2 for the PK scheduling. This information will be recorded on the appropriate Case Report Form (CRF) at the time of the PK (see Section 8.3).

Formulations* that were used in Version 1.0 include:

- Raltegravir 400 mg tablets (Isentress®) BID
- Maraviroc 150 mg tablets (Selzentry®) BID
- Etravirine 200 mg tablets (Intelicence™) BID
- Darunavir by weight* [as 75, 400 or 600 mg tablets (Prezista®)] BID

*P1058A will allow additional FDA-approved formulations as they become available-see below.

**Note:** The recommended oral dose for pediatric patients (6 to <18 years of age and weighing at least 44 lbs) of **Darunavir (PREZISTA®)** with ritonavir is based on body weight and should not exceed the recommended treatment-experienced adult dose (**Darunavir [PREZISTA®]/r 600/100 mg twice daily**).

**Tibotec Therapeutics recommends using Darunavir [PREZISTA®]/75mg tablets to determine an appropriate pediatric dose until 150mg tablets are made available.**

<table>
<thead>
<tr>
<th>Body weight</th>
<th>BSA</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 44 lbs (20 kg) - &lt; 66 lbs</td>
<td>0.80 m²</td>
<td>375 mg Darunavir (PREZISTA®)/50 mg ritonavir BID</td>
</tr>
<tr>
<td>≥ 66 lbs (30 kg) - &lt; 88 lbs</td>
<td>1.06 m²</td>
<td>450 mg Darunavir (PREZISTA®)/60 mg ritonavir BID</td>
</tr>
<tr>
<td>≥ 88 lbs (40 kg)</td>
<td>1.29 m²</td>
<td>600 mg Darunavir (PREZISTA®)/100 mg ritonavir BID</td>
</tr>
</tbody>
</table>
• Ritonavir 100 mg capsules or 80 mg/mL solution (Norvir®)-QD or BID-depending on PI and Group
• Atazanavir 300 mg capsule (Reyataz®) QD
• Tenofovir tablets-TDF formulations QD, may include:
  ◊ TDF 300 mg (Viread®)
  ◊ TDF 300 mg + emtricitabine (FTC) 200 mg (Truvada®) or
  ◊ TDF 300 mg + EFV 600 mg + FTC 200 mg (Atripla™)
• Lopinavir/ritonavir, LPV/r 400/100 mg (two 200/50 mg tablets or 5 mL oral solution BID, (Kaletra®), pediatrics-BID dose based on body weight.

Formulations that may be used in Version 2.0 include:
• Etravirine (Intecence™) 100 mg tablets, 200 mg tablets
• Darunavir (Prezista®) 400 mg tablets, 600 mg tablets
• Rilpivirine (Edurant™) 25 mg QD
• Complera™ QD (fixed dose formulation of rilpivirine [Edurant™] 27.5 mg, tenofovir 300 [Viread®] mg and emtricitabine [Emtriva®] 200 mg)
• Ritonavir (Norvir®) 100 mg capsules or tablets or 80 mg/mL solution (Norvir®)-QD or BID-depending on PI and Group
• Atazanavir (Reyataz®) 200 mg capsule, 300 mg capsule
• Newer formulations of the above agents with proven bioequivalence which may come available as per team decision.
Table 1. Regimens of Interest (ROI) for PK and allowed ARVs.

<table>
<thead>
<tr>
<th>Group</th>
<th>Regimens of Interest (ROI)</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry Inhibitor</th>
<th>CCR5 Antagonist</th>
<th>Integrate Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MVC 150 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>RAL 400 mg BID +</td>
<td>YES³</td>
<td></td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>RAL 400 mg BID</td>
</tr>
<tr>
<td></td>
<td>ATV/r 300/100 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>RAL 400 mg BID +</td>
<td>YES</td>
<td>ETV⁴</td>
<td>NO</td>
<td>DRV/r², LPV/r</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF 300 mg QD</td>
<td></td>
<td>EFV,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>ETV 200 mg BID +</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/r, per weight, BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>MVC 150 mg BID +</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/r 300/100 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>MVC 150 mg BID +</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>___</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r 400/100 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>MVC 600 mg BID +</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>___</td>
<td>___</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAL 400 mg BID +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ETV 200 mg BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>DRV/r 800/100 mg QD</td>
<td>YES</td>
<td>NO</td>
<td>ETV</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETV,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>DRV/r 800/100 mg QD +</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>ETV 200 mg BID or 400 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Unboosted (without ritonavir)</td>
<td>NO TDF</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>ATV 400 mg QD or 600 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>RPV 25 mg QD³ or</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO LPV, TPV,</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>CompleraTM QD⁶ ±</td>
<td></td>
<td></td>
<td></td>
<td>IDV, SQV, FPV,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DRV/r 800/100 mg QD or</td>
<td></td>
<td></td>
<td></td>
<td>NFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/r 300/100 mg QD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td>RPV 25 mg QD³ or</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Complera™ QD⁶</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Groups G, H, I, J, K and L which have been grayed out were the regimens of interest in Version 1.0. These groups have been closed.

NOTES:

1Enfuvirtide, ENF, T-20 (Fuzeon®) a Fusion Inhibitor, is allowed in all groups.
2MVC 600 mg BID, if given with ETV, is recommended (Group H and I).
3TDF preferred (Group G).
4DRV + ETV not allowed in Group H. In Group H, if ETV is the optional NNRTI, then DRV/r cannot be the optional PI.
5Subject cannot be on H2 blockers and must take RPV with food.
6Complera™ (Emtricitabine [FTC] 200 mg + Rilpivirine [RPV] 27.5 mg + Tenofovir [TDF] 300 mg)

For questions on specific ARV regimens, if not addressed here, please ask the protocol team impaact.teamp1058A@fstrf.org. Enrollment of subjects receiving a new formulation of one or more drugs of interest not described in Table 1 may be considered but requires specific approval of the Protocol Team.
Optional ARVs
Other options as indicated in the Table 1. NRTIs, NNRTIs, ENF-as indicated by the provider, prescription and labeling. Please check the inclusion and exclusion criteria, allowed and disallowed medications lists. Please notify the team, if you have a question regarding a combination (impaaact.teamp1058A@fstrf.org).

6.0 SUBJECT MANAGEMENT

6.1 Subject Management Plan

P1058A will study specific ARV drug exposure in subjects who have been prescribed the regimens of interest by their primary physicians. Protocol participation requires but does not prescribe initial antiretroviral therapy. Laboratory results must be communicated promptly to the treating physician. Management of possible toxicity while on study is the responsibility of the treating physician at the site and should follow standard management practice at the site.

Expedited Adverse Event (EAE) reporting

EAE reporting to DAIDS is not being done as part of this study. ICH E2A-defined Serious Adverse Events (events resulting in death, that are life threatening, that result in persistent or significant disability/incapacity, that result in congenital anomaly/birth defect, or require inpatient hospitalization or prolongation of existing hospitalization) must be recorded on the appropriate CRF and must be reported to the IRB (unless written documentation is received by the IRB indicating such reporting is not needed) by the site principal investigators. Important medical events that may require intervention to prevent one of the outcomes listed above may also be considered to be serious. Please refer to drug labeling for individual study drugs for further information on toxicity. PK data will be shared with the responsible clinician; Section 6.2 describes the process for sharing PK data with the responsible clinician.

The DMC should email a listing of all new ICH E2A-defined SAEs on a weekly basis to the P1058A medical officers and chairs for review and further action as needed if safety signals are identified.

6.2 Subject PK Management Plan

Assays will be performed as described in Section 8.0 – Clinical Pharmacology Plan. Reports will include the AUC, and $C_{\text{min}}$, along with data from PK studies of dosages that have been shown to be safe and effective in adults. This information
will be included as background information to aid in interpretation of individual results and should not be construed as to imply a dosage adjustment recommendation.

Decisions regarding adjusting dosages in individual subjects will be at the discretion of the treating physician. Such decisions should consider resistance, tolerance, toxicity, adherence, and treatment goals. Given how little is known about PK/efficacy/toxicity relationships, caution is advised in trying to fine tune dosages when PK parameters are within the range observed in the majority of historical controls for which efficacy has been demonstrated. So that the PK results may be understood in light of the clinical situation and available data on the clinical significance of the pharmacokinetics of the drugs in question, site investigators may contact the protocol team impaact.teamp1058A@fstrf.org for consultation.

Re-enrollment of subjects who have completed the study will be an option in P1058A (see Section 3.4).

6.3 Criteria for Subject Discontinuation

- The subject or legal guardian refuses further participation and/or follow-up evaluations, including PK evaluations and repeat PK evaluation if the initial PK could not be adequately evaluated.
- 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 (Section 4.5) in the 14 days prior to performing the intensive PK.
- Pregnancy or breastfeeding.
- The study may be discontinued at any time by the IMPAACT Network, NIAID and/or NICHD, the Office for Human Research Protections (OHRP), the IRB or other governmental regulatory agencies, as part of their duties to ensure that research subjects are protected.

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design Issues

The primary observational groups are comprised of older children, adolescents and young adults. The regimen Groups have been defined in the SCHEMA.
For Groups in Version 1.0, an intensive 12-hour PK study was scheduled after at least 30 days on the combination of interest. For Groups in Version 2.0, an intensive 24-hour PK study will be scheduled after at least 30 days on the combination of interest. For all Groups, the intensive PK study should be performed within 35 days (5 weeks) of screening/entry evaluations. Groups N and O includes individuals receiving one of two possible dosing schedules, 200 mg BID or 400 mg QD of ETV and 400 mg QD or 600 mg QD of Unboosted ATV respectively. An integrative analysis allowing for heterogeneity in PK as a function of ETV and ATV dosing will be performed. Descriptive statistics and confidence intervals will characterize the results of this study of pharmacokinetic interactions, in many instances the first such data in children and/or adolescents and young adults. The primary objectives will focus on steady state PK of the regimens of interest in various combinations. The secondary objectives concern heterogeneities in PK associated with physical development, genetic variation and adverse event rate frequencies.

Since subjects must be receiving and stable on the specified antiretroviral regimen for at least 30 days prior to screening/entry, the study will not be able to identify inadequate PK or toxicity that may occur within the first 30 days after starting the regimen.

7.2 Outcome Measures

The primary outcome measures for each regimen are the pre-dosage concentration ($C_0$, $C_{12}$ [for Version 1.0] and $C_{24}$ [for Version 2.0]) and area under the concentration-time curve (AUC) over the dosing interval.

7.3 Stratification

None.

7.4 Accrual and Subject Number

Fifteen (15) evaluable subjects per regimen of interest with the exception of Groups I (ETV, 40 subjects) and O (Unboosted ATV, 25), target total = 200, as previously described in Section 3.3. Evaluable subjects are those subjects whose PK results can be adequately evaluated.

7.5 Statistical Power Considerations

A mean AUC for RAL of approximately 5.5 (SD approximately 3.8) h x mg/L was reported by the IMPAACT P1066 study team in April 2008 [12]. The protocol team denotes the target mean AUC as $T=5.5$. For a target interval of ($T/1.25$, $T*1.25$) N=30 individuals provides 76% power to detect a halving of...
RAL exposure, using a rule that declares under exposure to be present if the 90% CI lies entirely below the target interval. In order to achieve this level of power, the protocol team will pool over arms G and H, each of size N=15. For ETV, the mean (SD) AUC is 5.51 (4.71) and with these parameters, N=40 individuals yields 70% power to detect a halving of ETV exposure using the same rule. There is insufficient data available on MVC AUC targets to support a power calculation.

The following table presents sample size selection options for the main treatment regimens in Version 2.0. For a given sample size, we present the lower bound on mean AUC that could be detected in a 2-sided one sample test of null hypothesis that mean AUC takes on the value reported in literature.

<table>
<thead>
<tr>
<th>Arms M and N</th>
<th>DRV mean AUC 61106, SD 22455</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum detectable difference at 2-sided alpha=0.05, power 80%</td>
</tr>
<tr>
<td>N per arm=</td>
<td>MDD%</td>
</tr>
<tr>
<td>10</td>
<td>37%</td>
</tr>
<tr>
<td>15</td>
<td>29%</td>
</tr>
<tr>
<td>20</td>
<td>24%</td>
</tr>
<tr>
<td>25</td>
<td>21%</td>
</tr>
<tr>
<td>30</td>
<td>19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm O</th>
<th>unboosted ATV, median AUC 50, CV approximately 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum detectable difference at 2-sided alpha=0.05, power 80%</td>
</tr>
<tr>
<td>N per arm=</td>
<td>MDD%</td>
</tr>
<tr>
<td>10</td>
<td>50%</td>
</tr>
<tr>
<td>15</td>
<td>39%</td>
</tr>
<tr>
<td>20</td>
<td>33%</td>
</tr>
<tr>
<td>25</td>
<td>29%</td>
</tr>
<tr>
<td>35</td>
<td>24%</td>
</tr>
<tr>
<td>45</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arms P and Q</th>
<th>RPV mean AUC 5210, SD 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum detectable difference at 2-sided alpha=0.05, power 80%</td>
</tr>
<tr>
<td>N per arm=</td>
<td>MDD%</td>
</tr>
<tr>
<td>10</td>
<td>38%</td>
</tr>
<tr>
<td>15</td>
<td>30%</td>
</tr>
<tr>
<td>20</td>
<td>25%</td>
</tr>
<tr>
<td>25</td>
<td>22%</td>
</tr>
<tr>
<td>30</td>
<td>20%</td>
</tr>
</tbody>
</table>
For groups M and N the following sample size considerations have been derived on the basis of data reported by Boffito and colleagues [45]. DRV/r was administered at 800/100mg once daily, yielding average AUC (24h) of 61106 ngxh/ml (SD 22455). With a sample of 15 children per arm, we have 80% power to detect a 30% minimum detectable difference from this reported mean. For group O data on unboosted ATV suggests a coefficient of variation of about 50% for mg/m² dosing in studies of 20 children [33]. Since the estimated median AUC in these studies was about 50mcgh/mL, a sample size of 25 gives 80% power to see a 30% minimum detectable difference. For groups P and Q data on RPV (TMC278) 25 mg QD, yield average AUC (24h) of 5210 ngxh/ml (SD2001) [46]. With a sample of 15 children per group, we have 80% power to detect a 30% minimum detectable difference from this reported mean.

7.6 Monitoring

Monthly accrual and adverse event reports, if any, will be sent to the study team. PK results will be distributed as described in the Pharmacology Plan. The team will have monthly calls, or as needed, to discuss adverse event reports, accrual rates (more specifically in the RPV containing arms P and Q since the use of RPV may be limited in pediatrics), and PK outcomes.

7.7 Analysis

Analysis will consist of computing geometric mean and 90% CI for AUC, \( C_{\text{min}} \), \( C_{\text{max}} \) and comparing these to the target intervals described in Section 7.5. When a treatment of interest is present in multiple arms (e.g., RAL present in Groups G and H, DRV present in Groups M and N), the basic analysis will pool over the arms and test for homogeneity in distributions of PK measures for the treatment of interest. If there is evidence of inhomogeneity of PK for RAL in the RAL-containing arms and DRV in the DRV-containing arms, separate CI will be computed and reported. Descriptive statistics will be provided on PK within Tanner stage strata, genetic variation and adverse event rates (if any). Refer to section 6.1 for AE management. We remark that the analysis plan presented here is provisional, based on information available at the time of protocol construction. At the time of the analysis, the most relevant available comparison data will be used for interpretation of the findings in addition to those described in this plan.

Too few children will be enrolled into this study to stratify based upon age or BSA. However, if a sufficient range of ages enroll, a secondary analysis will be done. If there are sufficient numbers of subjects an exploratory secondary analysis can be done of the effects of tenofovir (TDF) and atazanavir/ritonavir (ATV/r) combined on raltegravir (RAL) PKs.
The criteria for analysis set forth here are for comparing population data on combinations to published data on monotherapy in other populations. These criteria are not meant to suggest norms or clinical targets for individual PK results.

8.0 CLINICAL PHARMACOLOGY PLAN

8.1 Pharmacology Objectives

The clinical pharmacology studies of IMPAACT P1058A are designed to meet four primary pharmacologic objectives as stated in the SCHEMA and Section 2.0. P1058A will assess the steady state pharmacokinetics of the following combinations, when administered to older children, adolescents and young adults:

- raltegravir in combination with atazanavir/ritonavir or tenofovir or maraviroc/etravirine; **due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.**
- etravirine and darunavir/ritonavir
- maraviroc in combination with atazanavir/ritonavir or lopinavir/ritonavir; **due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.**
- maraviroc (600 mg BID) in combination with raltegravir and etravirine (a PI sparing regimen); **due to lack of enrollment, the maraviroc regimen groups have been closed and analysis will not be done.**
- darunavir/ritonavir once daily
- darunavir/ritonavir once daily with etravirine
- unboosted atazanavir once daily
- rilpivirine or Complera™ once daily
- rilpivirine or Complera™ once daily with darunavir/ritonavir or atazanavir/ritonavir

8.2 Clinical Data and Sample Collection

Regimen, dosage, dosing intervals, and timing relative to meals will be reviewed at the screening/entry visit to ensure that entry criteria are met. The importance of adherence and of reporting deviations in adherence will be emphasized.

- A 1-week dosing recall history
- Recall of the meal associated with the last dosing
- Measurement of height and weight
- Tanner stage
- T-cell subsets
• Viral load
• Blood for pharmacogenetic analysis/storage will be obtained at the time of the PK study.

Once the PK visit is scheduled, a reminder call regarding the intensive PK study visit and reinforcing adherence will be made about 3 days prior to the PK visit. Study visit windows are ± 4 days, to allow for weekends or extended holidays. Subjects receiving QD ARV doses, should take them in the morning (beginning at least 3 days prior to the PK study day).

See Section 3.22 for criteria for rescheduling of intensive PK due to non-adherence.

A separate 5 mL sample for pharmacogenetics will be drawn during the PK study (timepoint is up to the site, processing will be in accordance with the P1058A Laboratory Processing Chart [LPC] and Laboratory Information Sheet [Spector]). Samples will be processed and stored by sites until shipment to the designated IMPAACT specialty laboratory for genetics is requested by the P1058A team (See Appendix I-Schedule of Evaluations). The LPC and any supplemental instructions will be available from the P1058A Protocol Specific Webpage, through the IMPAACT website (http://www.impaactgroup.org) and include sample collection details.

A plasma sample will be obtained, processed, stored and then shipped per LPC instructions, to the respective NIAID, NICHD repository for potential future resistance testing.

8.3 Intensive Pharmacokinetics

The PK study should be scheduled so that witnessed dosing of the ARV of interest is as close as possible to 12 hours (for twice daily regimens) or 24 hours (for once daily regimens) after the previous home dosing.

1) Witnessed dosing of the ARVs of interest (morning is specified for those that are QD) will be performed in conjunction with a meal that mimics what the subject would usually eat. A brief description of the type of meal will be collected on the PK Form.

2) Doses vomited within 15 minutes may be re-dosed once, with t = 0 to then be the time of repeat dosing.

3) If vomiting occurs > 15 minutes after dosing, the PK study must be cancelled and may be rescheduled (see Section 3.22 regarding rescheduling PK).
4) Blood samples (4 mL each) will be drawn through an intravenous catheter or peripheral venipunctures at 0, 1, 2, 4, 6, 8, and 12 hours post dosing (n = 7), 28 mL total. In Version 2.0, an additional blood sample will be drawn 24 hours post dosing (n = 8), 32 mL total.

All PK assays required by the protocol will be done either in the IMPAACT Pharmacology Laboratory at the University of Nebraska or University of Alabama-Birmingham (UAB).

8.4 Concentration Results

The following were examined in Version 1.0: raltegravir, with boosted atazanavir or tenofovir; etravirine with boosted darunavir; and finally, maraviroc with boosted atazanavir or Kaletra® or without a PI. Due to lack of enrollment, the maraviroc regimens will not be studied. In Version 2.0, the following will be examined: darunavir with and without etravirine, unboosted atazanavir and rilpivirine with and without boosted darunavir or boosted atazanavir.

AUC and $C_{\text{min}}$ will be reported in the Laboratory Data Management System (LDMS) and communicated to sites within six weeks of the UAB or U of Nebraska Pharmacology Laboratory obtaining samples. P1058A will not specify dosage adjustments.

8.5 Study Design, Modeling, and Data Analysis

Pharmacokinetic parameters will be determined from plasma concentration-time profiles for all compounds using noncompartmental methods [47]. Calculated pharmacokinetic parameters will be: area-under-the-curve (AUC$_{\tau}$), maximum plasma concentration ($C_{\text{max}}$), time to $C_{\text{max}}$ ($T_{\text{max}}$), minimum plasma concentration ($C_{\text{min}}$), oral clearance (CL/F), terminal apparent distribution volume ($V_z/F$), and elimination half-life ($t_{1/2}$). AUC$_{\tau}$ will be determined using the trapezoidal rule. $C_{\text{max}}$ and $T_{\text{max}}$ will be taken directly from the observed concentration-time data. CL/F will be calculated as dose/AUC. $V_z/F$ will be calculated as dose divided by the product of $\lambda_z$ and AUC. The elimination rate constant will be determined by linear regression of the terminal elimination phase concentration-time points; $t_{1/2}$ will be calculated as in $(2)/\lambda_z$.

8.6 Anticipated Outcomes

P1058A Version 1.0 examined combination ARV regimens that include raltegravir, boosted atazanavir or tenofovir; etravirine, and boosted darunavir; and maraviroc with boosted atazanavir or Kaletra® or maraviroc (600 mg BID) with raltegravir and etravirine as a PI-sparing regimen in HIV-infected older children,
adolescents and young adults. The new ARVs of interest (RAL, ETV and MVC) were fixed doses, given twice daily.

In Version 2.0, P1058A will examine combination ARV regimens that include darunavir and ritonavir once daily, darunavir and ritonavir once daily with etravirine, unboosted atazanavir once daily, rilpivirine once daily and rilpivirine once daily with darunavir/ritonavir or atazanavir/ritonavir in HIV-infected older children, adolescents and young adults. The new ARVs of interest (DRV/r, unboosted ATV and RPV) are fixed doses, given once daily, except for etravirine which may be given once or twice daily.

The ARV of interest and relationship between Tanner stage and antiretroviral pharmacokinetics will also be explored.

The target exposure ranges for all drugs that are measured, will be communicated to the sites, as part of the PK result reports. The DMC web utility will be used to communicate results (in a standardized way) as well.

In Version 1.0 repeat PKs were allowed for the non-fixed dose ARVs and as needed based on clinician input after consultation with the team, for DRV/r and ATV/r dose changes as well as MVC and RAL, if the physician requests it. In P1058A Version 2.0, if the treating physician decides to adjust the dose of DRV QD, ETV, unboosted (without ritonavir) ATV or RPV after completion of the PK study, and requests a repeat PK, it can be performed with approval of the P1058A team.

In Version 1.0, a potential exploratory analysis of the effects of the combination of TDF and ATV/r on the PK of RAL was considered if enough subjects enroll. However the analysis will no longer be done.

9.0 HUMAN SUBJECTS

9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the sample informed consent document (Appendix II) and any subsequent modifications must be reviewed and approved by the IRB responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. Assent requirements are site and IRB-specific. The sample 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). The repository consents and the issue of 
re-consent if a minor reaches the age of majority, will be according to site IRB 
policies.

Each site which receives US HHS funding and follows the United States Code of 
Federal Regulations Title 45-Public Welfare, Part 46-Protection of Human 
Subjects (also known as the Common Rule) should have on record at the site a 
plan that detects and addresses any change in guardianship occurring in pediatric 
subjects and determines when a study subject must have a consent process which 
involves a legally authorized representative (LAR) other than a family member 
with guardianship. The plan will include how the site determines when a LAR is 
initially or no longer needed and how frequently the LAR re-signs the consent. 
The plan should follow all IRB, local and state guidelines. The plan should be 
documented and filed in the appropriate regulatory file at a site but not submitted 
to the Protocol Registration Office (PRO).

The IMPAACT P1058A protocol registration materials will reference the 
applicable risk code, as determined by the site IRB, per Required Documentation 
of Risk/Benefit Category and Approval of Clinical Studies for Inclusion of 
Children by Institutional Review Boards Based on 45 CFR 46, Subpart D.

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be 
identified only by a coded number to maintain subject confidentiality. All records 
will be kept in a secured area. All computer entry and networking programs will 
be done with coded numbers only.

Clinical information will not be released without written permission of the 
subject, or subject’s parent or legal guardian, except as necessary for monitoring 
by the NIAID, NICHD, IMPAACT Network, IRB, the OHRP, or sponsor’s 
designee.

9.3 Study Discontinuation

The study may be discontinued at any time by the IMPAACT Network, NIAID, 
NICHD, the IRB or other government agencies (such as the OHRP) as part of 
their duties to ensure that research subjects are protected.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies.
11.0 BIOHAZARD CONTAINMENT

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

All infectious specimens will be sent using packaging that meets the requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substances, Category B, and Packing Instruction 650. Please refer to individual carrier guidelines (e.g. Federal Express or Airborne).
12.0 REFERENCES

Please refer to the RSC website, http://rsc.tech-res.com/ for current Package insert, Investigator Brochure and Risk List information concerning the ARVs mentioned in this study. Investigators are responsible for information distributed in Safety messages and Reports, if they are related to the regimens of interest.


Ref Type: Catalog

Ref Type: Catalog

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Ref Type: Report

Ref Type: Report


Ref Type: Abstract

Ref Type: Abstract


Ref Type: Catalog

Ref Type: Abstract

Ref Type: Abstract

Ref Type: Pamphlet

Ref Type: Grant
Ref Type: Report


Ref Type: Electronic Citation


41. FDA Edurant Prescribing Information. FDA. 2011. Ref Type: Electronic Citation


44. HIV InSite. HIV Insite. 2011. Ref Type: Electronic Citation


APPENDIX I
SCHEDULE OF EVALUATIONS

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen/Entry</th>
<th>Intensive PK</th>
<th>Repeat PK-per provider request</th>
<th>Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL EVALUATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical exam and Tanner stage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adherence to Studied Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LABORATORY EVALUATIONS-per the P1058A LPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>Local</td>
</tr>
<tr>
<td>Chemistries</td>
<td>1 mL</td>
<td>1 mL</td>
<td>1 mL</td>
<td>Local</td>
</tr>
<tr>
<td>Beta HCG (serum/urine) - females only</td>
<td>(1 mL)</td>
<td>(1 mL)</td>
<td>(1 mL)</td>
<td>Local</td>
</tr>
<tr>
<td>VIROLOGY AND SAMPLE STORAGE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma- storage</td>
<td>3 mL</td>
<td></td>
<td></td>
<td>Local</td>
</tr>
<tr>
<td>IMMUNOLOGY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute CD4 count and percentage</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>Local</td>
</tr>
<tr>
<td>PHARMACOLOGY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-hr or 24-hr Pharmacokinetics</td>
<td></td>
<td>28 - 32 mL</td>
<td>28 – 32 mL</td>
<td>UAB and U of Nebraska</td>
</tr>
<tr>
<td>(4 mL/timepoint)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacogenetics</td>
<td></td>
<td>5 mL</td>
<td></td>
<td>UCSD</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (mL), max.*</td>
<td>2 - 3 mL</td>
<td>43 - 48 mL</td>
<td>29 - 34 mL</td>
<td></td>
</tr>
</tbody>
</table>

*NIH Clinical Center guidelines for blood volume in research trials: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. Investigators should consider further limiting the volume of blood withdrawn for research purposes in patients with significant anemia or compromised cardiac output. In instances of clinical need, it is the responsibility of the patient’s attending physician to determine if phlebotomy in excess of the above limits may be permitted.
APPENDIX I (Cont.)

1. Screen/entry – may be combined. PK should take place within 35 days of screen/entry. If screen/entry procedures are split into two visits, there is no need to repeat procedures as long as all screen/entry procedures are completed ≤ 35 days from PK visit. For entry eligibility, historical laboratory results obtained up to 28 days before entry may be used, but the PK study must be completed within 35 days of these tests.

2. History: At screening/entry: HIV pediatric classification. At screen/entry and intensive PK visits: all medications within 14 days. At intensive PK visit: detailed history for studied medications, symptoms (adverse events) during PK.

3. Physical Exam: Height, weight, vital signs, Tanner Stage (will be posted as a separate document on the P1058A webpage - https://impaactgroup.org/ under Current Study Implementation Materials for P1058A).


6. Stored Specimen (plasma): This 5 mL blood sample may be drawn at any time during PK visit; the time = 0 blood draw or 12 hours post dose is recommended. In Version 2.0, blood sample may also be drawn at 24 hours post dose. Process per LPC, ship per current IMPAACT policy to the site specific repository.

7. Absolute CD4 count and percentage: Routine lymphocyte subsets are performed in real-time at a CLIA and IQA certified laboratory. If a site does not have a local laboratory that is CLIA/IQA certified contact Daniella Livnat (divnat@niaid.nih.gov) to locate the nearest laboratory. Process per LPC.

8. Intensive PKs: at 0, 1, 2, 4, 6, 8, and 12 or 24 hours post-dosing. (n = 7-8, 4 mL each timepoint). Total = 28-32 mL (about 6-7 teaspoons). 12-hour PK was done for Version 1.0. In Version 2.0, a 24-hour PK will be done and the 24-hour post-dose sample should be collected. Process and ship for real time PK per LPC to the designated IMPAACT Laboratory (University of Alabama at Birmingham and University of Nebraska). Repeat PK-per section 3.0. Subjects must have received the revised dose at least 14 days before the PK study can be repeated.

PK Visit: Subject contact should be made 3 days prior to PK visit as a reminder regarding intensive PK and reinforcement of adherence (Section 3.22). QD ARVs-change to morning dose. Study visit windows are ± 4 days, to allow for weekends or extended holidays.* The Guidelines of the NIH Clinical Center, in pediatric patients: no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period. Investigators should consider further limiting the volume of blood withdrawn for research purposes in patients with significant anemia or compromised cardiac output. In instances of clinical need, it is the responsibility of the patient’s attending physician to determine if phlebotomy in excess of the above limits may be permitted. The BSA entry criteria exclude any child that would approach this limit. If the PK visit cannot be performed within ≤ 35 days from entry visit, contact the protocol team. If the team allows PK visit > 35 days from entry visit, clinical and laboratory evaluations must be repeated before the PK visit. Visit schedules must be approved by protocol team. Please note the type of meal on the PK form.

9. Pharmacogenetic samples: 5 mL. (May be drawn at any time during the PK study visit), process per LPC. Three analyses for genetic polymorphisms for each subject will be done at the IMPAACT-designated genetics laboratory (Dr. Steve Spector). The priority of blood samples is: 1) Screening labs (if visits are combined), 2) PK (first priority for PK visit) 3) Viral load 4) T-cell subsets 5) Pharmacogenetics and 6) Plasma storage. Standard conversion for participants: 5 mL = 1 metric teaspoon, 3 metric teaspoons = 1 metric Tablespoon (15 mL)
APPENDIX II

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

SAMPLE INFORMED CONSENT

Note: This is a sample informed consent based on required elements. Standard template language can be found at the following: (http://rsc.tech-res.com/humansubjectsprotection/).

P1058A: Intensive Pharmacokinetic Studies of New Classes of Antiretroviral Drug Combinations in Children, Adolescents and Young Adults, P1058A Version 2.0 dated 02/22/12

SHORT TITLE FOR THE STUDY: P1058A - New PK Studies

INTRODUCTION

You as used in this consent form refers to you and/or your adolescent or child (if he/she is a minor requiring consent).

You are being asked to take part in this research study because you have HIV, and you have been taking a combination of newer anti-HIV medications for at least 30 days, as prescribed by your provider. This is an on-going study of different combinations of newer anti-HIV medications to evaluate the available doses of the medications in children, adolescents and young adults. These combinations may include darunavir (Prezista®) boosted with ritonavir (Norvir®) or unboosted atazanavir (Reyataz®) or rilpivirine (Edurant™ or Complera™) as a fixed dose tablet that is taken once a day. Other allowed anti-HIV medications may include etravirine (Intelence®) and atazanavir (Reyataz®) boosted with ritonavir (Norvir®).

These combinations of anti-HIV medications are the regimens of interest for this new version of the study that you are being asked to participate, and are also known as Group M, N, O, P and Q in the study. Other combinations of anti-HIV medications were evaluated in a previous version of this study.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

The main purpose of this study is to measure the level of the newer anti-HIV medications in your blood when they are taken together. Some of the medications that will be studied may not yet be approved for older children and adolescents less than 18 years old. Newer types of anti-HIV medications that interfere with how the HIV gets into and grows in the cell are called entry and integrase inhibitors. When certain HIV medications are taken together, they can change the level of medication in your blood. This study will measure the blood levels of darunavir/ritonavir, a protease inhibitor in older children, adolescents and young adults, with or without etravirine; atazanavir, a protease inhibitor; and rilpivirine, a new NNRTI. This is called a pharmacokinetic, or PK study. Results from this study will be compared to the levels of drugs that have been found in other studies that showed that these medications were safe and effective. Any bad reactions that are caused by these anti-HIV medications will be noted.

As part of the PK study, genetic studies will be done using your blood samples, which will measure how your genes (DNA) may affect how your body handles these anti-HIV medication combinations (pharmacogenetics). Please note that these tests are considered investigational (used for research) and are not used as part of routine clinical care. This study will also compare older children, adolescents and young adults, based on body size and to see if there are differences based on developmental age (Tanner Stages).

You will be in one of these groups:

M. Darunavir (800 mg once-a-day) + ritonavir (100 mg once-a-day)

N. Darunavir (800 mg once-a-day) + ritonavir (100 mg once-a-day) + etravirine (200 mg twice-a-day or 400 mg once-a-day)

O. Atazanavir (400 mg once-a-day or 600 mg once-a-day)

P. Rilpivirine (25 mg once-a-day) or Complera™ (emticitabine 200 mg + rilpivirine 27.5 mg + tenofovir 300 mg once-a-day) + Darunavir/ritonavir (800/100 mg once-a-day) or Atazanavir/ritonavir (300/100 mg once-a-day)

Q. Rilpivirine (25 mg once-a-day) or Complera™ (emticitabine 200 mg + rilpivirine 27.5 mg + tenofovir 300 mg once-a-day)

Your doctor has prescribed one of these main combinations to treat your HIV infection. You may be taking some additional anti-HIV medications as well, which are allowed, if your doctor has prescribed these for you. Some combinations cause the dose of one or the other to be changed.
WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

This study has two visits for most participants:
1.) A combined screening/entry visit, which will take about 30 minutes to complete, and
2.) A PK study visit after at least **30 days** on the HIV medications, but no more than 5 weeks after you entered the study. It will take about **24 hours** to complete.
3.) Some participants may have a repeat screening visit and repeat study visit depending on the results of the first study visit and the recommendation of their doctor.

**Screening and Entry:**

If your clinic has recent results for you, from your routine care, the screening and enrollment visit for this study may be done at the same time. If not, then separate visits may be needed. A complete history and physical exam, and blood tests will be done to find out if you can enter the study. The blood collected at this visit will include routine laboratory tests. Less than one teaspoon of blood will be taken.

- Girls/women who have had their first menstrual period will have a pregnancy test at this visit. A small amount of urine or blood (less than ½ teaspoon) will be taken for this test. If you are pregnant, you will not be allowed to continue in this study. If the PK study is scheduled for another visit, the pregnancy test may be repeated. The test must be negative, for you to continue with the **24-hour** PK study.

Your site doctor or nurse will talk to you about your anti-HIV medication combination and the importance of not missing doses and also about the risks of pregnancy.

- Your stage of sexual development will be determined. For girls/women, this will be done by looking at how developed the breasts are and the amount of pubic hair. For boys/men, this will be done by measuring the size of the testes. (There are 5 Stages in the Tanner Scales).

**PK Study Visits:**

Your doctor or nurse will contact you using your preferred mode of contact 3 days before the scheduled PK study visit to discuss this clinic visit and the importance of taking your doses on time. You will be told if you have to switch and take some of your anti-HIV medications in the morning. You will need to bring all of your HIV medications to this study visit. During this visit, your blood levels of anti-HIV medications will be checked.

The PK study visit may be re-scheduled if you are not available on the scheduled day of the visit or if you use a medication that is not allowed within 14 days before the visit. The PK study visit may also be re-scheduled if any of the following happen for the HIV medications
that are being evaluated: you missed any of the 2 doses before the visit, you missed at least 2 doses within 7 days before the visit or you did not switch the time you take the once-a-day medications to take them in the morning during the 3 days before the visit.

A complete history and physical exam and routine blood tests will be done. You will be asked about any missed doses of your HIV medications in the past 2 weeks. About 1 teaspoon of blood will be taken for routine laboratory tests, to check your viral load (amount of HIV in the bloodstream), and CD4+ T-cell counts (the number of cells in the bloodstream that fight HIV). For female participants, a urine or blood sample will be collected again, for a pregnancy test, if needed.

While in the clinic, you will be given a dose of your anti-HIV medications with a meal that is similar to what you would normally eat. You will have about 1 teaspoon of blood taken before you take your anti-HIV medications (time 0). At 1, 2, 4, 6, 8, 12 and 24 hours after you have taken your anti-HIV medications, another blood sample will be taken. About 1 teaspoon of blood will be taken each time. The samples will be used to measure your blood levels of the anti-HIV medications. Sometimes a heparin-lock is used when more than one blood sample is taken over a period of time. A heparin-lock is a small tube left in the vein until all of the blood samples have been taken. Then it is removed. This allows blood to be taken from a vein many times without sticking you again. About 7 teaspoons of blood will be taken in all, for the PK tests. Additional blood (one to two teaspoons or so) will be taken as part of some of the timepoints during the PK study visit for the special studies (genetic tests) that will be done using your blood, at a later time. The most blood that can be drawn from you at this visit is about 3 tablespoons.

Results of the 24-hour study drug level measurements will be sent to your doctor within 6 weeks. Your doctor will discuss the results of these as well as your routine tests with you. If your doctor decides to change your HIV medications, you may be able to re-enroll in this study by signing a new consent, if the new HIV-medications are also in one of the Groups being studied.

Based on the results of your blood levels of anti-HIV medications, your doctor may recommend adjusting the dose of your anti-HIV medications. Any adjustment to your dosage is the decision of your doctor and is not required by this study.

A repeat 24-hour PK study may be done as part of this study if the results of the first PK study could not be measured or you are taking certain anti-HIV medications and your doctor decides to change the dose you are taking and wants to do another PK. If your doctor changes your dose, a repeat 24-hour PK study may be scheduled for you after you start on the new dose.
APPENDIX II (Cont.)

You should tell your nurse or doctor before you take any new medications or enroll in clinical trials.

Early Discontinuation/Off treatment Follow-up:
If the PK visit is not completed, you will not be asked to return for a final study visit.

Other Information:
Storage of blood samples required for the study:

Some of your blood will be taken and stored (with usual protectors of identity) and used for genetic testing as part of this study. The genetic testing will be done to explain differences in the amount of medicine in the blood of different individuals. No other genetic testing will be done with this sample. About 1 teaspoon of blood will be taken for this purpose.

Storage of blood samples for future testing:

If you agree, about 1 teaspoon of extra blood will be taken when you have the PK study visit. This sample will be stored with protection of your identity. This sample may be used for future IMPAACT-approved HIV-related research.

Please write your initials in one of the spaces below. ‘YES’ means that you agree for the IMPAACT network to store the extra sample. ‘NO’ means that the extra sample will NOT be stored. You may still remain in the study, no matter which you choose. Even if you agree now, you may withdraw your approval for the storage of your extra sample at any time in the future.

________ YES  __________ NO

FOR NIAID SITES:
Your samples will be stored at an assigned IMPAACT laboratory where only approved researchers will have access to them. People who work at the facility will also have access to your samples to keep track of them, but these people will not have information that directly identifies you. Your samples will not be sold or directly used to produce commercial products. All proposed research studies that ask to use your samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your samples will be stored.

The researchers do not plan to contact you with the results of studies done using your stored samples. Because research studies are often done with experimental procedures, results of such studies should not be used to make decisions about your medical care. If the researchers decide that the result of a certain study provides important information for your medical care, then your
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 samples stored for future research studies. You can still participate in this study even if you make this decision. You may withdraw your consent for the storage and use of your samples at any time. Your request must be in writing. If you withdraw your consent, all efforts possible will be made to destroy the stored samples.

Left over blood will be stored for future IMPAACT-approved HIV-related research. If the blood sample is identified as coming from you, then you will need to give permission for this research in the future. If all identifying information is removed from the blood sample, then testing may be done without your permission.

Please read the following statements carefully and then mark only one checkbox.

I agree to allow my or my child’s blood samples to be stored for use in this study and future IMPAACT/DAIDS-and NIH-approved, HIV-related research studies. (This may include genetic-related research).

☐ __________ Date

I am giving permission only for storage of the blood for this study. I will need to give permission in the future for specific testing to be done if the blood remains identified with my or my child’s information. I understand I may contact the Principal Investigator (insert name of site) or IRB/EC [insert contact information] to withdraw my consent, if I so choose.

☐ __________ Date

FOR NICHD SITES:
Some of your 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 consent.

Data Sharing:
The information collected in this study may be used for other IMPAACT and/or DAIDS-approved, HIV-related research.
APPENDIX II (Cont.)

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 165 children, adolescents and young adults in total will take part in this study. There were 80 participants that took part in the previous version of this study. About 85 participants will take part in this new version.

Only the participants with PK study results that could be measured will be counted as taking part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study between 1 and 7 weeks depending on when you entered the study, and if any repeat PK is needed.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- This study is stopped or cancelled.
- The P1058A study team decides to stop this study early.
- You are not able to attend the study visits as required by this study.
- You are unable to do the PK study or a repeat PK study if it is needed because the results of the first PK study could not be measured.
- You no longer meet the requirements for entering this study.
- You need a treatment that you may not take while on this study.
- The study is no longer in your best interest.
- You are pregnant or breastfeeding.

WHAT ARE THE RISKS OF THE STUDY?

Because the medications that you are taking have been prescribed to you by your doctor before you were part of this study, taking these medicines is not considered part of the risks of being in this study. However, if you would like to have more information about the side effects of the drugs you are taking, the doctor or nurse at your site can discuss them with you.

Risks of Drawing Blood

You may faint, feel lightheaded, or feel some discomfort when blood is drawn or a heparin lock is inserted for this study. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body, or swelling of the surrounding skin may occur. There is also a small risk of minor infection at the blood draw site.
APPENDIX II (Cont.)

Other Risks

There may be a risk associated with breach of confidentiality. We can provide you with more information on this risk if you would like it (see the section WHAT ABOUT CONFIDENTIALITY).

There may be a risk associated with the physical exam, (Tanner Staging) that may cause you psychological discomfort or embarrassment.

ARE THERE RISKS RELATED TO PREGNANCY?

If you can become pregnant, a pregnancy test must be performed before you can enter this study and before you have blood drawn for the PK study. The test must be negative. The risks to unborn babies for each drug you may be prescribed will be discussed with you, by your provider.

If you are having sex that could lead to pregnancy, you must agree not to become pregnant. Because of the risk involved, you and your partner must agree to use two methods of birth control, including at least one form of barrier contraception that you discuss with the study staff.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. You may benefit from having the levels of HIV drugs in your blood measured. This information may help your doctor advise you about the best treatment for you. It is also possible that you 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 HAVE BESIDES THIS STUDY?

Alternatives to participation in this study, include no measurement of your PK levels and measurement of the level of HIV drugs in your blood by a commercial laboratory, both while continuing on the treatment regimen prescribed by your doctor. Your doctor can talk to you about the risks and benefits of the treatment options available to you.

Participation in this study is not part of your clinical care, and is voluntary. You may choose not to take part in this study or leave this study at any time. Please talk to your doctor about these and other choices available to you. The study staff will explain the risks and benefits of study participation.
WHAT ABOUT CONFIDENTIALITY?

All efforts will be made to keep your information confidential. We cannot guarantee absolute confidentiality. To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health (NIH). This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the (insert Name of Site) IRB, the National Institutes of Health (NIH), the Office of Human Research Protections (OHRP), the IMPAACT Network, study staff and study monitors.

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

WHAT ARE THE COSTS TO ME?

Your anti-HIV medications will not be provided to you by this study, so you must get these drugs through your primary care provider. [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 are taking part in a research study]. [This section may be deleted at the discretion of the IRB]

WILL I RECEIVE ANY PAYMENT?

You will receive a food allowance for clinic visits and additional payment to cover transportation costs. [Up to individual sites]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. 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 RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. **You will be treated the same no matter what you decide.** Your access to HIV medication will not change because of your decision and you will not lose any benefits that you are entitled to.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

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

For questions about your/your child’s rights as a research subject, contact:

- *Insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site*
- *Insert telephone number of above*
SIGNATURE PAGE

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

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

____________________________                ____________________________________
Participant’s Legal Guardian (print)        Legal Guardian’s Signature and Date
(As appropriate)                          

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

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

APPENDIX III

INFORMATION SHEET-(NICHD SITES ONLY)

IMPAACT P1058A- INTENSIVE PHARMACOKINETIC STUDIES OF NEW CLASSES OF ANTIRETROVIRAL DRUG COMBINATIONS IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS

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 P1058A, 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 III (Cont.)

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)

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.
APPENDIX III (Cont.)

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 (insert title), your child is being asked to have some (insert specimen source-
blood, urine, tissue, genital fluid, saliva, etc.) 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.

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APPENDIX III (Cont.)

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.

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APPENDIX III (Cont.)

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.

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YOUTH FACT SHEET (Version 2.0- 29 November 2005)

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?

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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?
APPENDIX IV (Cont.)

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.

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APPENDIX IV (Cont.)

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.

TEMPLATE CONSENT/ASSENT FORM

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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.

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