

Lab Processing Chart for IMPAACT Protocol Number P1097 Version 2.0

Title: 'Raltegravir Pharmacokinetics And Safety In Neonates'

Protocol Version: 2.0

LPC Version Date: 21MAR2014

LPC Edited/Updated: N/A

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Protocol-Required Non-Standard Reagents and Supplies		
Evaluation	Reagent or supply	Order information
Pharmacogenetic Dried Blood Spots	Protein Saver Cards #903, (Whatman® #10534612)	VWR# 28170-017, Fisher Scientific #NC9307519
	Gas-impermeable storage bag (Whatman #10548232)	VWR# 89027-022, Fisher Scientific #50853570
	Dessicant Packs (Whatman #10548234)	
	Humidity indicator Cards (Multisorb Des Manufacture #MS200032	VWR# 89027-024
	Whatman card drying rack (Whatman #10537173 or Whatman # 10539521)	Fisher Scientific #NC9511648
	Glassine Envelopes, 3 1/4 inches x 4 7/8 inches, 100-pack (Whatman #10548236) optional	VWR catalogue #89015-592

Maternal SoE and Specimen Processing

Section 1: Maternal Schedule of Laboratory Evaluations (Copied from Protocol Document v.2.0, Appendix I-B)

COHORT 2 MATERNAL SCHEDULE OF EVALUATIONS

	Screening/entry	Labor/delivery ⁶	Post-Delivery (1-5 days after delivery)
Informed Consent	X		
CLINICAL EVALUATIONS			
History	X ¹	X ²	X ²
PHARMACOKINETICS⁷			
Maternal RAL concentration ³	1mL ⁴	1mL ⁴	
	If enrolled after delivery	If enrolled before delivery	
OTHER⁷			
Cord Blood ^{3,5}		X	
TOTAL BLOOD	1mL	1mL	0mL

1. History data at Screening/entry includes documentation of HIV-1 infection, demographic data and antiretroviral dosing history 3 months prior to entry.
2. History data after Screening/entry includes antiretroviral dosing while on study, labor and delivery record, and obstetrical gestational age. It is strongly recommended that the site report, prospectively if possible, the mother to the Antiretroviral Pregnancy Registry (<http://www.apregistry.com/reg.htm>)
 US/Canada telephone: 800-258-4263, fax 800-800-1052
 Brazil: fax 888-259-5618
 International: phone: 910-679-1598, fax: 910-256-0637
 Email: pregnancyregistries@incresearch.com
3. Mother/infant pairs may be enrolled up to 48 hours after delivery. In these situations it may not be possible to collect the maternal and cord blood samples at labor and delivery.
4. For women enrolled prior to delivery, collect 1mL of maternal blood within one hour after delivery. For women enrolled after delivery, collect 1mL of maternal blood at the time of enrollment.
5. Draw cord blood immediately after cord is clamped.
6. Not applicable to women enrolled after delivery.
7. See the Laboratory Processing Chart (LPC) on the P1097 Protocol Specific Webpage on the IMPAACT website (<http://www.impaactnetwork.org/index.htm>) for collection, processing and shipping instructions.

Section 2: Maternal Safety/Clinical Laboratory Evaluations (Defer to local clinical specimen collection guidelines for tube types and collection volumes whenever discrepancies occur)			
Evaluation	DMC Test Code	Tests	CRF #
N/A	N/A	N/A	N/A

Section 3: Maternal Specimen Processing – Refer to Section 1 for collection volumes					
Evaluation	Tube Type	Special Collection Notes	CRF # DMC Test Code	Processing	Shipping
Plasma Pharmacokinetics Maternal RAL concentration	K2EDTA	Collect within 1 hour after delivery. Invert 8-10 times gently. Send immediately to local IMPAACT processing lab on ice for processing within 1 hour.	PKW0299 PKRAN	Centrifuge blood within one hour of collection at 1000 x g for 10 minutes at room temperature . Transfer all plasma (minimum 0.3mL) to pre-labeled 2mL cryovial. Store at -70°C or colder within 1 hour of collection.	U.S. labs ship to UAB Lab # 191 batched after last sample is drawn. Non-U.S. labs: ship as pass through BRI repository to final destination of UAB Lab # 191 batched after last sample is drawn.
Plasma Pharmacokinetics Cord Blood	K2EDTA	Collect a minimum of 1 mL blood within 1 hour after cord is clamped. Invert 8-10 times gently. Send immediately to local IMPAACT processing lab on ice for processing within 1 hour.	PKW0299 PKRAN	Centrifuge blood within one hour of collection at 1000 x g for 10 minutes at room temperature . Transfer all plasma (minimum 0.3mL) to pre-labeled 2mL cryovial. Store at -70°C or colder within 1 hour of collection.	U.S. labs ship to UAB Lab # 191 batched after last sample is drawn. Non-U.S. labs: ship as pass through BRI repository to final destination of UAB Lab # 191 batched after last sample is drawn.

Section 4: Maternal Evaluations by Visit					
Screening/Entry (LDMS Vst/Vst Unit= 0 / ENT)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Plasma Pharmacokinetics Maternal RAL concentration (To be collected ONLY from women enrolled after delivery.)	K2EDTA blood (1.0mL)	PKW0299	1 x 0.3mL (all plasma)	BLD/DPE/PL1 Time/Time Unit: 0 / RANDOM	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

Labor/delivery (LDMS Vst/Vst Unit= 0 / L&D)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Plasma Pharmacokinetics Maternal RAL concentration (To be collected ONLY from women enrolled before delivery.)	K2EDTA blood (1.0mL)	PKW0299	1 x 0.3mL (all plasma)	BLD/DPE/PL1 Time/Time Unit: 0 / RANDOM	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.
Plasma Pharmacokinetics Cord Blood	K2EDTA Cord blood (1.0mL)	PKW0299	1 x 0.3mL (all plasma)	CRD/DPE/PL1 Time/Time Unit: 0 / RANDOM	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

Infant SoE and Specimen Processing

Section 1: Infant Schedule of Laboratory Evaluations (Copied from Protocol Document v.2.0, Appendix II-B)

COHORT 2 INFANT SCHEDULE OF EVALUATIONS

	Birth/Entry	1-6 hours after birth ¹¹	12-24 hours after birth ¹¹	36-48 hours after birth	72-84 hours after birth	108-132 hours after birth	Week 1-2 (7-14 days after birth)	Week 6 (35-49 days after birth)
CLINICAL EVALUATIONS								
History				X ²			X ²	X ²
Physical exam	X ¹						X ³	X ³
LABORATORY EVALUATIONS (if not obtained for standard of care)								
Hematology ^{4,6}				0.5mL ⁴			0.5mL	
Chemistries ^{5,6}					1mL ⁵		1mL	
Bilirubin ^{6,7}				1mL ⁷				
PHARMACOGENETICS¹⁰								
Genotyping ⁸					0.125mL			
PHARMACOKINETICS*¹⁰								
Washout ⁹		0.25 mL	0.25 mL	0.25 mL	0.25mL	0.25mL	0.25mL	
TOTAL BLOOD	0mL	0.25mL	0.25mL	1.75mL	1.375mL	0.25mL	1.75mL	0mL
*See section 3.0 and 4.6 for criteria for infants eligible for pharmacokinetic (PK) blood sampling.								

1. Physical examination includes infant Apgar score, birth weight and length, head circumference, gestational age, gender, sex, and ethnicity.
2. History includes all non-protocol laboratory tests, HIV test results, antiretroviral agents for PMTCT, concomitant medications, signs and symptoms, diagnoses, and any intercurrent illnesses since the last visit, including any treatment to reduce bilirubin.
3. Complete physical exam includes temperature, heart rate, respiratory rate, weight, length, and head circumference.
4. Hematology to include CBC with differential and platelet count: If hematology testing was done as part of clinical care within 48 hours, report values obtained for clinical care and do not obtain additional study sample.
5. Chemistries include AST, ALT, creatinine and total and direct bilirubin: If chemistry testing was done as part of clinical care within 24 hours, report values obtained for clinical care and do not obtain additional study sample.
6. Both PK eligible and ineligible infants will have laboratory evaluations collected unless obtained as part of clinical care (see Footnotes 4, 5, and 7). If infant enrolls after birth, hematology, chemistries, and bilirubin should be obtained with first PK blood draw for those infants eligible for PK.
7. Bilirubin includes total and direct: If bilirubin testing was done as part of clinical care within 24 hours, report values obtained for clinical care and do not obtain additional study sample.
8. Genotyping (optional) for UGT1A1 polymorphisms will be done using dried blood spot on filter paper. Only infants who have PK sampling will have genotyping.
9. Only infants eligible for PK blood sampling (See Section 3.0 and 4.3). Collect 0.25mL of blood for each sample. Infants enrolled after delivery up to 48 hours may not have the initial PK samples obtained but will start as soon as possible. (Note: Infants enrolled close to the 48-hour time point should have the first PK blood sample collected within 4 hours of enrollment (i.e., within 52 hours after birth).
10. See the Laboratory Processing Chart (LPC) on the P1097 Protocol Specific Webpage on the IMPAACT Website (<http://www.impaactnetwork.org/index.htm>) for collection, processing and shipping instructions.
11. Skip visit if enrolled after scheduled time of visit.

Priority of blood draws should be: chemistries, hematology, pharmacokinetics, genotyping.

Section 2: Infant Safety/Clinical Laboratory Evaluations (Defer to local clinical specimen collection guidelines for tube types and collection volumes whenever discrepancies occur)			
Evaluation	DMC Test Code	Tests	CRF #
Hematology	N/A	Complete Blood Count, with platelets and differential	LBW0093
Chemistry	N/A	ALT (SGPT), AST (SGOT), Bilirubin (Total), Bilirubin (Direct), Creatinine	LBW0093
Bilirubin	N/A	Bilirubin (Total), Bilirubin (Direct)	LBW0093

Section 3: Infant Specimen Processing – Refer to Section 1 for collection volumes					
Evaluation	Tube Type	Special Collection Notes	CRF # DMC Test Code	Processing	Shipping
Pharmacogenetics DBS for Genotyping for UGT1A1 (Optional and ONLY for infants having PK sampling)	K2 or K3EDTA OR Heel stick	The DBS should be collected on Whatman Protein Saver Card #903 (Whatman #10534612). DBS cards should be prepared from blood drawn in EDTA (purple top) tubes or blood obtained by using heelstick method. Send to local IMPAACT processing lab.	SPW0437 PKGENO	See ACTG/IMPAACT Lab Manual on HANC portal: https://www.hanc.info/labs/labresources/procedures/ACTGIMPAACT%20Lab%20Manual/55-DriedBloodSpots-LTC-SOP-v2.0-19Mar2012.pdf for Dried Blood Spot specimen processing and storage procedures. Note: 25 uL of whole blood is applied to each spot on Whatman Protein Saver Card #903 card (Whatman #10534612). Each individual spot should be entered into LDMS as a separate aliquot and should be assigned its own Global Spec ID. Store filter paper in a non-permeable zip lock bag containing 2-3 desiccants per bag at -20°C or colder.	U.S. labs ship to Dr. Stephen Spector's Lab (LDMS Lab #173) on dry ice when requested by team. Non-U.S. labs: ship as pass through BRI repository to final destination of Dr. Stephen Spector's Lab (LDMS Lab #173) on dry ice when requested by team.
Pharmacokinetics Plasma for Raltegravir Washout	K2EDTA	Invert 8-10 times gently. Send immediately to local IMPAACT processing lab on ice for processing within 1 hour.	PKW0352 PKINT	Centrifuge blood within one hour of collection at 1000 x g for 10 minutes at room temperature . Transfer all plasma (minimum 0.1mL) to pre-labeled 2mL cryovial. Store at -70°C or colder within 1 hour of collection.	U.S. labs ship to UAB Lab # 191 batched after last sample is drawn. Non-U.S. labs: ship as pass through BRI repository to final destination of UAB Lab # 191 batched after last sample is drawn.

Section 4: Infant Evaluations by Visit

1-6 hours after birth (LDMS Vst/Vst Unit= 1 / WK)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Pharmacokinetics (Washout)	K2EDTA blood (0.25mL)	PKW0352	1 x 0.1mL (all plasma)	BLD/DPE/PL1 Time: X Time Unit: Hours	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

12-24 hours after birth (LDMS Vst/Vst Unit= 1 / WK)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Pharmacokinetics (Washout)	K2EDTA blood (0.25mL)	PKW0352	1 x 0.1mL (all plasma)	BLD/DPE/PL1 Time: X Time Unit: Hours	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

36-48 hours after birth (LDMS Vst/Vst Unit= 1 / WK)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Hematology	EDTA blood (0.5mL)	LBW0093	N/A	N/A	Send to local lab ambient
Bilirubin	SST or Red Top blood (1.0mL)	LBW0093	N/A	N/A	Send to local lab ambient
Pharmacokinetics (Washout)	K2EDTA blood (0.25mL)	PKW0352	1 x 0.1mL (all plasma)	BLD/DPE/PL1 Time: X Time Unit: Hours	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

72-84 hours after birth (LDMS Vst/Vst Unit= 1 / WK)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Chemistry	SST or Red Top blood (1.0mL)	LBW0093	N/A	N/A	Send to local lab ambient
Genotyping	K2 or K3 EDTA DBS OR DPE DBS	SPW0437	5 x 0.025mL spots on DBS card	BLD/EDT/DBS Or BLD/DPE/DBS	Store the sealed bags at -20°C or colder until ready to ship.
	Heel stick DBS	SPW0437	5 x 0.025mL spots on DBS card	HST/NON/DBS	Store the sealed bags at -20°C or colder until ready to ship.
Pharmacokinetics (Washout)	K2EDTA blood (0.25mL)	PKW0352	1 x 0.1mL (all plasma)	BLD/DPE/PL1 Time: X Time Unit: Hours	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

108-132 hours after birth (LDMS Vst/Vst Unit= 1 / WK)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Pharmacokinetics (Washout)	K2EDTA blood (0.25mL)	PKW0352	1 x 0.1mL (all plasma)	BLD/DPE/PL1 Time: X Time Unit: Hours	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

Week 1-2 after birth (LDMS Vst/Vst Unit= 1 OR 2 / WK)					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
Hematology	EDTA blood (0.5mL)	LBW0093	N/A	N/A	Send to local lab ambient
Chemistry	SST or Red Top blood (1.0mL)	LBW0093	N/A	N/A	Send to local lab ambient
Pharmacokinetics (Washout)	K2EDTA blood (0.25mL)	PKW0352	1 x 0.1mL (all plasma)	BLD/DPE/PL1 Time: 0 Time Unit: Random	Process within 1 hour of collection. Immediately after processing store at -70°C or colder.

Week 6 after birth-No specimen Collection at this visit					
Evaluation	Specimen	CRF	Aliquots	LDMS Code	Special Notes
N/A	N/A	N/A	N/A	N/A	N/A

Section 5: Helpful Links and Shipping Addresses

Prepare and ship specimens in accordance with IATA regulations and ACTN Guidelines for Category B substances. The ACTN Shipping Guidelines are posted on the HANC public website under Information for ACTG and IMPAACT Labs.

<http://www.hanc.info/labs/labresources/Pages/informationActgImpaactLabs.aspx>

<p>U.S. Shipping of DBS for genotyping:</p> <p>Stephen A Spector, M.D. University of California, San Diego Department of Pediatrics Division of Infectious Diseases Stein Clinical Research Bldg. Room 430 Attn: Rodney Trout 9500 Gilman Drive, Mail Code 0672 La Jolla, CA 92093-0672 Office Phone : 858-534-7055 Fax : 858-534-7411 Email : saspector@ucsd.edu</p> <p>LDMS Lab # 173</p>	<p>U.S. Shipping of Plasma for pharmacokinetics :</p> <p>Edward Acosta, Pharm. D. University of Alabama at Birmingham Attn: Kedria Walker Division of Pharmacology 1670 University Blvd. Volker Hall Room 270 Birmingham, AL 35294-0019 Phone: (205) 975-2461 Fax: (205) 934-6201 Email: kedria@uab.edu</p> <p>LDMS Lab # 191</p>	<p>Non-U.S. Shipping of DBS for genotyping:</p> <p>Pass-through shipment to BRI with final destination as LDMS Lab 173:</p> <p>BRI Repository</p> <p>Attn: John C. Ward Biomedical Research Institute (BRI) 12264 Wilkins Ave., Bay F Rockville, MD 20852</p> <p>Phone (301)881-7636 Fax (301)770-9811 Email: brirepository@aol.com</p> <p>LDMS Code: 999</p>	<p>Non-U.S. Shipping of Plasma for pharmacokinetics :</p> <p>Pass-through shipment to BRI with final destination as LDMS Lab 191:</p> <p>BRI Repository</p> <p>Attn: John C. Ward Biomedical Research Institute (BRI) 12264 Wilkins Ave., Bay F Rockville, MD 20852</p> <p>Phone (301)881-7636 Fax (301)770-9811 Email: brirepository@aol.com</p> <p>LDMS Code: 999</p>
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Section 6: Revision History			
Protocol Version	LPC Change Date	Page(s)	Description
2.0	21MAR2014		Cohort 1 SoEs and references removed throughout.
2.0	21MAR2014	1-2	Table of Contents added.
2.0	21MAR2014	3	Protocol Non-Standard Reagents list added.
2.0	21MAR2014	3,7	Maternal and Infant Cohort 2 SoEs inserted.
2.0	21MAR2014	3,7	Headings added to correspond to requested information in Table of Contents.
2.0	21MAR2014	6	Included LDMS Code Time in Time/Time unit.
2.0	21MAR2014	5-6, 10-13	Removed (P1097) after each CRF #.
2.0	21MAR2014	5, 10	Specimen processing instructions updated throughout.
2.0	21MAR2014	5-6, 10	Special Collection Notes edited to include processing time throughout.
2.0	21MAR2014	10-13	Infant CRF PKW0352 added.
2.0	21MAR2014	7	Section 5 removed after Maternal Section 4 and only listed after Infant Section 4.
2.0	21MAR2014	14	Section 5, Shipping instructions edited for U.S. and Non-U.S. Processing Labs.
2.0	21MAR2014	1-11	Renamed sections to distinguish between Maternal and Infant sections.
2.0	21MAR2014	15	Section 6 added.
2.0	21MAR2014	16-18	Section 7 added.
2.0	21MAR2014	5-6, 10-13	DPE Substituted for EDTA for Pharmacokinetic specimens
2.0	21MAR2014	10,12	DPE added as option for collection of Genotyping specimen

Section 7: Appendices

Appendix I: BRI Pass-through Instructions

This process is to be used **ONLY** if a Material Transfer Agreement (MTA) is required for the shipment of P1097 specimens and one is not in place with the protocol testing labs LDMS lab #173 or #191.

1. When creating the LDMS shipping batch, select the appropriate testing laboratory as the shipment destination based on the P1097 LPC.
2. When creating the LDMS shipment, **DO NOT** select lab 999 as the destination.
3. Pack the specimens according to network/protocol requirements and address the Saf-T-Pak\World Courier secondary packaging to the final shipment destination of LDMS Lab 173, Dr. Stephen Spector's lab or Lab 191, Dr. Edward Acosta's Lab.
4. Place the secondary packaging within a box and address the outer box to the BRI repository:

Biomedical Research Institute
c/o John C. Ward, Jr.
12264 Wilkins Avenue, Bay F
Rockville, MD 20852
Phone: (301)881-7636
Fax: (301)770-9811
Email: brirepository@aol.com

5. Be sure to include the correct "Pass Through" shipping notice inside the box addressed to BRI.
6. Be sure to send the LDMS shipping file and any necessary CRFs to the testing lab.
7. Indicate in the Explanation box on the shipment notice form that this is a "Pass-Through Shipment" going to LDMS Lab 173, Dr. Stephen Spector's lab or Lab 191, Dr. Edward Acosta's Lab.

Appendix 2: Shipping Notice for Using BRI as Intermediate Destination to Lab 191

P1097 PK Pass-Through Samples

LDMS Inventory/BRI Storage Not Required

Refresh dry ice as appropriate and ship to

LDMS Lab #191:

**(Shipments should be scheduled for arrival on
Tuesday through Thursday only)**

University of Alabama at Birmingham

ATTN: Kedria Walker

Division of Pharmacology

1670 University Blvd

Volker Hall Room 270

Birmingham, AL 35294-0019

FAX: (205) 934-6201

PHONE: (205) 975-2641

EMAIL: Kedria@uab.edu

Appendix 3: Shipping Notice for Using BRI as Intermediate Destination to Lab 173

P1097 DBS Pass-Through Samples
LDMS Inventory/BRI Storage Not Required
Refresh dry ice as appropriate and ship to
LDMS Lab #173:

**(Shipments should be scheduled for arrival on
Tuesday through Thursday only)**

University of California, San Diego
ATTN: Rodney Trout
Department of Pediatrics
Division of Infectious Diseases
9500 Gilman Drive, Mail Code 0672
Stein Clinical Research Bldg. Room 430
La Jolla, CA 92093-0672

FAX: (858) 534-7411
PHONE: (858) 534-7055
EMAIL: saspector@ucsd.edu