HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

CONSENT TO PARTICIPATE IN A RESEARCH STUDY AND RESEARCH SUBJECT HIPAA AUTHORIZATION

Protocol Title:	**5335s, Version 1.0, 12/31/14, Letter of Amendment 1, dated 6/23/16, Letter of Amendment 2, 6/19/17**: Coinfected Subjects Treated with HCV Direct-Acting Antivirals Plus Ribavirin: Intrahepatic HCV Dynamics and Pharmacology: A Substudy of A5329 A DIVISION OF AIDS/ AIDS CLINICAL TRIALS GROUP (ACTG) Study
Principal Investigator:	Pablo Tebas, MD 502 Johnson Pavilion, Philadelphia PA 19104 **(215) 349-8092**
Investigator:	Rajender Reddy, MD (215) 349-8352
Lead Study Nurse:	Yan Jiang, RN, BSN, MSN
Research Nurse	Eileen Donaghy, MSN, CRNP
24 hr. Emergency Contact:	Immunodeficiency Program Doctor on call (215) 662-6059

Introduction:

You are being asked to take part in this research substudy because you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS, and you are also infected with the hepatitis C virus (HCV), a virus that affects the liver. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: Dr. Pablo Tebas. The doctor who will perform the liver biopsies as part of this study is Dr. Rajender Reddy. 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. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Why Is This SubStudy Being Done?

There are two purposes to this substudy. The first purpose is to see how quickly HCV is removed from the liver after starting the A5329 study drugs (ABT-450/r/ABT-267 and ABT-333 and ribavirin (RBV).The second purpose is to compare the levels of the A5329 study drugs in the liver and blood.

To be eligible for this substudy, you must be enrolled in A5329 and be able to have a liver biopsy.

How Many People Will Take Part in This Study?
Up to 12 people will take part in this study. About 2 people are expected to enroll at the University of Pennsylvania.

How Long Will I Be In This Study?
You will be in the A5335s substudy approximately 10 days. **If your substudy Visit 8 (Day 7) is rescheduled, you will be in the A5335s substudy up to 84 days, depending on when Visit 8 is rescheduled.** After the substudy is completed, you will continue to be in A5329 until that study is completed.

What Do I Have To Do If I Am In This Study?
A5335s Substudy Visits
The substudy staff can answer any questions you have about individual substudy visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

Substudy Visit 1 (Entry/Day 0)	Substudy Visit 2 (Day 1)	Substudy Visit 3 (Day 2) Substudy Visit 4 (Day 3) Substudy Visit 5 (Day 4) Substudy Visit 6 (Day 5) Substudy Visit 7 (Day 6)	Substudy Visit 8 (Day 7)[1]	Day 10[2]
Core Needle Biopsy of the Liver			Core Needle Biopsy of the Liver	Followup Call
			Sampling of the Liver with small needle	
Eat Breakfast at Site	Eat Breakfast at Site	Eat Breakfast at Home	Eat Breakfast at Site	
24 Hour Blood Sampling for HCV Levels	Single Blood Draw	Single Blood Draw	12 Hour Blood Sampling for Drug Levels	
Morning Dose Study and HIV Drugs at Site	Morning Dose Study and HIV Drugs at Site	Morning Dose Study and HIV Drugs at Site	Morning Dose Study and HIV Drugs at Site	
Eat Lunch at Site	Eat Lunch at Home	Eat Lunch at Home	Eat Lunch at Site	
Eat Dinner at Site	Eat Dinner at Home	Eat Dinner at Home	Eat Dinner at Site	
Evening Dose Study and HIV Drugs at Site	Evening Dose Study and HIV Drugs at Home	Evening Dose Study and HIV Drugs at Home	Evening Dose Study and HIV Drugs at Site	
Eat Snack at Site	Eat Snack at Home	Eat Snack at Home	Eat Snack at Site	

[1] If you miss the second core needle biopsy (CNB2) on Day 7 due to anemia or pain from your first core needle biopsy (CNB1), then CNB2, FNA, and the plasma PK measurements will be rescheduled to Day 14 after confirming resolution of your anemia or pain. If you miss the CNB2 on Day 7 and on Day 14, CNB2, FNA, and the plasma PK measurements will be scheduled anytime within 84 days after your enrollment into A5335s, as long as you are still on A5329 study medications.

[2] The post-biopsy phone evaluation will occur on Day 10. If you miss Day 7 and the CNB2 occurs on Day 14, the post-biopsy phone evaluation will occur on Day 17. If you miss CNB2 on Days 7 and 14, the post-biopsy phone evaluation will occur 3 days after the CBN2.

Screening
At screening, substudy staff will review your A5329 study records. You will be asked about your medical history and medicines you take to see if you are able to have a liver biopsy.

If you do not enroll into the substudy A5335s
If you decide not to take part in this substudy or withdraw from the substudy, your participation in A5329 will not be affected.

If you do not enroll into A5329
If you do not enroll in A5329, you cannot enroll in this substudy.

Substudy Visit 1(Entry/Day 0) and Substudy Visit 2 (Day 1): Core Needle Liver Biopsy and 24 Hour Blood Sampling
Substudy visit 1 may occur at the site's Clinical and Translational Research Center (CTRC). You must fast (nothing by mouth) for 8 hours before the visit. If you have not fasted, your visit will be rescheduled. Your weight, height, and vital signs will be taken, and you will have a catheter inserted in your arm to allow blood to be drawn. A core needle biopsy of the liver will be performed. The doctor may numb the skin where the needle enters your body. Ultrasound (sound waves) or x-rays may be used to locate the area to be biopsied. After the core needle biopsy, you will be monitored closely for signs and symptoms of complications. Your hemoglobin may be drawn to check for bleeding.

If you did not have a liver biopsy for A5329, a portion of the liver will be examined for evidence of liver scaring. You will be told whether or not you have fibrosis and how much there is.

After the core needle liver biopsy, you will have 6 blood draws performed over 24 hours. Approximately 5 tablespoons of blood will be drawn for HCV viral load (amount of HCV in the blood), tests of the immune system and drug levels (HIV and HCV drug levels). You will eat breakfast. About 30 minutes after your breakfast, you will have your first blood draw. The results of these tests will not be given to you. After your first blood draw, you will take your HIV medications and your first dose of study drugs.

The next 5 blood draws will be 4, 6, 12, 18, and 24 hours after you have taken your HIV and HCV study drugs. You will eat lunch 4 hours after your first dose of study drug, dinner 5 hours after lunch, and a snack 3 hours after dinner. You will be given your evening dose of ARV and study drug 30 minutes after the start of your evening snack.

In the morning, you will have blood drawn for immune tests and HCV viral load. You will be given the morning dose of your study drugs. The study nurse will give you your evening dose of study drugs to take at home. To complete substudy visits 1 and 2, you will be at the site for about 28 hours.

Substudy Visit 3 (Day 2), Visit 4 (Day 3), Visit 5 (Day 4), Visit 6 (Day 5) and Visit 7 (Day 6)
You should eat breakfast approximately 30 minutes before you come in for your visit. You will have blood drawn for tests of the immune system and HCV viral load. You will be asked if you have pain from the biopsy. You will be given the morning dose of your study drugs and HIV drugs. The study nurse will give you your evening study drug dose to take at home, and you will take HIV drugs in the evening.

Substudy Visit 8 (Day 7): Core Needle Liver Biopsy, Fine Needle Liver Sampling, and Blood Draw over 12 Hours

Visit 8 may occur at the site's CTRC. You must fast (nothing by mouth) for 8 hours before the visit. If you have not fasted, your visit will be rescheduled. Your weight, height, and vital signs will be taken, and you will have a catheter inserted into your arm to allow blood to be drawn. A core needle biopsy of the liver will be performed. The doctor may numb the skin where the needle enters your body. Ultrasound or x-rays may be used to locate the area to be biopsied. You will also have a fine needle aspiration of the liver. Fine needle aspirates require that a doctor put a very thin needle into your liver to obtain liver cells. The needle that is used for the fine needle aspiration is much smaller than the needles that are used to obtain the core liver biopsy. After the procedures, you will be monitored closely for signs and symptoms of complications. Your hemoglobin may be drawn to check for bleeding. The results of these tests will not be given to you.

After the procedures, you will have breakfast and then 6 blood draws performed over 12 hours. Approximately 5 tablespoons of blood will be drawn to access drug levels, immune tests and HCV viral load. About 30 minutes after your breakfast, you will have your first blood draw.

After the first blood draw, you will be given the morning dose of your HIV drugs and your study drugs. The next 5 blood draws will be 1, 2, 4, 6, and 12 hours after you have taken your drugs. You will eat lunch 4 hours after your first dose, dinner 5 hours after lunch, and a snack 3 hours after dinner. You will be given your evening dose of HIV drugs and study drugs 30 minutes after the start of your evening snack. Following the completion of the blood draws, you will be discharged. We anticipate that you will be at the CTRC for about 14 hours.

Day 10

Substudy staff will call you 3 days after your last visit to ask you how you are feeling. You will continue to be followed in the main study A5329.

Dietary Restrictions

Do not consume any grapefruit, Seville oranges, starfruit, or products containing any of these fruits in the 3 days (72 hours) before substudy visit 1 (entry/day 0), and substudy visit 8 (day 7) and before taking your morning and evening dose of study drugs on all substudy visits.

Other

Some of your blood and fluid/tissue that are left over after all required substudy testing is done may be stored and used for future ACTG-approved HIV- and HCV-related research. Your sample will be identified by a number. Refusing to have your blood or tissue samples stored will not affect your participation in this substudy. We will not store your samples with any information that will identify you. These samples may be stored for an indefinite period. You will not receive the results of testing performed on any of these samples.

Researchers will make reasonable efforts to obtain and destroy data and/or samples if consent is withdrawn but you should know that in some cases it may not be possible to retrieve data and/or samples. *Please indicate at the end of this consent if you agree to allow your leftover blood and fluid/tissue to be used for future ACTG-approved HIV- and HCV-related research.*

Why Would The Doctor Take Me Off This SubStudy Early?

The substudy doctor may need to take you off the substudy early without your permission if:

- The substudy is cancelled

- A Study Monitoring Committee (SMC) recommends that the substudy be stopped early (An SMC is an outside group of experts who monitor the substudy.)
- You are not able to complete the substudy visit 1(entry) and substudy visit 2 (day 1) evaluations
- You are not able to complete the substudy visit 8 (day 7) evaluations (note that these evaluations may be rescheduled anytime within 84 days after your enrollment into A5335s, as long as you are still on A5329 study medications).
- You stop taking the A5329 study drugs or your HIV drugs before your substudy visit 8 (day 7)
- Your primary care provider or investigator thinks the substudy is no longer in your best interest
- You withdraw your consent for the substudy A5335s
- You become pregnant or begin breast feeding

What Are The Risks Of The SubStudy?

Risks of Social Harm
Although the study site will make every effort to protect your privacy and confidentiality, it is possible that others could find out that you are participating in this substudy and that social harm may result (because you could become labeled as being infected with HIV and HCV). For example, you could be treated unfairly or discriminated against by family members, friends, and/or the community.

Risks of Drawing Blood
Taking blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting, or infection. You may experience temporary discomfort at the intravenous (IV) site.

Risks of Liver Biopsy and Fine Needle Aspiration
There are risks and possible undesirable consequences associated with the procedures including, but not limited to, pain, bleeding, infection, organ damage, and/or death. The most common complications related to liver biopsy are pain and bleeding. Fewer than one in 100 people who undergo this procedure will have a severe complication.

Before these procedures, your medical history will be reviewed to make sure that you do not have a history of bleeding problems and other reasons you should not have a biopsy. In the case of severe bleeding, you may need a transfusion. The local anesthesia may not numb the area sufficiently and you may feel some minor discomfort, which may be more frequent than bleeding or infection. Also, in rare cases, you may have an allergic reaction to the drug used in this type of anesthesia.

Unknown Risks
There may also be side effects, other than listed above that we cannot predict. You should call us when you think you are having any of the problems listed above, or even if you are having problems that are not on this list. Medications such as Morphine or Tylenol will be given to make side effects that occur less serious and less uncomfortable.

Are there Risks Related to Pregnancy?

Pregnant women are not allowed to participate.

Are There Benefits to Taking Part in This Study?

You will not directly benefit from this substudy, but information learned from this study may help others with HIV and HCV.

What Other Choices Do I Have Besides This Study?
If you decide not to participate in this substudy, your decision will not affect your enrollment in the main study (A5329).

What About Confidentiality?
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protections (OHRP) or other government agencies as part of their duties, Food and Drug Administration (FDA), the University of Pennsylvania institutional review board (IRB), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, other government agencies and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Your personal information may be given out if required by law. If you test positive for HIV or if a CD4 or HIV viral load is done at a study visit, by law we have to report the result to the City of Philadelphia Health Department/PA Department of Health. Personal identifiers such as name, sex, date of birth, address, and phone number will be reported. For more information about the requirements reporting infectious diseases to the City of Philadelphia Health Department, please visit https://hip.phila.gov/ReportDisease. For more information about the requirements reporting infectious diseases to the PA Health Department, please visit: http://www.health.pa.gov/Your-Department-ofHealth/Offices%20and%20Bureaus/epidemiology/Pages/Reportable-Diseases.aspx# V620aZ3D9eU.

HIPAA AUTHORIZATION
The authorization part of the consent gives more detailed information about how your personal health information may be used and disclosed by the University of Pennsylvania Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What information about me may be collected, used or shared with others?

- Name, address, telephone number, email address, dates directly related to you such as date of birth and clinic visits.
- Personal and family medical history
- Current and past medications or therapies
- Information from questionnaires administered in the study
- Results of tests and procedures you will undergo during this research
- Social Security Number, Medical record number

Why is my information being used?
Your information is important for the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The Principal Investigator and the Investigator's study team
- Other authorized personnel at Penn, including offices that support research operations.
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside the School of Medicine, might receive my information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your information, including the results of the research study tests and procedures. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- ACTG Data Coordinating Center, Frontier Science Technology Research Foundation (FSTRF): Data for this study will be recorded on case report forms, keyed into a central database and electronically submitted to the Data Coordinating Center. The data will be cleaned and stored at this facility until it is ready to be analyzed.
- Statistical Data Analysis Center (SDAC): Approved data will be downloaded from FSTRF to the statistical data center for the AACTG at the Harvard School of Public Health. Specific study reports will be periodically provided to the study team and data safety review board to monitor if the trial is safe.
- AbbVie: The pharmaceutical company that is supplying the drugs for the main study.
- Contract Research Organization (PPD, Inc): Monitors from PPD will visit the AACTG on a quarterly basis to review data and correct mistakes before the data are sent to SDAC for analysis.
- Regulatory and safety oversight organizations: Data from this study will be made available to the The Office of Human Research Protections and to the National Institutes of Health/Division of AIDS (DAIDS)/National Institute for Allergy and Infectious Disease (NIAID), for them to evaluate the safety and efficacy of the treatments being used in this study.

Once your personal health information is disclosed to others outside of the School of Medicine, it may no longer be covered by federal privacy protection regulations. Data are reported to the sponsor on Case Report Forms that identify you by your unique study number and not your name, date of birth or medical record number. Information regarding your health, such as side effects of the study drug you experience will be reported only by code number. All samples collected for analysis will be labeled with your study number, visit number and date of your visit.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You must do so in writing to the Principal Investigator at Infectious Disease Division, 502 Johnson Pavilion Philadelphia PA 19104. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission, you will not be able to stay in this study.

Will I be able to access my records?
Since this is a blinded study (treatment or placebo is not known to participant or study team), you will be able to access some or all of your medical records after the study is over. The Principal Investigator is not required to release research information to you that is not part of your medical record.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

What Are the Costs To Me?
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 substudy.

Will I Receive Any Payment?
There are 10 visits required for this substudy; all compensation listed here is in addition to that for the main study. For the screening visit and Days 1, 2, 3, 4, 5, 6, and 10 visits you will be compensated $50 for each visit attended; total of $400. At the entry visit and Day 7 visit when both biopsy and pharmacokinetic sample collections are required, you will be compensated $300. Compensation will be provided for all visits on a ClinCard (debit card). The total compensation for the study is $1000 if all

required visits are attended. If you are requested by the study team to come in for an unscheduled visit, you will be compensated $25 for that visit.

There is no other form of compensation available such as reimbursements for parking, tokens or child care. In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

What Happens If I Am Injured?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania or the National Institutes of Health to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the 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. Your healthcare provider will treat you the same no matter what you decide.

We 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?

If you have questions about this study or a research-related injury, please contact the research team listed on page 1 of this consent form.

For questions about your rights as a research subject, contact:

- Director of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614

CONSENT

On page 4 of this consent form you were informed about optional tests to be done on your leftover blood/tissues.

Please indicate below "yes" or "no" and initial and date whether you approve the use of these extra stored samples for future testing. Note that you can withdraw your consent for research on stored specimens at any time you want and the specimens will be discarded. Your refusal or withdrawal of consent for the storage of these samples will not affect your study participation since storage of leftover samples is not a requirement for the study.

My tissue may be stored/saved for future experiments solely for use in ACTG-approved HIV-HCV- or other liver disease related research: ☐ ***Yes*** ☐ ***No***

My blood may be stored/saved for future experiments solely for use in ACTG-approved HIV-HCV- or other liver disease related research: ☐ ***Yes*** ☐ ***No***

Genetic material (DNA or RNA) from my blood or liver tissue may be stored/saved for future experiments solely for use in ACTG-approved HIV-HCV- or other liver disease related research: ☐ ***Yes*** ☐ ***No***

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information.

Name of Subject (Please Print)	Signature of Subject	Date
Name of Person Obtaining Consent (Please Print)	Signature	Date

IRB Approval From: 08/01/2017 To: 03/05/2018