

A5329

**Interferon-Free Therapy for Chronic Hepatitis C Virus Genotype 1 Infection in
Participants with HIV-1 Coinfection Receiving Concurrent Antiretroviral Therapy
(C_ASSENT)**

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

**Sponsored by:
The National Institute of Allergy
and Infectious Diseases**

**Industry Support Provided by:
AbbVie**

IND # 122,987

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**FINAL Version 2.0
June 8, 2016**



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STUDY MANAGEMENT

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Protocol E-mail Group

Sites should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5329 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org

Clinical Management

For questions concerning entry criteria, toxicity management, concomitant medications (ConMed), and coenrollment, contact the protocol team. Send an e-mail message to actg.coreA5329@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Immunology

For questions specifically related to immunologic tests, contact the protocol immunologist. Send an e-mail message to actg.coreA5329@fstrf.org (ATTN: Donald Anthony).

Pharmacology

For questions specifically related to pharmacologic laboratory tests, contact the protocol pharmacologists. Send an e-mail message to actg.coreA5329@fstrf.org (ATTN: Gene Morse and Charles Venuto).

Virology

For questions specifically related to virologic laboratory tests, contact the protocol virologists. Send an e-mail message to actg.coreA5329@fstrf.org (ATTN: **William Meyer and David Wyles**).

Data Management

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at www.fstrf.org.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and Laura Weichmann (weichman@fstrf.org) directly.
- For other questions, send an e-mail message to actg.coreA5329@fstrf.org (ATTN: Laura Weichmann).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration

For randomization/**participant** registration questions or problems and study identification number SID lists.

- Send an e-mail message to rando.support@fstrf.org.

STUDY MANAGEMENT (Cont'd)

- Call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at 716-898-7301.

Computer and Screen Problems

Contact the SDAC/DMC programmers.

- Send an e-mail message to actg.support@fstf.org or call 716-834-0900 x7302.

Protocol Document Questions

For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to actg.coreA5329@fstf.org (ATTN: Denise Barr).

Copies of the Protocol

To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG website (<https://www.actgnetwork.org>).

Product Package Inserts and/or Investigator Brochures

To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration

For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Study Product

For questions or problems regarding study product, dose, supplies, records, and returns, call Lynette Purdue, protocol pharmacist, at 301-496-8213.

Study Drug Orders

Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions

For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions

Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or Fax 1-800-275-7619 or 301-897-1710.

Phone Calls

Sites are responsible for documenting any phone calls made to A5329 team members.

- Send an e-mail to actg.coreA5329@fstf.org.

Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ABT-267	ombitasvir, A-1233617
ABT-333	dasabuvir, A-998821
ABT-450	paritaprevir, A-1043422
ABT-450/r	ritonavir-boosted paritaprevir
ABT-450/r/ABT-267	150/100/25 mg fixed-dose combination tablet
APRI	aspartate aminotransferase to platelet ratio index
ATV	atazanavir
BOC	boceprevir
CMP	comprehensive metabolic panel
DAA	direct-acting antivirals
DAA+/-RBV therapy	OBT/PTV/r/ + DSV +/- RBV
DRV	darunavir
DRV/r	ritonavir-boosted darunavir
DDI	drug-drug interaction
DSV	dasabuvir, non-nucleoside inhibitor (NNI) of HCV NS5B polymerase
DTG	dolutegravir
Exviera	dasabuvir, AbbVie
FTC	emtricitabine
HCC	hepatocellular carcinoma
HCV	hepatitis C virus infection
IAS	International Antiviral Society
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
INI	integrase inhibitor
kPa	kilopascal
LPC	laboratory processing chart
MRI	magnetic resonance imaging
NK	natural killer
NNI	non-nucleoside polymerase inhibitor
NS5A	non-structural 5A (NS5A) protein of hepatitis C virus (HCV)
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
OATP1B1	organic anion transporting polypeptide transporter
OBT	ombitasvir, inhibitor of HCV NS5A
PegIFN	pegylated interferon
PI	protease inhibitor
PTV	paritaprevir, inhibitor of HCV NS3/4A PI
PTV/r	ritonavir-boosted paritaprevir
PTV/r/OBT	150/100/25 mg fixed-dose combination tablet

GLOSSARY (Cont'd)

RAL	raltegravir
RBV	ribavirin
RVR	rapid virologic response
RTV or /r	ritonavir
SDD	spray-dried solid dispersion
SVR _x	sustained virologic response (at X weeks)
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TVR	telaprevir
Viekira Pak	OBT, PTV, and RTV tablets; DSV tablets
VF	virologic failure
vRVR	very rapid virologic response

SCHEMA

A5329

Interferon-Free Therapy for Chronic Hepatitis C Virus Genotype 1 Infection in **Participants** with HIV-1 Coinfection Receiving Concurrent Antiretroviral Therapy
(**C_ASCENT**)

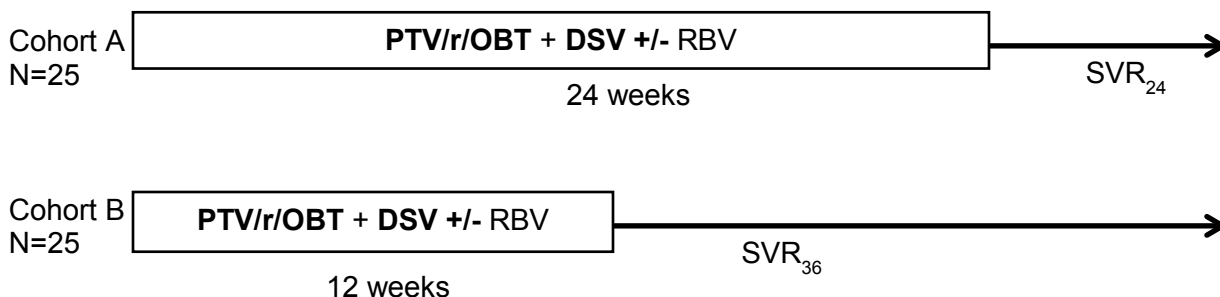
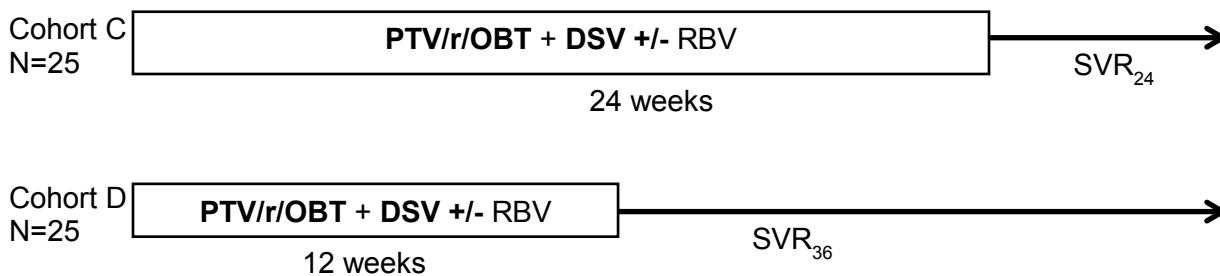
<u>DESIGN</u>	Non-randomized, open-label, phase II study of interferon (IFN)-free hepatitis C virus (HCV) therapy for 24 or 12 weeks in sequentially enrolled cohorts of participants with HIV-1 coinfection who are taking protocol-defined antiretroviral treatment (ART).
<u>DURATION</u>	Up to 48 weeks per participant
<u>SAMPLE SIZE</u>	100 participants , 25 participants per cohort
<u>POPULATION</u>	<p>HCV genotype 1a or 1b and HIV-1 coinfecting participants (HCV treatment-naïve or HCV treatment-experienced) who are on a concurrent integrase inhibitor (INI)-based (raltegravir [RAL] or dolutegravir [DTG]) or protease inhibitor (PI)-based (darunavir [DRV] or atazanavir [ATV]) ART regimen.</p> <p>Participants will be categorized according to evidence of cirrhosis (yes or no).</p> <p>For each 25-participant cohort, the number of participants enrolled with cirrhosis will be limited to 7.</p>
<u>REGIMENS</u>	<p>Among participants taking an INI-based (RAL or DTG) ART regimen for HIV-1: 24 (Cohort A) or 12 (Cohort B) weeks of HCV treatment with HCV direct-acting antivirals (DAA) paritaprevir/ritonavir/ombitasvir (PTV/r/OBT) + dasabuvir (DSV) +/- ribavirin (RBV) therapy (DAA+/-RBV therapy):</p> <ul style="list-style-type: none"> • Drug 1: PTV/r/OBT (150/100/25 mg; two 75/50/12.5 mg fixed-dose combination tablets) orally (PO) once a day (QD) plus • Drug 2: DSV (250 mg) PO twice per day (BID) plus • Drug 3: RBV (1000 or 1200 mg weight-based) dosed in two divided doses PO BID (participants with HCV genotype 1a only; participants with HCV genotype 1b will not receive RBV) <p>Among participants taking a HIV-1 PI-based (DRV or ATV) ART regimen for HIV-1: 24 (Cohort C) or 12 (Cohort D) weeks of HCV treatment with HCV DAA+/-RBV therapy:</p> <ul style="list-style-type: none"> • Drug 1: PTV/r/OBT (150/100/25 mg; two 75/50/12.5 mg fixed-dose combination tablets) PO QD plus • Drug 2: DSV (250 mg) PO BID plus

SCHEMA (Cont'd)

- Drug 3: RBV (1000 or 1200 mg weight-based) dosed in two divided doses PO BID (**participants with HCV genotype 1a only; participants with HCV genotype 1b will not receive RBV**)

Details for the qualifying ART concomitant regimens are in protocol section 5.4.1.

Each cohort will **include** two steps: on-HCV treatment (Step 1) and post-HCV treatment **follow-up** (Step 2).

Group 1: INI-based (DTG or RAL) ART regimen (48 weeks total)**Group 2: HIV-1 PI-based (ATV or DRV) ART regimen (48 weeks total)**

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Combination therapy with the hepatitis C virus (HCV) direct-acting antiviral (DAA) treatment regimen of **paritaprevir (PTV)/r (ritonavir)/ombitasvir (OBT)** plus **dasabuvir (DSV)**, **with and without** ribavirin (RBV) (DAA+/-RBV therapy) will be safe and well tolerated.

1.1.2 DAA+/-RBV therapy will result in sustained virologic response (SVR₁₂) rates higher than 70% corresponding to the SVR₁₂ rates observed with telaprevir (**TVR**) and boceprevir (**BOC**) plus **pegylated interferon** (PegIFN)/RBV.

1.2 Primary Objectives

1.2.1 To evaluate the safety and tolerability of DAA+/-RBV therapy in **participants** coinfecting with HIV-1.

1.2.2 To estimate the efficacy of DAA+/-RBV therapy in HCV/HIV-1 coinfecting **participants**, as measured by the **SVR** at 12 weeks (SVR₁₂) after DAA+/-RBV therapy discontinuation, where SVR₁₂ is defined as HCV RNA in the blood less than the assay lower limit of quantification (LLOQ).

1.3 Secondary Objectives

1.3.1 To evaluate HIV-1 virologic failure (VF), defined in section 7.3, in HCV/HIV-1 coinfecting **participants** during coadministration of antiretroviral therapy (ART) and DAA+/-RBV therapy.

1.3.2 To evaluate acquisition of major HIV-1 resistance mutations in HCV/HIV-1 coinfecting **participants** who experience HIV-1 VF during coadministration of ART and DAA+/-RBV therapy and during the initial four-week period following discontinuation of DAA+/-RBV therapy.

1.3.3 To characterize HCV resistant variants before, during and after the initial 12 week period following discontinuation of DAA+/-RBV therapy in all **participants** not attaining SVR₁₂.

1.3.4 To estimate the population plasma **pharmacokinetic** (PK) parameters of DAA+/-RBV therapy, during coadministration with **antiretrovirals** (ARVs) in HCV/HIV-1 coinfecting **participants**, and to compare the **participant**-specific PK parameters obtained with those reported in prior studies for HIV-1 seronegative **participants**.

1.3.5 To assess the relationship of markers of immune activation, including IP10 and sCD14, measured before, during and after administration of DAA+/-RBV therapy and DAA+/-RBV therapy outcome (SVR₁₂) and/or the presence of HCV resistance mutations before, during and after administration of DAA+/-RBV therapy.

- 1.3.6** To estimate the efficacy of DAA+/-RBV therapy HCV/HIV-1 coinfecting **participants**, as measured by the sustained virologic response at 24 weeks (SVR₂₄) after DAA+/-RBV therapy discontinuation where SVR₂₄ is defined as HCV RNA in the blood less than the assay LLOQ.

1.4 Exploratory Objectives

- 1.4.1 To evaluate LPS, IL-6, CD4+, and CD8+ T cell **HLA DR/CD/38** coexpression, natural killer (NK) 16+56- subset frequency and NKP30, NKG2A, IFN α 1/IFN α 2 expression, hyaluronic acid (HA), D-dimer, high-sensitivity C-reactive protein (hsCRP), and I-FABP measured before, during, and after administration of DAA+/-RBV therapy.
- 1.4.2 To describe the kinetics of innate and adaptive immune responses over the course of HCV treatment with DAA+/-RBV therapy to gain insight into mechanisms underlying innate and adaptive immune impairment.
- 1.4.3 To explore associations of ARV and DAA PK parameters with covariates such as cirrhosis classification and, presence of single nucleotide polymorphisms in the human genome.
- 1.4.4 To explore associations of **participant**-specific ARV and DAA PK parameters with HIV-1 and/or HCV VF, and with occurrence of selected toxicities including elevation in serum alanine aminotransferase (**ALT**) levels.
- 1.4.5 To estimate the population plasma PK parameters of ARVs when taken alone and when taken with DAA+/-RBV therapy in HCV/HIV-1 coinfecting participants, and to compare the participant-specific PK parameters before versus after dosing to steady-state of the DAA+/-RBV therapy.**

2.0 INTRODUCTION

2.1 Background

Shared risk factors and routes of transmission have resulted in a disproportionate prevalence of chronic HCV infection in those with HIV-1 infection. Across **participants** enrolled in ACTG studies the HCV antibody prevalence was found to be 16% [1]. Following the introduction of highly active antiretroviral therapy (HAART), end stage liver disease, largely due to HCV, has emerged as a leading cause of mortality in HIV-1 infected **participants** [2]. HCV infection in those with HIV-1 also results in accelerated liver disease progression and poor response to PegIFN + RBV therapy [3-5]. In addition to marginal efficacy, PegIFN therapy is particularly problematic in this population due to the high prevalence of co-morbidities such as depression and cytopenias (eg, neutropenia). In practice, these limitations have led to low rates of HCV treatment in **participants** with HIV-1 coinfection [6]. Despite encouraging preliminary results from phase IIb studies of HCV

protease inhibitors (PIs), **TVR** and **BOC**, added to PegIFN/RBV in this population there is a great medical need for effective, IFN-free HCV treatment options in the **HCV/HIV-1** coinfecting population [7, 8]. Accordingly, a key portion of the ACTG Hepatitis Transformative Science Group's (HEPTSG) mission is to advance therapy for HCV infection through the study of novel HCV antivirals.

Therapy for chronic HCV infection has evolved rapidly with the introduction of multiple DAAs targeting distinct aspects of the viral life-cycle. In particular, DAAs targeting the HCV NS3/4A protease, NS5A protein, and the NS5B RNA polymerase are among the most promising and have been evaluated in combination with PegIFN and RBV as well as in IFN-free combinations. Specific compounds of interest for this protocol include; 1) **PTV**, an NS3/4A PI, 2) **OBT** an NS5A inhibitor, and 3) **DSV** a non-nucleoside NS5B polymerase inhibitor (NNI). **This combination (OBT, PTV, RTV + DSV tablets [Viekira Pak]) constitutes an HCV treatment regimen approved by the US Food and Drug Administration (FDA) on December 19, 2014, for the treatment of chronic HCV genotype 1 infection in persons with and without HIV-1 coinfection. AbbVie released addenda dated November 19, 2015, for the PTV, OBT, and DSV IBs dated June 10, 2015.**

PTV is a highly selective and potent NS3/4A PI with a sub-nanomolar 50% effective concentration (EC_{50}) against HCV genotypes 1a and 1b in vitro [Investigational Product: **PTV, ABT-450** (A-1043422); AbbVie; 8th Edition, **June 10, 2015**]. **PTV** is highly protein bound (99.5%) with metabolism primarily via cytochrome P450 (CYP) isoenzyme 3A4. RTV or r dosed at 100 mg daily increases the area under the concentration time curve (AUC) and C_{24} of a single 300 mg dose of **PTV** by 50 and >300-fold, respectively. **PTV** is a moderate inhibitor of the organic anion transporting polypeptide transporter, (OATP1B1 [SLCO1B1]), and an inhibitor of UGT1A1 (IC_{50} 4.4 μ M). **PTV** does not inhibit the CYP isoforms 1A2, 2C9, 2C19, 2D6, or 3A4 in human liver microsomes. **PTV** with RTV has generally been safe and well tolerated in both healthy human volunteers and HCV infected individuals. In the ongoing pivotal phase II M11-652 study (n=448; detailed below) Grade 3 ALT elevations (>5x ULN) were noted in 5 **participants** (0.9%). Importantly, these elevations were associated with a higher dose of **PTV/r** (200/100 mg) (4 **participants**); concomitant increases in bilirubin were not seen and ALT elevations resolved with continued dosing of **PTV** in most cases. In this same study, asymptomatic Grade 3 bilirubin elevations, presumed due to inhibition of OATP1B1, were seen in 1.9% of **participants** and resolved with continued therapy.

OBT is a potent NS5A inhibitor with an in vitro EC_{50} of 56-190pM in the presence of 40% human serum assayed in a genotype 1 subgenomic replicon system [Investigational Product: **OBT, ABT-267** (A-1233617); AbbVie; 6th Edition, **June 10, 2015**]. **OBT** is highly protein bound (99.98%) with a half-life of 18-26 hours and is primarily metabolized by CYP 3A4. Despite predominantly CYP 3A4 metabolism, RTV 100 mg only increased **OBT** exposure by about 50%. The bioavailability of **OBT** is decreased by roughly 40% in the fasted state. **OBT** has a low potential for drug-drug interaction as evidence by a lack of inhibition of CYP isoforms with the exception of weak inhibition of CYP 2C8. **OBT** has been safe and well tolerated in both healthy volunteers and HCV infected **participants**. At this time no apparent **OBT** specific side effects or laboratory abnormalities have been identified beyond those expected with coadministration of either PegIFN and RBV or **PTV/r**.

DSV is a potent NS5B NNI with EC₅₀s in genotype 1 replicon cells of 21-99nM (40% human serum) [Investigational Product: **DSV, ABT-333** (A-998821); AbbVie; 8th Edition, **June 10, 2015**]. **DSV** is also highly protein bound (>99%) with a half-life of 5-8 hours and is primarily metabolized by CYP 2C8, and to a lesser extent, CYP 3A4. Of note the formulation of **DSV** (dosed at 400 mg twice per day [BID]) used in phase II studies has been improved resulting in a roughly 50% increase in bioavailability resulting in dosing at 250 mg BID in subsequent studies. Ingestion of **DSV** with a high fat meal increases exposure by about 40%. **DSV** has a low potential for drug-drug interactions with inhibition (IC₅₀) of CYP 2C9 and 2C19 at 9 and 18μM, respectively. The IC₅₀ for CYP 3A4 inhibition is >40 μM. During in vitro electrophysiology assays **DSV** was found to have an IC₅₀ of 0.3μg/mL in the human Ether-á-go-go Related Gene (hERG) assay. During intensive electrocardiogram (EKG) monitoring studies in healthy volunteers at doses of 1200-2000 mg, **DSV** increased the corrected QT interval by no more than 6.4msec. [See Investigational Product: **DSV, ABT-333**]. Based on the **DSV** dose of 250 mg BID with the new formulation the expected impact on the QTc interval is minimal. Similar to **OBT**, **DSV** has been well tolerated in both healthy volunteers and HCV-infected **participants** without clear unique side effects or associated laboratory abnormalities beyond those attributed to **PTV/r** in a dose related fashion.

While multiple HCV DAA combination regimens are being developed, some of the most promising are based on various combinations of HCV DAAs paired with RTV boosted **PTV** (**PTV/r**). In two small studies (PILOT [NCT01306617] and CO-PILOT [NCT01221298]), **PTV/r** was studied in combination with two different NNIs (**DSV** or ABT-072) plus RBV. This combination was administered for 12 weeks to HCV mono-infected **participants** who were HCV treatment-naïve and **participants** who had been previously treated with PegIFN/RBV and failed to achieve a SVR. Among the treatment-naïve **participants**, SVR was observed in 91-95% of **participants**, whereas SVR was achieved in only 47% of **participants** with prior treatment failure [9, 10].

In a follow-up phase II study, 570 HCV genotype 1 monoinfected **participants** are being treated with the **PTV/r** in combination with a NS5A inhibitor (**OBT**) with or without the NNI (**DSV**) and/or RBV [11]. This study (M11-652, NCT01464827) has enrolled both HCV treatment-naïve and treatment-experienced, null virologic responders and is testing different lengths of therapy (8, 12, and 24 weeks) as well as different combinations of ARVs. Treatment-naïve **participants** treated with DAA+/-RBV therapy for 12 weeks showed SVR₁₂ rates of 99% and sustained virologic response at week 24 (SVR₂₄ rates) of 96% in an intention to treat analysis [11]. Omission of RBV in the 12-week arm resulted in an SVR₁₂ rate of 90% and SVR₂₄ of 87%. Based on the excellent response rate in the treatment-naïve population for 12 weeks, it is not surprising that extension of the duration to 24 weeks resulted in a similar SVR₁₂ rate (93%). Among the more difficult to treat population of null responders to prior PegIFN/RBV, this regimen given for 12 weeks led to SVR₁₂ and SVR₂₄ in 93% of **participants**. Extension to 24 weeks in the null responder population increased the SVR₁₂ to 98% and SVR₂₄ to 95%. The regimen was safe and well tolerated for durations of therapy up to 24 weeks.

In November 2012, phase III clinical trials were initiated for HCV mono-infected **participants** who are HCV treatment-naïve (SAPPHIRE-I, NCT01716585), and treatment-experienced (NCT01715415, SAPPHIRE-II) including those with cirrhosis (TURQUOISE-II see below). Of

note, these studies are utilizing a once a day (QD), fixed-dose combination tablet that contains two DAAs plus RTV (**PTV/r/OBT**) plus BID dosing of **DSV** and RBV (DAA+/-RBV therapy). In addition, studies are underway to evaluate **PTV/r/OBT** without RBV and without **DSV** (PEARL-I, NCT01685203).

In Study M11-646 (SAPPHIRE-I), a total of 631 **participants** were randomized and received at least one dose of study drug, of which 67.7% had HCV genotype 1a and 32.3% had HCV genotype 1b. The SVR₁₂ rate for treatment-naïve **participants** receiving 3-DAA + RBV for 12 weeks was 96.2%. **VF** was noted in 7/322 (2.2%) genotype 1a **participants** (on treatment **VF**: n=1; relapse: n=6) and 1/151 (0.7%) genotype 1b **participants** (relapse).

In Study M13-098 (SAPPHIRE-II), a total of 394 **participants** were randomized and received at least one dose of study drug, of which 58.4% had HCV genotype 1a, 41.4% had HCV genotype 1b, 49.0% were prior pegIFN/RBV null responders, 21.9% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers. The SVR₁₂ rate for treatment-experienced **participants** receiving 3-DAA + RBV for 12 weeks was 96.3%. **VF** (all relapse) was noted in 5/173 (2.9%) genotype 1a **participants** and 2/123 (1.6%) genotype 1b **participants**.

The above regimen is also being studied in the HCV mono-infected **participants** with compensated cirrhosis in a phase III randomized controlled trial. The M13-099 study (TURQUOISE-II, NCT01704755) enrolled compensated cirrhotic **participants**. A total of 380 **participants** were randomized and received at least one dose of study drug, of which 68.7% had HCV genotype 1a, 31.3% had HCV genotype 1b, 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders, 8.2% were prior pegIFN/RBV partial responders, and 13.7% were prior pegIFN/RBV relapsers.

The SVR₁₂ rates for **participants** with compensated cirrhosis treated with 3-DAA + RBV for 12 or 24 weeks were 91.8% and 95.9%, respectively. **VF** was noted in 13/208 (6.3%) **participants** (on treatment **VF**: n=1; relapse: n=12) receiving the 12-week regimen and 4/172 (2.3%) **participants** (on treatment **VF**: n=3; relapse: n=1) receiving the 24-week regimen.

In Study M14-490 (TURQUOISE-III), a total of 60 HCV mono-infected patients with compensated cirrhosis and HCV genotype 1b were treated with 3-DAA (Viekira Pak) alone (no RBV) for 12 weeks. SVR₁₂ was achieved in all 60 patients with no **VF**. Based on this result, HCV treatment guidelines [16] were modified to state that patients infected with HCV genotype 1b should be treated with 3-DAA (Viekira Pak) alone, including those with cirrhosis and HIV-1 infection.

In Part 1a of the study M14-004 (TURQUOISE-I), 63 patients with HIV-1 and HCV genotype 1a or 1b coinfection were treated with 12 or 24 weeks of 3D (Viekira Pak) + RBV.

2.2 Rationale

Based on the **FDA approval of this combination** and the immense medical need in the **HCV/HIV-1** coinfecting population, a study of DAA+/-RBV therapy in this population is attractive and **continues to be** urgently needed.

Rationale for inclusion of raltegravir (RAL) or dolutegravir (DTG) plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC) as protocol-defined ART regimen **Group 1**

RAL is a well-tolerated HIV strand transfer integrase inhibitor (**INI**) that is currently a component of recommended first line therapy for adults with susceptible HIV-1 infection by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents [41]. Important for this study, RAL has a low potential for drug-drug interactions (DDIs) due to its primary metabolism via UGT1A1. Further, DAA+/-RBV therapy was coadministered with RAL 400 mg BID to steady state for a duration of 14 days in healthy volunteers. Based on the preliminary PK analysis, no clinically relevant changes in **PTV**, **OBT**, **DSV**, or **DSV M1** exposures (based on comparison with historical data) were observed during coadministration of DAA+/-RBV therapy with RAL. The exposures of RAL during coadministration with DAA+/-RBV therapy were 2- to 2.3-fold of RAL administered alone. Based on the U.S. FDA summary basis of approval for RAL, up to a 2-fold increase in RAL exposures are expected to be safe and well tolerated. In addition, in the phase III studies of RAL, coadministration of RAL with acid suppressing agents, which showed 3- to 4-fold increases in RAL exposures in phase I studies, were demonstrated to be safe [38]. Given the high therapeutic index of RAL and the lack of an effect of RAL on the **DAA** regimen it is appropriate to proceed with a study in coinfecting **participants** with HCV on a RAL-based ART regimen.

TDF in combination with FTC and 3TC are nucleos(t)ide reverse transcriptase inhibitors that are well tolerated and currently a component of recommended first line therapy for adults with susceptible HIV-1 infection by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents [41]. PK studies for 7 to 14 days analysis shows that TDF (300 mg QD) and FTC (200 mg QD) exposures at steady state were not affected ($\leq 25\%$ higher) by coadministration of **OBT**, **PTV/r** + **DSV**. The steady state exposures of **PTV**, **DSV** and **OBT** were also not affected (up to $\pm 30\%$ change) when **PTV/r** + **DSV** + **OBT** were coadministered with TDF and FTC. The coadministration of multiple doses of TDF and FTC with **PTV/r** + **DSV** + **OBT** was safe and well tolerated. Accordingly, no dose adjustment is expected to be required for RAL plus TDF and FTC or 3TC, **PTV/r**, **DSV**, and **OBT** during coadministration.

DTG is a well-tolerated HIV strand transfer INI that is currently a component of recommended first line therapy for adults with susceptible HIV-1 infection by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents [41]. Important for this study, DTG has a low potential for DDIs as it does not inhibit nor induce CYP isoenzymes. DTG is primarily metabolized by UGT1A1, with minor contribution by CYP3A4. It is also a substrate for the transporters P-glycoprotein and breast cancer resistance protein. A PK study performed in healthy adults (n=12) administered DTG (50mg QD) and OBT/PTV/r (25/150/100mg QD) with DSV (250 mg BID) (AbbVie study

M14-228). DAA exposures (C_{\max} , AUC, and C_{trough}) were minimally affected. There was a 34% and 28% decrease in PTV and RTV C_{trough} concentrations, respectively, which were not considered clinically significant changes. OBT, DSV, and DSV M1 metabolite exposures were up to 16% lower. DTG exposures (C_{\max} , AUC, and C_{trough}) were 22% to 38% higher. These PK changes are not considered to be clinically significant, and therefore, no dose adjustment is expected for the DAA regimen or DTG.

Rationale for inclusion of darunavir (DRV) or **atazanavir (ATV)** plus TDF/FTC or **ABC/3TC** or **DTG** as protocol defined ART regimen **Group 2**

DRV is a well-tolerated HIV-1 **PI** that is currently a component of recommended first line therapy for adults with susceptible HIV-1 infection by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents [41].

In healthy volunteers, the DAA+/-RBV therapy (containing 100 mg of RTV) was coadministered with DRV 600 mg + RTV 100 mg BID and DRV 800 mg + RTV 100 mg QD to steady state for a duration of 14 days. Preliminary PK analysis shows that during coadministration of the DAA+/-RBV therapy with DRV 600 mg + RTV 100mg BID, the steady state exposures of **OBT** were unaffected (only about 25% lower), while **PTV** and **DSV** were modestly lower (up to \pm 45% lower). During coadministration of the DAA+/-RBV therapy with DRV 800 mg + RTV 100 mg QD, the steady state exposures of **OBT** and **DSV** were unaffected, while **PTV** exposures were modestly higher (about 30% to 50%). DRV exposures (C_{\max} and AUC) at steady state were not affected (up to 25% lower) following coadministration of the DAA+/-RBV therapy with DRV + RTV QD and BID regimens; but, DRV C_{12} levels were about 43% lower and C_{24} levels were only about 10% lower during coadministration of DRV 600 mg + RTV 100 mg BID with 3- HCV DAA combination. Similarly, DRV C_{24} levels were about 50% lower during coadministration of DRV 800 mg + RTV 100 mg QD with the DAA+/-RBV therapy. The comparable C_{\max} , AUC and lower C_{12} or C_{24} levels of DRV observed with coadministration are not expected to significantly affect the safety or efficacy based on prior DRV clinical trials. The **PK-pharmacodynamic (PK-PD)** analyses of DRV from two large phase III trials, the ODIN and ARTEMIS studies, showed no apparent relationships between DRV AUC₂₄ and C_{trough} (C_{24}) and the change in log₁₀ HIV-1 viral load from baseline at Week 48 and the proportion of **participants** achieving plasma viral load ≤ 50 copies/mL at Week 48 [39, 40]. In these studies, the median DRV C_{trough} was about 37-fold higher than the EC_{50} of the wild-type virus. Hence, during coadministration with the DAA+/-RBV therapy, DRV C_{24} from the DRV 800 mg + RTV 100 mg QD regimen is expected to be ~18-fold higher, while DRV C_{12} and C_{24} from the DRV 600 mg + RTV 100 mg BID regimen are expected to be ~18-fold and ~33-fold higher, respectively, than the EC_{50} of the wild-type virus. The coadministration of DRV + RTV as QD and BID regimens with the DAA+/-RBV therapy was safe and well tolerated with adverse events (AEs) and laboratory abnormalities being mostly mild and not clinically significant. There were no clinically significant changes from baseline in vital signs, clinical laboratory tests or EKGs. Accordingly, adjustment is expected to be required for **ritonavir-boosted darunavir (DRV/r)** QD plus TDF and FTC or 3TC, **PTV/r**, **DSV**, and **OBT** during coadministration. **Participants** will be required to switch to DRV 600 mg BID with **RTV** dosed separately only with the **evening** dose of DRV since the **morning** dose of DRV is boosted by the RTV coformulated with ABT-450 and ABT-267.

ATV is an HIV-1 PI and is considered an alternative agent for use in cART for adults with susceptible HIV-1 infection according to the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents [41]. ATV is metabolized by CYP3A4 and is recommended to be dosed at 300 mg with 100 mg of RTV QD. ATV inhibits CYP3A4 and CYP2C8, as well as, UGT1A1. Because of inhibition of UGT1A1, the main adverse effect associated with ATV/r is reversible indirect hyperbilirubinemia. The safety and PKs of ATV/r (300/100 mg) with PTV/r/OBT (150/100/25 mg QD) and with DSV (250 mg BID) has been studied in healthy volunteers (Abbvie Study M13-394). A total of 24 participants received ATV QD in the morning or evening. The RTV component of ATV was administered as part of the 3-DAA regimen for those taking ATV in the morning. For ATV in the evening, RTV 100 mg was coadministered with the evening dose of ATV and thus, participants received 200 mg total daily of RTV (100 mg with the DAA and 100 mg with the evening dose of ATV). PTV C_{max} and AUC during coadministration with ATV QD (morning) and QD (evening) were up to 1.5- to 2-fold and 2- to 3-fold, respectively. PTV C_{trough} were 3.2-fold and 12-fold higher during coadministration with ATV QD (morning) and QD (evening), respectively. OBV and DSV (and M1 metabolite) exposures were minimally affected (up to 25%) during coadministration with ATV/r in the morning or evening. ATV QD (morning) AUC and C_{max} were comparable when given with the DAAs, while C_{trough} was approximately 9% lower with the DAAs. RTV QD (morning) C_{max} was approximately 20% lower, and AUC and C_{trough} were up to 10% lower with coadministration of the DAAs. ATV QD (evening) AUC approximately 20% higher and C_{trough} was 68% higher when coadministered with the DAAs, while C_{max} values were comparable. RTV BID (evening) C_{max} and AUC were 35% and 125% higher, respectively, while C_{trough} was approximately 14-fold higher during coadministration with DAAs. Grade 3 total bilirubin elevations were observed when ATV/r was given with 3-DAA; however, these were common during dosing with ATV/r alone and did not worsen when the DAAs were added.

Rationale for enhanced HIV-1 RNA monitoring during coadministration of DAA therapy
While unlikely based on the available healthy volunteer DDI data and the delivery of the HCV regimen for only 12 or 24 weeks, the potential for HIV-1 viral failure during this study presents unique issues due to the use of low-dose RTV to boost levels of **PTV**. **Participants** experiencing HIV-1 VF would be exposed to 100 mg of RTV daily and could potentially select for HIV-1 PI resistance mutations. RTV monotherapy at 400-600 mg BID sequentially selects for resistance mutations beginning with the V82A/F mutant followed by the accumulation of additional mutants at positions 54, 71, and 36 in the protease gene over the course of weeks to months [12]. Whether the exposure obtained with 100 mg of RTV is sufficient to select for HIV-1 protease resistance mutations is unknown. In addition the V82A/F mutant does not confer significant cross-resistance to commonly used PIs such as DRV or ATV; given that the selection of additional protease mutants requires extended exposure, frequent HIV-1 RNA monitoring is likely to prevent the accumulation of clinically significant HIV-1 PI resistance mutations. The excellent preliminary efficacy data for the proposed HCV treatment regimen [11], combined with the high burden of HCV disease in the coinfecting population and the need for more effective therapies present an overall favorable risk-benefit profile for the proposed study. Importantly, the risk of exposure of replicating HIV-1 to low-dose RTV is further reduced by 1) limiting duration of RTV-containing HCV treatment to 12 or 24 weeks; 2) enrollment of **HCV/HIV-1** coinfecting

participants with documented suppression of HIV-1 RNA for at least 6 months prior to HCV treatment; 3) frequent monitoring of HIV-1 RNA, utilizing a strategy that is based on the intensive HIV-1 RNA monitoring framework used in A5294 (treatment of **participants** taking HIV-1 PI-based ART during the administration of **BOC**, a HCV PI, known to result in lower exposure to the HIV-1 PI).

Rationale for omission of RBV in treatment regimens for participants with genotype 1b HCV infection

The role RBV plays in virologic response to the study regimen has been evaluated in several large studies. In two companion phase III studies, treatment-naïve non-cirrhotic participants with genotype 1a (n=305) and genotype 1b (n=419) were randomized to treatment with PTV/r/OBT plus DSV with or without weight-based RBV for 12 weeks [13]. Genotype 1a participants treated without RBV had a significantly lower SVR₁₂ rate compared with those who received RBV (90.2% vs. 97.0%). In contrast, no such difference in SVR rates was seen in genotype 1b participants; 99.5% without RBV versus 99.0% with RBV. Based on these data, the prescribing information [14] and guidelines recommendations omit RBV from treatment regimens for genotype 1b non-cirrhotic patients.

Until recently, data on the treatment of genotype 1b cirrhotic patients with PTV/r/OBT plus DSV in the absence of RBV was lacking. The recently published phase IIIb TURQUOISE III study addressed this issue in an open-label single arm study of 60 treatment-naïve and treatment-experienced genotype 1b cirrhotic participants treated for 12 weeks with PTV/r/OBT plus DSV alone [15]. A 100% SVR₁₂ rate was seen in this study strongly suggesting, despite the lack of a control arm, that RBV can be omitted from this regimen when treating genotype 1b patients including those with cirrhosis and treatment experience. Notably, the Infectious Diseases Society of America/American Association for the Study of Liver Diseases (IDSA/AASLD) guidelines have been updated, supporting the approach of omitting RBV from the treatment regimen for all genotype 1b patients [16].

Despite the lack of a dedicated trial evaluating the role of RBV in HIV-1 coinfecting genotype 1b patients, we believe omission of RBV is justified in the treatment regimens of genotype 1b participants in this study because: 1) the compelling data that RBV is not needed to optimize results in HCV monoinfected genotype 1b patients, 2) generally similar results seen in HIV-1-HCV coinfecting patients when compared with HCV mono-infected participants treated with DAA regimens and 3) the increased risk of side effects and AEs when RBV is included in an HCV treatment regimen. While RBV side effects can certainly be managed, in this case, there is no compelling reason to believe inclusion of RBV will offer any benefit to genotype 1b HIV-1 coinfecting participants. Based on this assessment, weight-based RBV will not be administered to genotype 1b-infected participants in Version 2.0 of the A5329 protocol.

Rationale for inclusion of **participants with compensated cirrhosis**

Coinfecting **participants** with cirrhosis form a group with a significant unmet medical need as currently available therapies are both poorly tolerated and of limited efficacy in this

population. The DAA regimen of once daily (QD), fixed-dose combination tablet which contains two DAAs plus RTV (ABT-450/r/ABT-267) plus BID dosing of ABT-333 and RBV (DAA+/-RBV therapy) is being studied in the HCV mono-infected **participants** with compensated cirrhosis in a phase III randomized controlled trial (M13-099, NCT01704755). A total of 380 **participants** were randomized and received at least one dose of study drug. The SVR₁₂ rates for **participants** with compensated cirrhosis treated with 3-DAA + RBV for 12 or 24 weeks were 91.8% and 95.9%, respectively. **VF** was noted in 13/208 (6.3%) **participants** (on treatment **VF**: n=1; relapse: n=12) receiving the 12-week regimen and 4/172 (2.3%) **participants** (on treatment **VF**: n=3; relapse: n=1) receiving the 24-week regimen.

Safety data from this trial suggests a safety profile consistent with the known profile for the DAA+/-RBV therapy. The majority of treatment-emergent **AEs** were mild or moderate in severity, with few events occurring more frequently in the 24-week arm compared with the 12-week arm. Serious adverse events (**SAEs**) occurred in 5.5% overall, with similar rates in each arm, and few patients discontinued because of **AEs** (2.1% overall). Hemoglobin decline of Grade ≥ 2 occurred in 7.2% of patients in the 12 week arm and 11.0% in the 24 week arm. For patients in both treatment duration arms, hemoglobin decline was successfully managed with ribavirin dose modifications, without a negative impact on SVR₁₂. Bilirubin elevation occurred at a higher frequency in this cirrhotic population than observed in clinical trials of the same regimen in patients without cirrhosis. Elevations in indirect bilirubin with this regimen are likely related to ribavirin-associated hemolysis, along with inhibition of the bilirubin transporter OATP1B1 by **PTV**, as has been reported for other NS3 **PIs**. Bilirubin levels were not treatment limiting, typically peaked at about two weeks of treatment, were not associated with elevations in ALT, and resolved to baseline levels during the post-treatment period.

Given the available preliminary data and high unmet medical need in this population, coinfecting patients with cirrhosis form a priority population for study in A5329. **However, patients with decompensated cirrhosis (Child-Pugh classification B and C) are excluded from enrollment in A5329. This is based on the report from the FDA of 26 patients with advanced liver disease who experienced serious liver injury during treatment with 3-DAA in the post-market setting. While details of these patients and their treatment are limited, 3-DAA is contraindicated in this patient population, and such patients are not eligible for participation in A5329.**

Rationale for peripheral immune activation, inflammation, and adaptive immunity studies
NK cell function is regulated by a balance of activating and inhibitory receptors/signals. NK phenotype correlates with course of HCV infection. Pairing of NK cell inhibitory KIR2DL3 and its weaker binding ligand (HLA-C1) are associated with self-clearance of HCV [17], and KIR2DL3 genotype and increased NKG2C expression are associated with response to IFN- α therapy [18-20]. In addition to the conventional CD56+ NK cells, a CD16+CD56- NK cell subset has been observed to expand during chronic HIV-1 [21, 22], and HCV infection [23]. The degree of peripheral blood CD16+CD56- NK cell expansion in chronic HCV infection is negatively associated with PegIFN/RBV treatment response [23]. We have recently performed an analysis of immunologic predictors of PegIFN/RBV response in HCV-HIV-1 coinfection using samples from 28 **participants** within the PegIFN/RBV arm of A5071.

These preliminary data from NWCS322 indicate baseline CD16+CD56- NK expansion negatively predicts therapy response during HCV-HIV-1 coinfection [24]. Other data from our group indicate that in HCV mono-infection IL28B genotype and race are associated with CD16+56- NK subset **IFN- α R** expression, which in turn is associated with **IFN- α** induced pSTAT1 and viral decline magnitude [25]. The dependence of these factors on each other are yet to be determined, and whether these relationships hold with a larger sample size, or are extended to HCV/HIV-1 coinfection is not known.

Persistent activation of the immune system is well described during progressive HIV-1 infection. This can be quantified by soluble markers including cytokines and sCD14, as well as markers of T, B, NK, and myeloid cell activation [26-28]. Because immune activation may be predictive of HIV-1 disease progression [29], it has been proposed that immune activation directly contributes to disease pathogenesis [27]. HCV infection is also associated with elevated levels of sCD14 and activated CD8+ T cells [30-32], and these markers likewise correlate with HCV and HIV-1 disease progression in the context of HCV mono-infection or HCV/HIV-1 coinfection [30, 31]. Downstream effects of immune activation include increased T cell turnover, accumulation of effector T cells within lymph nodes, and increased availability of targets for HIV-1 infection [27]. Effects such as these may directly contribute to impaired host control of HIV-1 and other pathogens within the infected host [33]. Whether immune activation plays a role in predicting outcome of HCV therapy has been unclear. Our data from NWCS322 suggest monocyte activation as reflected by plasma sCD14 level, and perhaps T cell immune activation, predict IFN therapy response [24]. Recent data published by another group is supportive of the same concept [34]. Additionally, in our data set sCD14 level correlated with baseline HCV level and CD16+CD56- NK cell frequency, and greater frequencies of CD16+CD56- NK cells at baseline correlated with lower rate of HCV decline during PegIFN/RBV therapy [24]. Again, the dependence of these variables upon each other is not known. However, it appears that a number of parameters of innate immune activation are associated with each other, and also with therapy outcome. One possibility is that in vivo IFN conditioning attributable to host response to chronic HCV infection contributes to these observations. Specifically, IFN may, in combination with HCV itself, directly activate monocytes (resulting in sCD14 release) and activate NK cells (resulting in NK subset skewing, IFN resistance, yet preservation of IFN signaling in the appropriately conditioned NK cells with the favorable IL28B genotype).

Whether these factors predict IFN free therapy response, relapse, or resistance is not known. Furthermore, the interaction between the innate and adaptive immune systems during HCV immune restoration has not been clarified. The presence of HIV-1 coinfection is further likely to modulate this interaction. The present study offers a unique opportunity to begin to explore these issues.

Rationale for formulating the primary outcome of SVR₁₂ based solely upon LLOQ of the assay

The assays for HCV RNA can yield false positives below the linear range of the assay (ie, <LLOQ). In a recent retrospective analysis by FDA of the **BOC** and **TVR** phase III trials [35], it was observed that in the post treatment setting a result of target detected but <LLOQ was generally a false positive whereas during HCV antiviral therapy, the same result was typically a true positive. Because the probability that a person would be truly HCV-infected at post-treatment week 12 and have viremia <LLOQ is very low, the SVR₁₂ outcome for A5329 will be based upon being <LLOQ to define 'response' without regards to whether target is detected or not (TD versus TND). This follows the recommended terminology and definition recently published by FDA and the Forum for Collaborative HIV Research [36]. Moreover, this formulation of the primary outcome parallels the definition being used in the other planned and on-going studies of this HCV DAA regimen. Outcomes using HCV RNA, particularly those during the HCV treatment period, will separately describe those unquantifiable (U using the nomenclature proposed by the Forum [37]), as TND (target not detected) versus TD (target detected). More details about this are in section 9.0 (Statistical Considerations), and the study's Statistical Analysis plan.

Rationale for PK substudy A5334s of RAL and DRV/r before and during combined administration with the HCV DAA+/-RBV regimen

A5334s is an open-label, two-arm, intensive PK substudy of DDIs in **participants** enrolling in A5329. Based on the DDIs observed in healthy volunteers described above, substudy A5334s will test the hypothesis that HCV/HIV-1 coinfecting **participants** will have lower exposure to DRV and similar exposure to RAL during coadministration with **PTV/r/OBT**, and **DSV**. A5334s will provide important data on possible PK changes that may occur in **participants** with HCV/HIV-1 coinfection who are being treated for both infections. Potential **participants** for substudy A5334s will be in screening for A5329 with no known eligibility violations and plans to enroll in A5329 within the next 7 calendar days following enrollment in substudy A5334s. **Participants** enrolled in substudy A5334s will not be permitted to enroll in the Liver Biopsy Substudy A5335s described below.

Overall, substudy A5334s will enroll 12 **participants** each in ART #1 and #2 (total of 24 **participants**) which is expected to yield 10 **participants** per ARV regimen with complete PK data at each of the intensive PK substudy visits. The first PK visit will occur 1 to 7 days prior to initiating **PTV/r/OBT**, **DSV**, and RBV, **participants** will complete a 12-hour intensive PK study to characterize **participant**-specific ARV disposition in the absence of HCV DAA+/-RBV therapy. Four weeks after starting **PTV/r/OBT**, **DSV**, and RBV, 12-hour intensive PK sampling will be repeated, to characterize the disposition of both ARVs and HCV drugs when they are coadministered.

After the second intensive PK evaluation at approximately week 4 on study A5329, participation in substudy A5334s will be complete.

Additional details may be found in substudy protocol A5334s entitled: "Pharmacokinetic Studies of **RAL** and **DRV/r** before and During Combined Administration with **PTV/r/OBT**, **DSV** and RBV in **HCV/HIV-1** Coinfecting **Participants**: A Substudy of A5329".

Rationale for liver biopsy substudy A5335s to assess intrahepatic HCV dynamics and pharmacology

The HCV kinetic responses to antivirals are indicative of distinct mechanisms of viral control: First phase decline of HCV RNA is thought to be due to impaired release of virions by infected hepatocytes, while second phase decline is associated with clearance of infected hepatocytes. Eradication of HCV from the liver during treatment with HCV DAA+/-RBV therapy depends on: i) the suppression of new hepatocyte infections; ii) the clearance of HCV-infected hepatocytes; iii) Intrahepatic HCV drug concentrations. To date, the most common route for failure to achieve SVR following treatment with HCV DAA+/-RBV therapy has been HCV viral relapse, indicating the failure of HCV therapy to clear HCV-infected hepatocytes; however, the mechanism of such treatment failure is unknown. The substudy will provide first estimates of hepatic clearance of HCV-infected hepatocytes in an **IFN**-free regimen during HCV/HIV-1 coinfection and of intrahepatic drug concentration in **participants** on an **IFN**-free regimen.

Substudy A5335s is an open label, intensive tissue and serum/plasma viral kinetics (VK) and PK study in **participants** enrolled in A5329. Potential **participants** for substudy A5335s will be in screening for A5329 with no known eligibility violations and will not be permitted to enroll in the PK substudy A5334s (described above). Twelve (12) **participants** will be enrolled in substudy A5335s and will undergo liver biopsy #1 before administration of HCV DAA+/-RBV therapy (day 1) for single cell laser capture microdissection (scLCM) and histologic staging. HCV DAA+/-RBV therapy will be administered following liver biopsy intensive HCV VK assessments. On Day 8, **participants** will undergo liver biopsy #2 for scLCM and measurement of HCV DAA drug concentrations. After the evaluations, including second liver biopsy at approximately week 1 on A5329, participation in substudy A5335s will be complete.

Using scLCM of 400-500 hepatocytes per liver biopsy, intrahepatic HCV RNA will be quantified in single hepatocytes along with the expression of **IFN** stimulated genes (ISGs) and intra-hepatic DAA drug concentrations. The primary objective of substudy A5335s is to estimate the 1-week change in intrahepatic HCV infection on DAA+/-RBV using scLCM.

Additional details may be found in the substudy protocol A5335s entitled: "Coinfected **Participants** Treated with HCV Direct-Acting Antivirals Plus Ribavirin: Intrahepatic HCV Dynamics and Pharmacology: A Substudy of A5329."

3.0 STUDY DESIGN

Non-randomized, open-label, study of IFN-free HCV therapy in sequentially enrolled cohorts receiving HCV therapy for 12 or 24 weeks, respectively, in **participants** with HIV-1 coinfection on qualifying ART regimens.

By having the longer treatment-period (24 week) cohorts enroll first, and then subsequently enrolling the shorter treatment-period (12 week) cohorts, follow-up among these groups is anticipated to facilitate a more uniform timing of closure to follow-up to allow the study to proceed to the final analysis phase in an expedient

manner. Each cohort will be analyzed separately. See section 9.0 for more details on analysis.

DAA+/-RBV therapy will include a **RTV** boosted NS3/4A **PI**, **PTV/r**; an NS5A inhibitor, **OBT**; an NS5B non-nucleoside polymerase inhibitor, **DSV**; **with or without** weight-based RBV. The study will consist of two study cohorts per ART regimen (n=25 per cohort). Each cohort will occur in two steps: on-HCV treatment (Step 1) and post-HCV treatment **follow-up** (Step 2).

4.0 SELECTION AND ENROLLMENT OF **PARTICIPANTS**

4.1 Step 1 Inclusion Criteria

4.1.1 Men and women age ≥ 18 to ≤ 70 years at study entry.

4.1.2 Body mass index (BMI) from ≥ 18 to < 38 kg/m² within 42 days of study entry. BMI is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).

4.1.3 HIV-1 infection, documented by any licensed rapid HIV-1 test or HIV-1 enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV-1 and/or E/CIA, or by HIV-1 antigen, or plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a US FDA-approved kit.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test must be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (eg, indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.4 CD4+ cell count ≥ 200 cells/uL and CD4+ cell percentage $\geq 14\%$ within 42 days of study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification.

4.1.5 On a stable, qualifying ART regimen for at least 8 weeks prior to entry.

NOTE: Qualifying ART regimens are detailed in section 5.4.1.

NOTE: Changes in DRV dosing from QD to BID are permitted within the 8 week window. For **participants** on DRV/r, the dose of DRV/r must be 600/100 PO BID for at least 2 weeks prior to study entry.

- 4.1.6 HIV-1 RNA <50 copies/mL for at least 6 months prior to study entry by any US laboratory that has a CLIA certification or its equivalent. HIV-1 RNA testing must have been performed at least once during the 6 months prior to study entry.

NOTE: Single detectable HIV-1 viral loads at ≥ 50 copies/mL are not exclusionary if followed by an HIV-1 viral load <50 copies/mL.

NOTE: For **participants** on DRV/r, HIV-1 virologic suppression as detailed in 4.1.6 must have been attained while the **participant** was taking a dose of 800/100 mg PO QD.

- 4.1.7 Presence of chronic HCV infection, defined as:

Positive for anti-HCV antibody or HCV RNA at least 6 months before screening, and positive for HCV RNA at the time of screening.

OR

Positive for HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection any time prior to study entry.

- 4.1.8 HCV treatment-naïve **or unsuccessful treatment with pegylated or standard IFN alfa with or without RBV.**

NOTE: No prior exposure to HCV NS3/4A PI (including but not limited to **TVR**, **BOC**, simeprevir), NS5A inhibitors (including but not limited to daclatasvir or ledipasvir), NS5B NNI or NI inhibitors (including but not limited to sofosbuvir) is allowed.

- 4.1.9 HCV genotype 1a or 1b infection **confirmed by testing at the A5329 VSL Quest Diagnostics. Please refer to the laboratory processing chart (LPC) on the A5329 protocol-specific web page (PSWP).**

- 4.1.10 Serum HCV RNA >10,000 IU/mL obtained within 42 days prior to study entry by any assay performed **by the designated A5329 VSL Quest Diagnostics.**

- 4.1.11 The following laboratory values obtained within 42 days prior to study entry.

- Absolute neutrophil count (ANC) $\geq 750/\text{mm}^3$
- Hemoglobin ≥ 12 g/dL for men and ≥ 11 g/dL for women
- Platelet count $\geq 90,000/\text{mm}^3$
- International normalized ratio (INR) ≤ 1.5
- **Participants** with known inherited bleeding disorder and INR ≥ 1.5 may be enrolled
- Calculated creatinine clearance (CrCl) using Cockcroft-Gault method ≥ 60 mL/min
- ALT ≤ 7 x upper limit of the normal range (ULN)
- Aspartate aminotransferase (AST) ≤ 7 x ULN range

- Total bilirubin **<3 mg/dL for participants not on ATV and <6 mg/dL for participants on ATV**
- Direct bilirubin $\leq 1.5 \times \text{ULN}$
- Albumin $\geq 3.5 \text{ g/dL}$
- Serum alfa-fetoprotein (AFP) $\leq 100 \text{ ng/mL}$

4.1.12 Classification of liver disease as cirrhotic or non-cirrhotic prior to study entry according to criteria in section 6.4.3.

4.1.13 **Participants** classified as cirrhotic must have no evidence of hepatocellular carcinoma (HCC) as indicated by a negative ultrasound (U/S), computed tomography (CT) scan or magnetic resonance imaging (MRI) within 6 months prior to study entry.

NOTE: **Participants** who have an U/S with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

4.1.14 **Females** of reproductive potential (defined as women who have not been post-menopausal for at least 24 consecutive months, ie, who have had menses within 24 months prior to study entry, or women who have not undergone surgical sterilization, specifically hysterectomy, tubal ligation, and/or bilateral oophorectomy) must have a negative serum or urine pregnancy test with a sensitivity of $\leq 25 \text{ mIU/mL}$ within 42 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent.

4.1.15 All **participants** must agree not to participate in a conception process (eg, active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization).

4.1.16 If participating in sexual activity that could lead to pregnancy, the **participant** (men and women) **with HCV genotype 1a infection who will receive RBV must** agree to use two reliable methods of contraception simultaneously while receiving study treatment and for 6 months after stopping study treatment **and participants (men and women) with HCV genotype 1b infection who will not receive RBV must agree to use two reliable methods of contraception simultaneously while receiving study treatment and for 30 days after stopping study treatment.**

A combination of TWO of the following contraceptives **MUST** be used appropriately:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- IUD (intrauterine device)

NOTE: Hormone-based contraceptives are **NOT** considered an acceptable form of contraception.

4.1.17 **Participants** who are not of reproductive potential (women who have been post-menopausal for at least 24 consecutive months or have undergone hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy or men who have documented

azoospermia) are eligible without requiring the use of contraceptives. Acceptable documentation of sterilization and menopause is specified below.

Written or oral documentation communicated by clinician or clinician's staff of one of the following:

- Physician report/letter
- Operative report or other source documentation in the **participant** record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary
- Laboratory report of azoospermia
- Follicle stimulating hormone-release factor (FSH) measurement elevated into the menopausal range as established by the reporting laboratory.

4.1.18 Ability and willingness of **participant** to provide written informed consent.

4.2 Step 1 Exclusion Criteria

4.2.1 Breastfeeding.

4.2.2 Pregnant sexual partner **for male participants with HCV genotype 1a infection who will receive RBV. This criterion does not apply to male participants with HCV genotype 1b infection who will not receive RBV.**

4.2.3 Known allergy/sensitivity or any hypersensitivity to components of study drugs or their formulation.

4.2.4 Acute or serious illness requiring systemic treatment and/or hospitalization within 42 days prior to study entry.

4.2.5 Active hepatitis B infection (positive HBsAg) within 42 days prior to study entry.

4.2.6 History of decompensated liver disease (including but not limited to encephalopathy, variceal bleeding, or ascites) prior to study entry.

4.2.7 Any cause of liver disease other than chronic HCV infection, including but not limited to the following:

- Hemochromatosis
- Alpha-1 antitrypsin deficiency
- Wilson's disease
- Autoimmune hepatitis
- Alcoholic liver disease
- Drug-related liver disease

NOTE: Steatosis and steatohepatitis on a liver biopsy coincident with HCV-related changes would not be considered exclusionary unless the steatohepatitis is considered to be the primary cause of the liver disease.

- 4.2.8 Uncontrolled or active depression or other psychiatric disorder within 24 weeks prior to study entry that in the opinion of the site investigator might preclude adherence to study requirements.
- 4.2.9 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
- 4.2.10 Serious illness including uncontrolled seizure disorders, active coronary artery disease within 24 weeks prior to study entry, or other chronic medical conditions that in the opinion of the site investigator might preclude completion of the protocol.
- 4.2.11 Presence of active or acute AIDS-defining opportunistic infections within 12 weeks prior to study entry.

NOTE: A list of AIDS-defining opportunistic infections as defined by the CDC can be found in Appendix I.

- 4.2.12 Active or history of malignancy within 5 years prior to study entry other than basal cell carcinoma of the skin and/or cutaneous Kaposi's sarcoma (KS) and/or cervical or anal dysplasia or carcinoma in situ.
- 4.2.13 Clinically significant abnormal EKG, or EKG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) >450 msec within 42 days of study entry.

For Fridericia's correction, refer to the calculator located on the FSTRF website at www.fstrf.org.

- 4.2.14 Use of colony stimulating factors, such as granulocyte colony stimulating factor (GCSF) or erythropoietin within 42 days of study entry.
- 4.2.15 Infection with any HCV genotype other than genotype 1, or mixed genotype infection any time prior to study entry.
- 4.2.16 History of major organ transplantation with an existing functional graft any time prior to study entry.
- 4.2.17 History of hemoglobinopathy (eg, thalassemia) or any other cause of or tendency to hemolysis any time prior to study entry.
- 4.2.18 Child-Pugh score of >6 at screening (cirrhotic **participants** only).

NOTE: To calculate the Child-Pugh score, refer to the following website:
<http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality>

4.3 Step 2 Inclusion Criteria

- 4.3.1 Completion or premature discontinuation (including HCV VF) of Step 1 study treatment (ie, HCV) regimen.

NOTE: See section 8.1 for premature treatment discontinuation.

4.4 Step 2 Exclusion Criteria

- 4.4.1 Premature study discontinuation.

NOTE: See section 8.2 for premature study discontinuation.

4.5 Study Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory 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 must be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites must implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site specific ICFs and indicates successful completion of the amendment protocol registration process. A copy of the final amendment Registration Notification issued by the DAIDS PRO must 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.

Once a candidate for study entry has been identified, details will be carefully discussed with the **participant**. The **participant** will be asked to read and sign the approved protocol consent form.

For **participants** from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) **Participant** Enrollment System.

4.5.1 **Participant** Registration

At the study entry visit, **participants** will be enrolled according to standard ACTG data management procedures.

For **participants** from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.6 Coenrollment Guidelines

- Sites are encouraged to coenroll **participants** in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Coenrollment in A5128 does not require permission from the A5329 protocol chairs.
- **Participants** enrolled in A5329 may coenroll in only one of the two substudies, A5335s or A5334s. Coenrollment into both substudies is not permitted.
- For specific questions and approval for coenrollment in other studies, sites must contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

A5329 study drugs consist of **PTV/r/OBT plus DSV with or without weight-based RBV. Participants with HCV genotype 1a infection will take weight-based RBV plus PTV/r/OBT plus DSV. Participants with HCV genotype 1b infection will take PTV/r/OBT plus DSV only.**

All **participants** will receive the same dose of **PTV/r/OBT** and **DSV**. **For participants with HCV genotype 1a infection, the RBV dose will be based on the participant’s body weight at entry.** Changes in weight after study entry do not require a change in RBV dose. After study entry, changes in RBV dose will be only for toxicity management.

No changes in dose are permitted for **PTV/r/OBT** or **DSV**.

5.1 Regimens, Administration, and Duration

ACTG A5329 Version 2.0 revises the study treatment regimens to add the alternative of DTG for Cohorts A and B, add the alternative of ATV for Cohorts C and D, and eliminate RBV for all cohorts for participants with HCV genotype 1b.

Administration Instructions for All Cohorts

- **Participants** (with a negative pregnancy test, if applicable) will be administered the first dose of study drugs by the study site personnel and receive instructions for self-administration of all study drugs through the end of the Treatment Period depending on the duration of their assigned treatment cohort as detailed above. DAA+/-RBV therapy must be started within 72 hours of study entry.
 - **Participants** will be instructed to take study medication at the same time(s) every day.
 - All study drugs should be taken with approximately 240 mL of water within ½ hour after eating food.
 - All tablets of the study drug regimen are to be taken at the same time (within minutes of the other tablets).
 - Separate the morning and evening doses by 12 hours.
 - If on DRV **or** ATV regimens (Cohorts C and D), the morning dose of DRV **or** ATV is to be taken with the morning dose of the study drug regimen.
- 5.1.1 Cohort A (currently on the qualifying RAL **or** DTG regimen) (24-week duration).
- **PTV/r/OBT** 75 mg/50 mg/12.5 mg tablets x 2 tablets for a total dose of 150 mg **PTV/100 mg RTV/25 mg OBT** orally (PO) every morning with food.
 - **DSV** 250 mg 1 tablet PO every 12 hours with food.
 - **For participants with HCV genotype 1a only, RBV will be dosed as follows:**
 - **Participants** weighing >75 kg: RBV 600 mg PO every 12 hours with food for a total daily dose of 1200mg.
 - **Participants** weighing ≤75 kg: **RBV PO every 12 hours with food in divided doses of 400 mg and 600 mg for a total daily dose of 1000 mg.**
- 5.1.2 Cohort B (currently on the qualifying RAL **or** DTG regimen) (12-week duration).
- **PTV/r/OBT** 75 mg/50 mg/12.5 mg tablets x 2 tablets for a total dose of 150 mg **PTV/100 mg RTV/25 mg OBT** PO every morning with food.
 - **DSV** 250 mg 1 tablet PO every 12 hours with food.
 - **For participants with HCV genotype 1a only, RBV will be dosed as follows:**
 - **Participants** weighing >75 kg: RBV 600 mg PO every 12 hours with food (1200 mg per day).
 - **Participants** weighing ≤75 kg: RBV 400 mg PO every morning with food and 600 mg PO every evening with food (1000 mg per day).
- 5.1.3 Cohort C (currently on the qualifying DRV BID **or** ATV regimen) (24-week duration).
- **PTV/r/OBT** 75 mg/50 mg/12.5 mg tablets x 2 tablets for a total dose of 150 mg **PTV/100 mg RTV/25 mg OBT** PO every morning with food.
 - **DSV** 250 mg 1 tablet PO every 12 hours with food.
 - **For participants with HCV genotype 1a only, RBV will be dosed as follows:**
 - **Participants** weighing >75 kg: RBV 600 mg PO every 12 hours with food (1200 mg per day).
 - **Participants** weighing ≤75 kg: RBV 400 mg PO every morning with food and 600 mg PO every evening with food (1000 mg per day).

- The morning dose of DRV **or** ATV is to be taken with the morning dose of the study drug regimen.
- Omit the concomitant (non-study) medication **RTV** 100 mg tablet taken with the morning DRV **or** ATV dose while taking DAA+/-RBV therapy.

5.1.4 Cohort D (currently on the qualifying DRV BID **or** ATV regimen) (12-week duration).

- **PTV/r/OBT** 75 mg/50 mg/12.5 mg tablets x 2 tablets for a total dose of 150 mg **PTV**/100 mg **RTV**/25 mg **OBT** PO every morning with food.
- **DSV** 250 mg 1 tablet PO every 12 hours with food.
- **For participants with HCV genotype 1a only, RBV will be dosed as follows:**
 - **Participants** weighing >75 kg: RBV 600 mg PO every 12 hours with food (1200 mg per day).
 - **Participants** weighing ≤75 kg: RBV 400 mg PO every morning with food and 600 mg PO every evening with food (1000 mg per day).
- The morning dose of DRV **or** ATV is to be taken with the morning dose of the study drug regimen.
- Omit the concomitant (non-study) medication **RTV** 100 mg tablet taken with the morning DRV **or** ATV dose while taking DAA+/-RBV therapy.

5.2 Study Product Formulation and Preparation

Each dose of open-label DAA study drug will be dispensed in the form of tablets (**PTV/r/OBT**, **DSV**, and RBV).

The formulations are as follows:

- **PTV/r/OBT** will be provided as 75 mg/50 mg/12.5 mg tablets. **PTV/r/OBT** will be taken PO as 2 tablets QD in the morning which corresponds to a 150 mg. **PTV**/100 mg **RTV**/25 mg **OBT** dose QD.
- **DSV** will be provided as 250 mg tablets. **DSV** will be taken PO as 1 tablet BID, which corresponds to a 250 mg dose BID.
- RBV will be provided as 200 mg tablets **for participants with HCV genotype 1a only**. RBV has weight-based dosing of 1000 to 1200 mg QD taken as divided doses 600 mg BID or 400 mg QD in the morning/600 mg QD in the evening (BID).

Storage conditions for all medications are from 15° to 25°C (59° to 77°F).

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

DAA+/-RBV therapy will be available through the NIAID Clinical Research Products Management Center (CRPMC). **PTV/r/OBT** and **DSV** are manufactured and provided by AbbVie, Inc. Ribasphere® (ribavirin, RBV) is manufactured by DSM Pharmaceuticals, Inc. for Kadmon Pharmaceuticals, LLC. The site pharmacist must obtain the study product(s) for this protocol by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or –sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at:

<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/NonFDAApprovedProducts.pdf>.

ART will not be provided through the CRPMC.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At US CRSSs, all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, site investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the updated ACTG Drug Interactions Database located at: http://tdm.pharm.buffalo.edu/home/di_search/Search.

5.4.1 Qualifying Antiretroviral Regimens

Participants must currently be on one of the following HIV-1 ART regimens for at least 8 weeks prior to entry.

The N(t)RTIs combinations in the stable, qualifying ART regimen must be **one of the following**:

- TDF **or** TAF PO QD plus FTC PO QD (individual ARV components or as the fixed-dose combination TDF/FTC [Truvada] **or** TAF/FTC [Descovy])
- TDF **or** TAF PO QD plus 3TC PO QD or PO BID (individual ARV components)
- ABC PO QD plus 3TC PO QD (individual ARV components or as the fixed-dose combination ABC/3TC (EPZICOM or when dosed with DTG, TRIUMEQ)

Participants with cirrhosis receiving abacavir should receive ABC 200 mg BID (re: Ziagen Package insert, dosing for hepatic impairment).

Participants will maintain the same dose and dosing interval of their NRTI backbone upon initiating the DAA+/-RBV therapy.

INI ART regimen group: The **INI** in the stable qualifying ART regimen must be **one of the following:**

- RAL 400 mg PO BID
- **DTG 50 mg PO QD alone or as part of a combination tablet or DTG 50 mg PO BID**

RAL or DTG will be maintained at the same dose and dosing interval upon initiating the DAA+/-RBV therapy.

PI regimen group: The **PI** in the stable qualifying ART regimen must be **one of the following:**

- DRV 800mg PO QD coadministered with RTV 100 mg PO QD or **DRV 800 mg/Cobicistat 150 mg PO QD**
- **ATV 300 mg PO QD coadministered with RTV 100 mg PO QD**

More details on PIs:

Participants taking DRV ART (boosted by RTV or Cobicistat) are required to modify their regimen and be on a stable BID **RTV**-boosted BID DRV regimen for at least 2 weeks prior to study entry:

- DRV 600 mg PO BID coadministered with RTV 100 mg PO BID.

In this study, the DAA+/-RBV therapies are **PTV/r/OBT 150/100/25 mg QD + DSV 250 mg BID + weight-based RBV**. The DAA morning dose includes 100 mg of RTV. Hence, **participants** receiving the HIV-1 DRV ART regimen that includes DRV PO BID coadministered with RTV PO BID will stop the morning RTV component of their HIV-1 ART regimen upon initiating the DAA+/-RBV therapy. The AM DRV dose should be coadministered with the **morning** dose of DAA+/-RBV therapy.

In the case of DAA+/-RBV therapy interruption or discontinuation, **participants** on the DRV ART regimen should resume the AM RTV component of their HIV-1 ART regimen (RTV 100 mg BID with DRV 600 mg PO BID).

NOTE: **Participants** on the DRV ART regimen may return to 800 mg/100 mg DRV/r daily dosing once they have been off the HCV DAA regimen for at least 2 weeks.

In this study, the DAA+/-RBV therapies are **PTV/r/OBT 150/100/25 mg QD + DSV 250 mg BID + weight-based RBV**. The DAA morning dose includes 100 mg of RTV. Hence, **participants** receiving the HIV-1 ATV ART regimen that includes ATV coadministered with RTV PO QD will stop the RTV component of their HIV-1 ART regimen upon initiating the DAA+/-RBV therapy. The ATV dose should be coadministered in the morning with the morning dose of DAA+/-RBV therapy.

In the case of DAA+/-RBV therapy interruption or discontinuation, participants on the ATV ART regimen should resume the RTV component of their HIV-1 ART regimen (RTV 100 mg QD with ATV 300 mg PO QD).

5.4.2 Prohibited and Precautionary Medications

Refer to the Prohibited and Precautionary Medication Tables posted on the PSWP.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events (Cohorts A and C)

Evaluation (Cohorts A and C)	Screening	Entry	Step 1: On Treatment (Weeks)								Treatment Completion	Step 2: Post-treatment (weeks)			HCV VF Confirmation	HIV-1 VF Confirmation	Premature Study and /or Treatment Discontinuation Evaluations ¹	
			2	4	6	8	10	12	16	20		24	(R+4)	(R+12)				(R+24)
			Window ± 3 days									Window ± 7 days						
Documentation of HIV-1	X																	
Documentation of Chronic HCV Infection	X																	
Documentation of Cirrhosis Status	X																	
Medical History	X	X																
Medication History	X	X																
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EKG	X							X			X						X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Creatinine Clearance	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Liver Function Tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
INR	X							X			X		X					
Pregnancy Testing	X	X		X		X		X	X	X	X	X	X	X			X	
HBsAg	X																	
CD4+	X	X		X				X			X			X			X	
IFN Gamma-Induced Protein 10 (IP-10) and sCD14 Plasma Samples		X	X	X				X			X	X	X		X		X	

Evaluation (Cohorts A and C)	Screening	Entry	Step 1: On Treatment (Weeks)								Treatment Completion	Step 2: Post-treatment (weeks)			HCV VF Confirmation	HIV-1 VF Confirmation	Premature Study and /or Treatment Discontinuation Evaluations ¹
												R=Registration to Step 2					
			2	4	6	8	10	12	16	20		24	(R+4)	(R+12)			
			Window ± 3 days									Window ± 7 days					
IL28B Genotype		X															
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 Resistance Testing																X	
Serum HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HCV Genotype/Subtype	X																
Serum AFP	X																
Calculated Child-Pugh Score for Cirrhotic Participants	X							X			X		X				X
Radiographic or Liver U/S Tests for Cirrhotic Participants ²	X																
Stored Plasma for HCV and HIV-1 Resistance Testing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Stored Plasma for Analysis of Soluble Markers of Immune Activation/Immunity		X	X	X		X		X	X	X	X	X	X	X	X		X
Stored PBMC for Analysis of Cellular Markers of Immune Activation and Adaptive Immunity (Advanced Flow Cytometry)		X		X				X		X	X		X				X
Stored PBMC for Analysis of Proviral HIV-1 DNA		X															
Single Convenience PK Sample for quantification of ARV and DAA concentrations		X															X

Evaluation (Cohorts A and C)	Screening	Entry	Step 1: On Treatment (Weeks)								Treatment Completion	Step 2: Post-treatment (weeks)			HCV VF Confirmation	HIV-1 VF Confirmation	Premature Study and /or Treatment Discontinuation Evaluations ¹	
			2	4	6	8	10	12	16	20		24	(R+4)	(R+12)				(R+24)
			Window ± 3 days									Window ± 7 days						
Single PK Sample, 2-10 hours post-dose ³ , for quantification of ARV and DAA concentrations			X	X	X	X	X	X							X	X		
Single PK sample for quantification of plasma RBV and RBV-TP from RBCs obtained via dried blood spot (genotype 1a participants only)				X		X									X	X		

¹ All **participants** who discontinue treatment before the scheduled end of treatment must enter the post treatment evaluations as outlined.

² See 6.4.13 below regarding U/S, CT or MRI. Sites should consider imaging study to rule out HCC.

³ See 6.4.16 below regarding time of day to schedule the visit for optimal PK sampling. Timing of dose and sample collection must be recorded.

6.2 Schedule of Events (Cohorts B and D)

Evaluation (Cohorts B and D)	Screening	Entry	Step 1: On Treatment (Weeks)					Treatment Completion	Step 2: Post-treatment (PT) (Weeks)				HCV VF Confirmation	HIV-1 VF Confirmation	Premature Study and /or Treatment Discontinuation Evaluations ¹
			R=Registration to Step 2												
			2	4	6	8	10	12	(R+4)	(R+12)	(R+24)	(R+36)			
Window ± 3 days						Window ± 7 days									
Documentation of HIV-1	X														
Documentation of Chronic HCV Infection	X														
Documentation of Cirrhosis Status	X														
Medical History	X	X													
Medication History	X	X													
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG	X							X							X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Creatinine Clearance	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Liver Function Tests	X	X	X	X	X	X	X	X	X	X	X	X	X		X
INR	X							X		X					
Pregnancy Testing	X	X		X		X		X	X	X	X	X	X		X
HBsAg	X														
CD4+	X	X		X				X			X	X			X

Evaluation (Cohorts B and D)	Screening	Entry	Step 1: On Treatment (Weeks)					Treatment Completion	Step 2: Post-treatment (PT) (Weeks)				HCV VF Confirmation	HIV-1 VF Confirmation	Premature Study and /or Treatment Discontinuation Evaluations ¹
			R=Registration to Step 2												
			2	4	6	8	10	12	(R+4)	(R+12)	(R+24)	(R+36)			
Window ± 3 days								Window ± 7 days							
IFN Gamma-Induced Protein 10 (IP-10) and sCD14 Plasma Samples		X	X	X				X	X	X		X	X		X
IL28B Genotype		X													
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Plasma HIV-1 Genotype Resistance Testing														X	
Serum HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Plasma HCV Genotype/Subtype	X														
Serum AFP	X														
Calculated Child-Pugh Score for Cirrhotic Participants	X							X		X					X
Radiographic or Liver U/S Tests for Cirrhotic Participants ²	X														
Stored Plasma for HCV and HIV-1 Resistance Testing		X	X	X	X	X	X	X	X	X	X	X	X	X	
Stored Plasma for Analysis of Soluble Markers of Immune Activation/Immunity		X	X	X		X		X	X	X	X	X	X		X

Evaluation (Cohorts B and D)	Screening	Entry	Step 1: On Treatment (Weeks)					Treatment Completion	Step 2: Post-treatment (PT) (Weeks) R=Registration to Step 2				HCV VF Confirmation	HIV-1 VF Confirmation	Premature Study and /or Treatment Discontinuation Evaluations ¹	
			2	4	6	8	10		12	(R+4)	(R+12)	(R+24)				(R+36)
			Window ± 3 days						Window ± 7 days							
Stored PBMC for Analysis of Cellular Markers of Immune Activation and Adaptive Immunity (Advanced Flow Cytometry)		X		X				X		X					X	
Stored PBMC for Analysis of Proviral HIV-1 DNA		X														
Single Convenience PK Sample, for quantification of ARV and DAA concentrations		X													X	
Single PK Sample, 2-10 hours post-dose ³ , for quantification of ARV and DAA concentrations			X	X	X	X	X	X					X	X		
Single PK sample for quantification of plasma RBV and RBV-TP from RBCs obtained via dried blood spot (genotype 1a participants only)				X		X							X	X		

¹ All **participants** who discontinue treatment before the scheduled end of treatment must enter the post treatment evaluations as outlined.

² See 6.4.13 below regarding U/S, CT or MRI. Sites should consider imaging study to rule out HCC.

³ See 6.4.16 below regarding time of day to schedule the visit for optimal PK sampling. Timing of dose and sample collection must be recorded.

6.3 Timing of Evaluations

6.3.1 Screening Evaluations

Screening evaluations must occur prior to the **participant** being enrolled to the study or starting any study medications, treatments, or interventions.

Screening evaluations to determine eligibility must be completed within 42 days prior to study entry unless otherwise specified. In addition to data being collected on **participants** who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured on a Screening Failure Results form and entered into the ACTG database.

Screening evaluations that determine eligibility are entered on the eligibility checklist. Beginning at study entry, all evaluations, including screening evaluations that do not determine eligibility are recorded on the case report form (CRF) and keyed into the database.

6.3.2 Entry Evaluations

Study entry evaluations must occur at least 24 hours after screening evaluations unless otherwise specified. Entry evaluations must occur prior to dispensation of study treatment. DAA+/-RBV therapy must be started within 72 hours of study entry.

6.3.3 Post-Entry Evaluations

On-Treatment Evaluations

Evaluations must occur after registration and after study treatment is dispensed. Study visits must be scheduled on the weeks indicated in sections 6.1 and 6.2, within the ± 3 day visit window, as appropriate for the visit.

Treatment Completion Evaluations

Clinical assessment and laboratory evaluation, as outlined in sections 6.1 and 6.2, will be performed at treatment completion.

Post-Treatment Evaluations

Following treatment completion, **participants** will immediately enter Step 2 and undergo evaluations as outlined in sections 6.1 and 6.2, within the ± 7 day visit window, as appropriate for the visit.

6.3.4 Study Completion Evaluations

Final study visit occurs at week R+24 (**Cohorts A and C**) or week R+36 (**Cohorts B and D**), where R=registration to Step 2.

6.3.5 Event-Driven Evaluations

HCV VF Confirmation

HCV VF, as defined in section 7.3.1, must **have a confirmatory specimen drawn within one week after the results of the initial sample have been received for participants** with suspected HCV VF using criteria for HCV VF in section 7.3.1. HCV VF stemming from the criterion of HCV RNA \geq LLOQ at week 6 does not require confirmation.

HIV-1 VF Confirmation

HIV-1 VF, as defined in section 7.3.2, must be confirmed in all **participants** within 2 weeks after results have been received. **Participants** with confirmed HIV-1 RNA \geq 200 copies/mL will have a corresponding stored sample submitted for HIV-1 resistance genotyping.

6.3.6 Discontinuation Evaluations

Evaluations for Registered Participants Who Do Not Start Study Treatment

All case report forms (CRFs) must be completed and keyed for the period up to and including week 0.

Premature Treatment Discontinuation Evaluations

Participants who discontinue study treatment for any reason will have the premature treatment discontinuation evaluations performed as per the SOE.

At the time of premature discontinuation evaluations, these **participants** will then enter the post-treatment evaluation period (Step 2) and will be followed as per the SOE.

Premature Study Discontinuation Evaluations

Participants who prematurely discontinue from the study will have the premature study discontinuation evaluations performed as per the SOE prior to being taken off the study.

6.4 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document:
<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf>

All non-screening evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified.

A subset of AEs recorded on the CRF requires more detailed reporting on the CRF. The reporting requirements of these events are detailed in sections 6.4.6 and 6.4.8.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.4.1 Documentation of HIV-1

Section 4.1.3 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.4.2 Documentation of Chronic HCV Infection

Positive for anti-HCV antibody or HCV RNA at least 6 months before screening, and positive for HCV RNA at the time of screening

OR

Positive for HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection any time prior to study entry.

6.4.3 Documentation of Cirrhosis Status

Participants will be considered to be non-cirrhotic if the absence of cirrhosis is documented by one of the following criteria:

- Liver biopsy within 24 months prior to study entry demonstrating the absence of cirrhosis; or
- HCV FibroSURE score of <0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) <2 within 6 months of study entry; or
- FibroScan result of <12.5 kPa within 6 months of study entry.

The APRI can be calculated with the following formula:

$$\text{AST (IU/L)} / \text{AST upper limit of normal} \div \text{platelet count (x10}^9\text{/L)} \times 100.$$

An online calculator is available at: <http://hepatitisc.uw.edu/page/clinical-calculators/apri>

Participants will be considered to have cirrhosis if it is documented by one of the following criteria:

- Liver biopsy at any time prior to study entry demonstrating cirrhosis; or
- HCV FibroSURE score of ≥ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≥ 2 within 6 months of study entry; or
- FibroScan result of ≥ 12.5 kPa within 6 months of study entry.

Participants with indeterminate blood tests (ie, discordant FibroSURE and APRI values) are required to have **results of** either a liver biopsy or FibroScan test to assess for cirrhosis.

Interpretation of Serum Markers from tests within 6 months prior to study entry for Liver Disease Classifications		
HCV FibroSURE	APRI	Classification
<0.72	<2	Non cirrhotic
≥0.72	≥2	Cirrhotic
<0.72	≥2	An additional test required to establish the liver disease classification as presence or absence of cirrhosis. This test may be either Transient Elastography (FibroScan) or Histology (liver biopsy). The liver disease will be classified according the result of the additional test
≥0.72	<2	An additional test required to establish the liver disease classification as presence or absence of cirrhosis. This test may be either Transient Elastography (FibroScan) or Histology (liver biopsy). The liver disease will be classified according the result of the additional test
Unable to report result	Any	An additional test required to establish the liver disease classification as presence or absence of cirrhosis. This test may be either Transient Elastography (FibroScan) or Histology (liver biopsy). The liver disease will be classified according the result of the additional test

Interpretation of Transient Elastography for Liver Disease Classifications	
Liver Stiffness (kPa) from testing within 6 months prior to study entry	Classification
<12.5	Non-cirrhotic
≥12.5	Cirrhotic

If data from more than one classification methodology are available, classification will be determined according to the histology or transient elastography results. If both histology and transient elastography are available, classification will be determined according to the histology result.

HCV FibroSURE/ APRI	Histology (Liver Biopsy within 2 years prior to study entry)	Transient Elastography (FibroScan) within 6 months prior to study entry	Classification
Any	Non cirrhotic	Not available	Non cirrhotic
Any	Cirrhotic (any time)	Not available	Cirrhotic
Any	Not available	<12.5	Non cirrhotic

HCV FibroSURE/ APRI	Histology (Liver Biopsy within 2 years prior to study entry)	Transient Elastography (FibroScan) within 6 months prior to study entry	Classification
Any	Not available	≥ 12.5	Cirrhotic
Any	Non cirrhotic	Any	Non cirrhotic
Any	Cirrhotic (any time)	Any	Cirrhotic

NOTE: **Participants** with a FibroSURE that is not reported as a numerical value (eg, “unable to be reported”) must **have** undergone either transient elastography or liver biopsy **prior to study entry** for liver disease stage classification.

6.4.4 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses. All diagnosis within the past 30 days and history of any of the following will be recorded:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis (**TB**)
- Chronic **HCV**

Any allergies to any medications and their formulations must also be documented.

6.4.5 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Medication Category	Complete History or Timeframe	Record on the CRF?
ART	Within 90 days before study entry	Yes
Prior ART failure with HIV-1 genotype/resistance profile (if available)	Complete history	Yes
HCV treatment	Complete history	Yes
Prescription drugs for treatment of opportunistic infections	Within 42 days before study entry	Yes
Prescription drugs for prophylaxis of opportunistic infections	Within 42 days before study entry	Yes
Prescription drugs (other)	Within 42 days before study entry	Yes
Non-prescription drugs	Within 42 days before study entry	Yes

6.4.6 Clinical Assessments

Complete Physical Exam

A complete physical examination must be performed at screening and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include vital signs (temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam

A targeted physical examination must be performed at study entry and all subsequent visits and is to include vital signs (temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the **participant** has experienced since the previous visit.

Height

Height (recorded in centimeters) will be measured at screening.

Weight

Weight (recorded in kilograms) will be measured at screening and all subsequent visits.

Signs and Symptoms

At study entry, all signs and symptoms regardless of grade, that occurred within 42 days before study entry must be recorded; post-entry, only signs and symptoms Grade ≥ 2 must be recorded. Record all signs and symptoms that led to a change in treatment, regardless of grade.

The signs and symptoms which lead to premature or permanent discontinuation of either HCV study treatment or HIV ARV treatment, or which met EAE or ICH SAE guidelines will require more detailed event reporting on the CRF.

NOTE: Any grade sign and symptom that led to a permanent discontinuation of HIV or HCV treatment is reported on the Event Report form. All Grade ≥ 2 sign and symptom are also reported on the Signs and Symptoms form.

Diagnoses

Any diagnoses that lead to either HIV or HCV treatment discontinuation **or meet EAE or ICH SAE guidelines will require more detailed reporting on the CRF.**

Concomitant Medications

Record all current prescription medications (with start and stop dates).

ARV Medications

Record all modifications to ARV medications including initial doses, **participant**-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation.

Study Treatment (Intervention) Modifications

Record all study drug modifications, including initial doses, **participant**-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than one day at each visit. Record any permanent discontinuation of treatment.

Detailed Adverse Event Reporting

After entry, more detailed reporting is required for the following: All Grade ≥ 3 ALT elevations, any event leading to premature HCV treatment discontinuation or HIV ARV discontinuation, and those events that meet EAE or International Conference on Harmonisation (ICH) reporting requirements.

6.4.7 EKG

An EKG will be performed at screening, week 12, week 24 (**Cohorts A and C only**), and at any premature study treatment discontinuation visits.

6.4.8 Laboratory Evaluations

All required laboratory values must be recorded, regardless of grade. ALT values Grade ≥ 3 , lab values that prompt premature HCV treatment or HIV-1 ARV discontinuation, or that meet EAE or ICH SAE guidelines will require more detailed event reporting on the CRF.

Chemistry

Sodium, potassium, chloride, bicarbonate/CO₂, blood urea nitrogen (BUN), creatinine, glucose, albumin, **and** uric acid.

Creatinine Clearance (CrCl)

CrCl will be calculated throughout the study using Cockcroft-Gault method. Refer to the Cockcroft-Gault calculator located on the FSTRF website at www.fstrf.org.

Hematology

Hemoglobin, hematocrit, white blood cell count (WBC), ANC, and platelets.

Liver Function Tests

Total bilirubin, indirect bilirubin, direct bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase.

International Normalized Ratio (INR)

This will be performed at a local laboratory.

Pregnancy Testing

Serum or urine β -HCG (urine test must have a sensitivity of ≤ 25 mIU/mL).

A second negative serum or urine pregnancy test result is required within 24 hours prior to starting study treatment.

Hepatitis B Surface Antigen (HBsAg)

HBsAg test must be done within 42 days prior to study entry.

6.4.9 Immunologic Studies

CD4+

Obtain absolute CD4+ cell count and percent within 42 days prior to study entry from a laboratory that possesses a CLIA certification or equivalent.

During the study, all laboratories must possess a CLIA certification or equivalent and must be certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

Advanced Flow Cytometry

Advanced flow analysis requires a CD4+ and WBC with differential from a sample obtained at the same time.

Peripheral blood NK cell subset (CD16+CD56-, CD16+CD56+, CD16-CD56+, CD56hi and dim) frequency and expression of **IFN- α R**, NKP30, and NKG2a will be measured by flow cytometry. Proportions of CD4+ and CD8+ T cells that express HLA DR, CD38, and PD1 will also be measured by flow cytometry. Proportions of live gated cells that are CD14+CD16+, CD14+CD16-, and CD16+CD14lo monocytes will be quantified by flow cytometry. Plasma sCD14 will be measured by ELISA.

IFN Gamma-Induced Protein 10 (IP-10)

Plasma IP-10 samples will be obtained at baseline, on treatment, and during post treatment follow up as indicated in the SOE.

Interleukin 28B (IL28) Genotype

Whole blood will be collected and shipped according to the A5329 LPC.

NOTE: IL28B will not be collected on **participants** with a documented baseline IL28B genotype result.

6.4.10 Virologic Studies**Plasma HIV-1 RNA**

Screening HIV-1 RNA must be performed within 42 days prior to study entry by a laboratory that possesses a CLIA certification or equivalent. Eligibility will be determined based on the screening value.

After the screening visit, HIV-1 RNA quantification assay will be performed in real-time at the protocol designated centralized laboratory. For study entry and post-entry evaluations, the laboratory must be certified by the DAIDS Virology Quality Assurance (VQA) Program. See the LPC for processing, shipping, and storage information.

Plasma HIV-1 Genotype Resistance Testing

If there is a confirmed HIV-1 VF (HIV-1 VL ≥ 200 copies) in a **participant** while taking HCV treatment (or within 4 weeks after permanent discontinuation), a plasma specimen must be obtained at the time of the confirmation sample and, if HIV-1 VF is confirmed with an HIV-1 VL ≥ 200 , the sample must be sent to the designated A5329 VSL for evidence of drug resistance.

Serum HCV RNA

HCV RNA samples on study will be processed and shipped to the designated A5329 VSL **Quest Diagnostics** for real-time quantitative HCV RNA analysis. **Please refer to the LPC.**

Screening HCV RNA must be performed within 42 days prior to study entry and will also be processed and shipped to the designated A5329 VSL Quest Diagnostics for real-time quantitative HCV RNA analysis. Please refer to the LPC.

Plasma HCV Genotype/Subtype

At screening, the HCV genotype/subtype result must be **confirmed by testing at the A5329 VSL Quest Diagnostics. Please refer to the LPC.**

6.4.11 Serum Alpha-Fetoprotein (AFP)

Serum AFP will be determined in all **participants** at screening.

6.4.12 Calculated Child-Pugh Pugh Score

Calculated Child-Pugh Score is needed only for those **participants** classified as cirrhotic at study entry.

To calculate the Child-Pugh score, refer to the following website:
<http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality>

6.4.13 Radiographic or Liver Ultrasound (U/S) Tests for Cirrhotic Participants

Participants classified as cirrhotic must have no evidence of HCC as indicated by a negative U/S, CT scan or MRI within 6 months prior to study entry.

Liver U/S for cirrhotic **participants** is needed only if imaging results (U/S, CT, or MRI) are not available within 6 months prior to study entry.

NOTE: **Participants** who have an U/S with results suspicious of HCC followed by a subsequent negative CT or MRI of the liver will be eligible for the study.

6.4.14 Stored Plasma

Stored Plasma for HCV and HIV-1 Resistance Testing

Plasma will be stored at the indicated visits for future HCV and/or HIV-1 sequencing to assess for resistance mutations. Samples will be shipped and stored according to the A5329 LPC.

Stored Plasma for Analysis of Soluble Markers of Immune Activation/Immunity

Stored plasma will be collected at the indicated visits for future studies and shipped according to the A5329 LPC.

6.4.15 Stored PBMCs

Stored PBMC for Analysis of Cellular Markers of Immune Activation and Adaptive Immunity (Advanced Flow Cytometry)

Stored PBMC will be collected at the indicated visits for future studies and shipped according to the A5329 LPC.

Stored PBMC for Analysis of Proviral HIV-1 DNA

Stored PBMC will be collected at the indicated visit for future studies and shipped according to the A5329 LPC.

6.4.16 PK Studies

For **participants** enrolled in the PK substudy A5334s, the A5329 PK sample for **measurement of HIV-1 ARVs and/or HCV DAAs** need not be drawn if the A5334s intensive samples are being collected the same day.

Participants who enroll in A5334s will be given supplemental instructions to take all medications on either a q12h or a q24h schedule to allow for accurate PK studies to be completed in the sub-study.

The prior three doses of all DAAs, RBV (**genotype 1a only**), and ARVs will be collected on the CRFs.

If any of the prior three doses are missed the PK sample collection should be rescheduled and obtained after the prior three doses are taken as scheduled.

Single convenience PK sample for quantification of ARV and DAA concentrations
Single convenience PK samples will be drawn at study entry and at the time of premature study and/or treatment discontinuation. A convenience sample is one that is obtained at no particular post-dose time. The exact time of the prior dose and the exact time of the blood sample should be recorded on the CRF.

Single PK sample, 2-10 hours post-dose for quantification of ARV and DAA concentrations

Single scheduled PK samples for ARVs and DAAs plasma drug quantification will be collected at the study weeks indicated in the Schedule of Events.

At weeks 2, 6 and 12, the visit should be scheduled such that the PK sample can be collected 2-4 hours after morning doses of the BID drugs. At week 8, the visit should be scheduled such that the PK sample can be collected 5-7 hours after morning doses of the BID drugs. At weeks 4 and 10, the visit should be scheduled such that the PK sample can be collected 8-10 hours after morning doses of the BID drugs. (If the **participant** is enrolled into the PK substudy A5334s, the parent study week 4 samples **for ARV and DAA assessment** should not be collected.) This distribution of sample times allows good representation across the dosing interval for each **participant**. At the time of HCV or HIV-1 VF, the visit should be scheduled such that the PK sample can be collected 2-10 hours after the morning doses of BID drugs. The exact time of the prior dose and the exact time of the blood sample should be recorded on the CRF.

Single PK sample for quantification of **plasma** RBV and RBV-TP from RBCs obtained via dried blood spot (genotype 1a participants only)

Single PK samples for RBV plasma drug quantification and RBV dried blood spots for triphosphate drug quantification, collected at weeks 4 and 8 and at the time of HCV or HIV-1 **VF**, should be collected around the same time as the scheduled PK sample for ARV and DAA quantification. (The sample need not be drawn at any particular time relative to the preceding RBV dose.) The exact time of the prior dose and the exact time of the blood sample should be recorded on the CRF.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity

It is expected that DAA+/-RBV therapy will be much better tolerated than conventional PegIFN-based HCV therapy. However, it is possible that some **participants** will experience transient or prolonged AEs related to (reasonable possibility) DAA+/-RBV therapy during the study. Some **participants** may need to adjust dosing of RBV. To minimize the effects of these dosing modifications on the eventual evaluation of the safety, tolerability, and activity of DAA+/-RBV therapy, the principles in the following sections will be used to determine the appropriate dose adjustment.

If possible, DAA+/-RBV therapy must not be held or eliminated. This recommendation stems from the very high SVR rates seen in HCV monoinfected phase IIb studies and concerns that extended periods of lowered drug concentrations in the blood may be associated with the replication of more resistant clones of the virus, resulting in a lack of sustained response.

Participants who develop a DAA+/-RBV therapy-related (reasonable possibility) mild or moderate AE or Grade 1 or 2 laboratory abnormality (other than those discussed separately for hemoglobin parameters (section 7.2.2), elevated total bilirubin (section 7.2.1), hepatic transaminase parameters (section 7.2.3), and CrCl parameters (section 7.2.4) may continue DAA+/-RBV therapy with **follow-up** per the study protocol. If the AE or laboratory parameter does not improve or normalize within two scheduled study visits and an etiology other than DAA+/-RBV therapy has not been determined, then the A5329 protocol team must be notified within 24 hours by e-mail at actg.corea5329@fstfrf.org to further discuss **participant** management. **Participants** may continue study drug; interruption of DAA+/-RBV therapy is not required.

With the exception of Grade ≥ 3 elevations in uric acid or glucose in **participants** with a history of diabetes mellitus, if a **participant** experiences a Grade ≥ 3 laboratory parameter during the study (other than those discussed in the toxicity management sections 7.2.1 through 7.2.4), the abnormal laboratory test must be repeated within 72 hours. If the Grade ≥ 3 abnormality is confirmed, DAA+/-RBV therapy must be interrupted and the laboratory parameter followed until it reaches Grade ≤ 1 . DAA+/-RBV therapy can be restarted if the laboratory parameter reaches Grade ≤ 1 within 7 days of DAA+/-RBV therapy interruption. If DAA+/-RBV therapy is interrupted and restarted and abnormality recurs at Grade ≥ 3 , then DAA+/-RBV therapy must be permanently discontinued. If the abnormality does not improve to Grade ≤ 1 within 7 days of interruption, DAA+/-RBV therapy must be permanently discontinued.

NOTE: If DAA+/-RBV therapy is held in **participants** on a DRV- or ATV-based ARV regimen 100 mg of RTV must be added to the **ATV or** morning DRV dose for as long as the DAA+/-RBV regimen is held.

If the site investigator believes that the confirmed Grade ≥ 3 laboratory abnormality can be managed medically without interruption, then the A5329 protocol team must be notified within 24 hours by e-mail at actg.corea5329@fstfrf.org to discuss continued

DAA+/-RBV therapy administration with medical management. If the laboratory abnormality does not improve with medical management within two scheduled study visits, then DAA+/-RBV therapy must be interrupted and the laboratory abnormality followed. If the laboratory abnormality does not improve within 7 days, then DAA+/-RBV therapy must be permanently discontinued. DAA+/-RBV therapy can be restarted if the laboratory parameter reaches Grade ≤ 1 within 7 days, of DAA+/-RBV interruption. If the laboratory abnormality recurs at Grade ≥ 3 upon restart, then DAA+/-RBV therapy must be permanently discontinued.

7.2 Management of Specific Toxicities

7.2.1 Elevated Bilirubin

Asymptomatic elevation of indirect (unconjugated) bilirubin is anticipated in this study due to the inhibition OATP1B1 from **paritaprevir** and hemolysis from RBV. Based on these mechanisms, elevations in direct bilirubin would be atypical; therefore, elevations in bilirubin which are predominantly direct must be worked up per the site investigator's usual management.

Participants may be maintained on DAA+/-RBV therapy for isolated elevations in total bilirubin which is predominantly indirect. These elevations are expected to be transient and asymptomatic and not associated with concomitant elevations in transaminases. For Grade ≥ 3 total bilirubin levels which are predominantly indirect, the site investigator may manage per his/her discretion and can refer to the paragraph on management of Grade ≥ 3 laboratory parameters above.

7.2.2 Anemia for Participants with HCV Genotype 1a Who Are Receiving RBV

Reductions in hemoglobin are a well characterized side effect of RBV exposure. Hemoglobin abnormalities must be managed according to Table 1. Management will be different for **participants** without a history of known cardiac disease and **participants** with cardiac disease.

If a **participant** experiences a hemoglobin decrease (as outlined in Table 1), a confirmatory test must be performed within 2 weeks. If the hemoglobin decrease is confirmed, the management guidelines in Table 1 must be followed. Depending on the rapidity and severity of anemia and any delays in obtaining confirmatory hemoglobin it may be advisable to initiate management measures while waiting for confirmatory testing.

Use of hematologic growth factors (such as erythropoietin [EPO]) or blood transfusions are not recommended; any use of growth factors must be discussed with the A5329 protocol team by e-mail at actg.corea5329@fstrf.org prior to institution. Management of hematologic growth factor therapy is the responsibility of the site investigator and growth factors will not be provided as part of A5329.

Table 1. Management of Hemoglobin Abnormalities **for Participants with HCV Genotype 1a Who Are Receiving RBV**

Hemoglobin in Participants with No History of Cardiac Disease	
Hemoglobin <10.0 g/dL, but ≥8.5 g/dL	DAA+RBV therapy may be continued.
	Reduce RBV dose by 200 or 400 mg and continue to monitor hemoglobin per protocol.
	If hemoglobin increases to ≥10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments. If Hb decreases to <8.5 g/dL see appropriate row below.
Hemoglobin <8.5 g/dL	Hold RBV. Restart RBV 600 mg once hemoglobin >10 g/dL. Remainder of DAA+RBV therapy may be continued.
	Manage the participant as medically appropriate.
Hemoglobin decrease of ≥4 g/dL between two scheduled study visits but hemoglobin ≥10 g/dL	Reduce RBV dose by 400 or 600 mg. Manage the participant as medically appropriate. DAA+RBV therapy may be continued.

Hemoglobin in Participants with History of Stable Cardiac Disease	
Hemoglobin decrease of ≥2 g/dL during a 4-week treatment period (Hb ≥10 g/dL) without symptoms and/or signs of cardiac disease	DAA+RBV therapy may be continued.
	Reduce RBV dose by 400 or 600 mg.
	Continue to monitor hemoglobin levels per protocol.
	If subsequent hemoglobin result is greater than the level that triggered the dose reduction, the site investigator may elect to increase RBV, with gradual dose increases in 200 mg increments at two-week intervals towards original dose.
	If hemoglobin does not increase; site investigator may manage the participant as medically appropriate. If hemoglobin decreases to <10 g/dL see appropriate row below.
Hemoglobin decrease of ≥2 g/dL during a 4-week treatment period (Hb ≥10 g/dL) with symptoms and/or signs of cardiac disease	If the participant has symptoms consistent with their cardiac disease manage participant as medically appropriate.
	Hold RBV. Restart RBV 600 mg once hemoglobin has increased by >1 g/dL and symptoms resolved.
	Other DAA+RBV therapy may be continued, consider management as for those without cardiac signs and symptoms in the rows above.
Hemoglobin decrease ≥4 g/dL between study visits but hemoglobin ≥10 g/dL	Hold RBV. Restart RBV 600 mg once hemoglobin has increased by >1 g/dL Site investigator must manage participant as medically appropriate.

Hemoglobin in Participants with History of Stable Cardiac Disease	
	Other DAA+RBV therapy may be continued.
Hemoglobin <10.0 g/dL, but ≥8.5 g/dL	DAA+RBV therapy may be continued.
	Reduce RBV dose by 400 or 600 mg and continue to monitor hemoglobin per protocol.
	If hemoglobin increases to ≥10 g/dL, may increase RBV; with gradual dose increases in 200 mg increments.
	If hemoglobin <10 g/dL despite 4 weeks at RBV 600 mg, permanently discontinue RBV (if alternative management of anemia is considered then the study team must be contacted); manage as medically appropriate. DAA therapy may be continued. If discontinuation of DAA+RBV therapy is being considered, contact the A5329 protocol team by e-mail at actg.corea5329@fstrf.org .
Hemoglobin <8.5 g/dL	Hold RBV. Restart RBV 600 mg once hemoglobin >10g/dL.
	Remainder of DAA+RBV therapy may be continued.
	Manage the participant as medically appropriate.

7.2.3 Transaminase Elevations

As discussed in section 2.0, **PTV/r** at higher doses has been associated with transaminase elevations in a minority of **participants**. At the dose being studied (**PTV/r** 150/100 mg) Grade 3 ALT elevations were seen in <1% of **participants**.

If a **participant** experiences an ALT level $\geq 5 \times$ ULN that is $\geq 2 \times$ Baseline, a confirmatory test must be performed within 72 hours. If the ALT is confirmed as a level that is $\geq 5 \times$ ULN that is $\geq 2 \times$ Baseline, the management guidelines in Table 2 must be followed.

Alternative management of ALT increases requires approval from the A5329 protocol team by e-mail at actg.corea5329@fstrf.org.

Table 2. Management of Confirmed ALT Levels $\geq 5 \times$ ULN and $\geq 2 \times$ Baseline

ALT $\geq 10 \times$ ULN or ALT $\geq 5 \times$ ULN but <10 \times ULN with symptoms and signs of hepatitis present (eg, jaundice, nausea, vomiting , abdominal pain)	Permanently discontinue study drugs. Update concomitant medications on CRF (if applicable) and evaluate and manage the participant as medically appropriate.
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<p>ALT $\geq 5 \times$ ULN but $< 10 \times$ ULN without symptoms or signs of hepatitis</p>	<p>Update concomitant medications on CRF (if applicable), and evaluate and manage the participant as medically appropriate. Continue study drugs and repeat LFTs and INR within 72 hours and as clinically indicated until resolution.</p> <p>If ALT values during follow-up are increased > 2-fold from the prior values, or increasing direct bilirubin, ($> 2 \times$ ULN), or increasing INR (> 2-fold), or symptoms/signs of hepatitis then permanently discontinue study drugs.</p>
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7.2.4 Changes in CrCl

CrCl will be calculated throughout the study using Cockcroft-Gault method

Refer to the Cockcroft-Gault calculator located on the FSTRF website at www.fstrf.org.

If a **participant** experiences a CrCl decrease to < 50 mL/min, a confirmatory test must be performed within 2 weeks. If calculated CrCl is confirmed to have decreased to < 50 mL/min, medical evaluation must include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter, and any dietary and herbal supplements.

In addition, the following must occur:

- Concomitant medication dose reduction based on CrCl must be done (if applicable).
- A5329 protocol team must be contacted by e-mail at actg.corea5329@fstrf.org to discuss whether dose modification or drug substitution may be required. Drug interactions between concomitant medications and the DAA+/-RBV therapy for example, could potentially increase antihypertensive medication exposure and may reduce renal function. If antihypertensive medications are adjusted, vital signs must be monitored to ensure appropriate blood pressure control.
- RBV dose must be adjusted per package insert. Alternative management of RBV dose in the setting of reduced renal function will require approval of the A5329 protocol team by e-mail at actg.corea5329@fstrf.org.
- A urine specimen must be obtained for urinalysis (including urine for albumin).
- Creatinine and chemistries must be repeated within 7 days and as clinically indicated until resolution or stabilized.
- CrCl value < 30 mL/min, all study medications will be discontinued.
- If CrCl does not improve in the subsequent two scheduled study visits (two CrCl values still < 50 mL/min) then consideration of discontinuation of all potentially nephrotoxic medications must be undertaken. Continuation of the study regimen will be considered on a case-by-case basis in

conjunction with discussion with the A5329 protocol team by e-mail at actg.corea5329@fstfrf.org.

- Changes to the ART regimen require notification and should not be instituted without discussion with the A5329 protocol team by e-mail at actg.corea5329@fstfrf.org.
- Continue further medical management as appropriate.
- If CrCl improves, consideration must be given to the readjustment of any dose modifications that have been made.

7.3 Virologic Failure

7.3.1 HCV VF

The following criteria will be considered evidence of HCV VF. **Participants** demonstrating any of the following will be permanently discontinued from DAA+/- RBV treatment, and entered into Step 2 for post-treatment **follow-up**:

- Confirmed increase from nadir in HCV RNA (defined as two consecutive HCV RNA measurements of $>1 \log_{10}$ IU/mL above nadir) at any time point;
- Failure to achieve HCV RNA $<$ LLOQ by week 6
- Confirmed HCV RNA \geq LLOQ (defined as two consecutive HCV RNA measurements \geq LLOQ) at any point after HCV RNA $<$ LLOQ during HCV treatment;

NOTE: Confirmatory HCV RNA should be **drawn** as soon as possible and no **later** than **one** week after receiving initial HCV RNA VF result. **Please refer to the LPC.**

All **participants** who discontinue DAA+/-RBV therapy **because of** HCV VF will continue in the study following the post-treatment SOE, which is Step 2 (see sections **6.1 and 6.2**).

7.3.2 HIV-1 VF

Plasma HIV-1 RNA will be monitored throughout the study. Since all **participants** will be taking a qualifying ART regimen, HIV-1 viral failure will be defined as follows:

- Confirmed increase in HIV-1 RNA to ≥ 200 copies/mL at any time after study entry until 4 weeks after permanent discontinuation of DAA+/-RBV therapy.

Since “blips” in HIV-1 RNA may be observed in individuals on ART in the absence of HIV-1 VF, any increase in plasma HIV-1 RNA ≥ 200 copies/mL must be confirmed with repeat testing as soon as possible (not to exceed 2 weeks). For **participants** with confirmed HIV-1 VF, a plasma specimen obtained at the time of confirmation will be sent to the designated A5329 VSL for evidence of

HIV-1 drug resistance. Confirmed HIV-1 failure specimens must have repeated detection of ≥ 200 copies/mL for HIV-1 drug resistance testing. Results will be reported back to sites in real-time from the designated A5329 VSL.

Clinical management of HIV-1 VF will be handled by local site investigators according to current HIV treatment guidelines and local standard of care.

Participants who experience confirmed HIV-1 VF may require discontinuation of DAA+/-RBV therapy.

- **Participants** at \geq week 12 of DAA+/-RBV therapy should discontinue HCV DAA+/-RBV therapy in the event of confirmed HIV-1 VF. (These **participants** will enter Step 2 and continue follow-up in the post-treatment evaluation schedule).
- **Participants** at $<$ week 12 of DAA+/-RBV therapy may continue on HCV therapy if the investigator believes that the confirmed HIV-1 VF can be managed medically without DAA+/-RBV therapy discontinuation.
 - The A5329 core team should be contacted prior to discontinuation of HCV DAA+/-RBV therapy (actg.corea5329@fstrf.org)

Clinical management of HIV-1 VF will be handled by local site investigators according to current HIV treatment guidelines and local standard of care; however, the A5239 protocol core team must be contacted to discuss continued DAA+/-RBV therapy before any switch to the ART regimen in the event of HIV-1 VF (actg.corea5329@fstrf.org).

- The core team and the local site PI must discuss HIV treatment options and agree on an appropriate HIV-1 salvage regimen for **participants** to continue on HCV DAA+/-RBV study treatment.
- Investigators should consult section 5.4.2 and the table of contraindicated medications (posted on the PSWP) to inform discussions with the A5329 core team regarding the potential for a modified ART regimen for HIV-1 VF. Possible modified ART regimens should take into account the unique characteristics of the **participant** and the **participant's** HIV-1 treatment history as well as known and/or anticipated drug interactions with DAA+/-RBV therapy.
- If no reasonable salvage HIV regimens compatible with continued HCV DAA+/-RBV treatment are deemed available for an individual **participant** with HIV-1 VF then the **participant** must discontinue HCV DAA+/-RBV therapy (and enter Step 2 in order to continue post-treatment **follow-up** evaluations).

7.4 Adjustments in ART regimens following cessation of HCV DAA+/-RBV therapy

Following completion of dosing with DAA+/-RBV therapy, study **participants** on DRV or **ATV** ART regimen will resume the HIV-1 ART regimen doses and dosing intervals used

for the 2 weeks prior to entry. Specifically, **RTV** 100 mg must be administered with the **morning** dose of DRV **or** **ATV** to replace the **RTV** dose which was part of the HCV DAA +/- RBV therapy.

NOTE: **Participants** on the DRV ART regimen may return to 800 mg/100 mg DRV/r daily dosing once they have been off the HCV DAA regimen for at least 2 weeks.

7.5 Pregnancy

All participants

For all participants (either female participants who become pregnant or male participants whose partners become pregnant), intrapartum complications and/or pregnancy outcome will be recorded on a CRF 6 months following the end of the pregnancy. If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact her/him regarding pregnancy outcomes 6 months following the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on a CRF.

Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com (phone: 1-800-258-4263; fax: 1-800-800-1052).

Participants with HCV genotype 1a who are receiving RBV

For participants with HCV genotype 1a who are receiving RBV, pregnancy (either female participants or male participants whose partners become pregnant) will result in immediate permanent discontinuation of RBV therapy and participants will be counseled on the teratogenicity of RBV. Participants will remain on DAAs and be followed per the Schedule of Events (sections 6.1 and 6.2) in Step 1 (on-HCV treatment) and Step 2 (post-HCV treatment) until study completion.

Participants with HCV genotype 1a who are receiving RBV and who become pregnant while taking study treatment or within 6 months after discontinuing study treatment and male participants who have sexual partners who become pregnant during this time will have their pregnancies reported to the RBV Pregnancy Registry (www.RibavirinPregnancyRegistry.com).

Participants with HCV genotype 1b

For participants with HCV genotype 1b, participants (either female participants who become pregnant or male participants whose partners become pregnant) will remain on DAAs and be followed per the Schedule of Events (sections 6.1 and 6.2) in Step 1 (on-HCV treatment) and Step 2 (post-HCV treatment) until study completion.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent and Premature Study Drug Discontinuation

- HCV VF (see section 7.3.1)
- Drug-related toxicity requiring permanent discontinuation (see section 7.1 Toxicity)
- Requirement for prohibited concomitant medication.
- Pregnancy (**in a female participant or the male participant's female partner**) or breast-feeding. (**These participants will discontinue RBV only, if applicable, but remain on DAAs.**)
- Completion of treatment as defined in the protocol.
- Request by **participant** to terminate treatment.
- In the site investigator's judgment, **participant** repeatedly noncompliant with study drugs as prescribed.
- Failure by the **participant** to attend **three** or more consecutive clinic visits.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

8.2 Premature Study Discontinuation

- Request by the **participant** to withdraw.
- Request of the primary care provider or site investigator if s/he thinks the study is no longer in the best interest of the **participant**.
- **Participant** judged by the site investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), SMC, ACTG, other government agencies as part of their duties, site investigator, or industry supporter.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Open-label, study of IFN-free HCV therapy for 24 or 12 weeks in **participants** with HCV/HIV-1 coinfection on specific ART regimens. DAA+/-RBV therapy (study treatment intervention) will include a NS3/4A protease inhibitor plus an NS5A inhibitor plus an NS5B non-nucleoside, plus weight-based RBV **among those infected with HCV genotype 1a**.

NOTE: In Version 1.0 of this study, all participants (regardless of HCV genotype), received RBV as part of the HCV study treatment regimen. See below for further discussion of the implications of this change.

The study will consist of sequentially enrolled study cohorts determined by ARV regimen and direct allocation (not randomized) to the duration of DAA+/-RBV therapy (24 followed by 12 weeks).

INI-based ARV regimen group (RAL or DTG)

Cohort A: DAA (+RBV **for genotype 1a**) HCV therapy for 24 weeks

Cohort B: DAA (+RBV **for genotype 1a**) HCV therapy for 12 weeks

PI-based ARV regimen group (DRV or ATV)

Cohort C: DAA (+RBV **for genotype 1a**) HCV therapy for 24 weeks

Cohort D: DAA (+RBV **for genotype 1a**) HCV therapy for 12 weeks

NOTE: In Version 1.0, the HIV ARV regimens allowed in the cohorts were more restrictive (current INI-based regimen group was formerly RAL only, and current PI-based regimen group was formerly DRV only). The allowed NRTIs as part of the ARV regimen were also more restricted for all participants regardless of cohort in Version 1.0.

Because of the sequential nature of study design that meant that only Cohorts A and C enrolled under protocol Version 1.0, the distribution of ARV regimens that participants are taking may vary between the longer HCV treatment-period Cohorts (A and C), and the shorter HCV treatment-period Cohorts (B and D) which are anticipated to accrue exclusively under Version 2.0 of the protocol.

Additionally, as result of the sequential cohort study design and exclusion of RBV among HCV genotype 1b participants only among those enrolled during Version 2.0 means that the longer HCV treatment cohorts may represent a mixture of HCV treatments among those with HCV genotype 1b.

In general, analyses for the study will not be performed differently or adjusted for protocol version, and will combine all available data across participants enrolling or participating in any version of the study. Any exceptions to this general rule will be noted either in the analysis section below, or in the study's statistical analysis plan (SAP). The version changes will not affect the key analyses, because each cohort will be described and analyzed separately in this phase II study with small sample sizes.

Each study Cohort (A-D above) will enroll a total of 25 participants (for a total of 100 participants).

Study follow-up is 48 weeks following study entry for each **participant**. Each cohort will occur in two steps: on-HCV treatment (Step 1) and post-HCV treatment **follow-up** (Step 2).

The primary completion date will be prior to each **participant's** study completion; primary completion based upon the SVR₁₂ outcome will be 12 weeks following HCV treatment discontinuation. Assuming completion of HCV treatment without premature stopping, this will be at the week 24 visit for those assigned to a short duration cohort

(12 weeks of anti-HCV treatment), and at the 36 week visit for those assigned to a longer duration cohort (24 weeks of anti-HCV treatment).

Data will be summarized **by individual Cohort (A, B, C, and D, as defined above) for analyses, but will not be analyzed separately by protocol version, as noted above.**

9.2 Outcome Measures

9.2.1 Primary Outcome Measures

9.2.1.1 Primary Efficacy Outcome Measure: SVR₁₂ evaluated at least 12 weeks post HCV treatment discontinuation. Responders will be those whose HCV RNA is less than the assay LLOQ. For those whose HCV early responses prior to SVR₁₂ evaluation meet the guidelines for HCV VF, their SVR₁₂ outcome will be defined as non-response. (Other considerations for the primary outcome are outlined below in analyses section 9.6 or in the **SAP**.)

9.2.1.2 Primary Safety and Tolerability Outcome Measures:

9.2.1.2.1 SAEs as defined by ICH criteria

9.2.1.2.2 Premature HCV study treatment discontinuation due to any reason other than HCV VF

9.2.1.2.3 Signs/Symptoms Grade ≥ 3 during HCV study treatment and up to 30 days following HCV study treatment discontinuation

9.2.1.2.4 Diagnoses leading to HCV study treatment or HIV-1 ARV discontinuation

9.2.1.2.5 Laboratory Abnormalities Grade ≥ 3 during HCV study treatment and up to 30 days following HCV study treatment discontinuation

9.2.2 Secondary Outcome Measures

9.2.2.1 HIV-1 VF as defined in section 7.3 above

9.2.2.2 Presence of genotypic mutations conferring major resistance to any HIV-1 PI at time of HIV-1 RNA VF (or confirmation of HIV-1 RNA VF)

9.2.2.3 Baseline, end of treatment and PTwk12 (post-treatment week 12 = same time as SVR₁₂ evaluation) sCD14 levels; and baseline, end of treatment and PTwk12 IP10 levels as biomarkers of immune activation

9.2.2.4 HCV mutations conferring resistance to any component of the HCV treatment regimen in the first sample with a HCV VL >1000 IU/mL

among the subset of **participants** who are non-responders for SVR₁₂ (PTwk12 measurement if available, and premature treatment discontinuation or final available specimen otherwise)

NOTE: **The** exact list of relevant mutations **is** given in study's SAP.

9.2.2.5 SVR₂₄

9.2.3 Exploratory Outcome Measures

9.2.3.1 Participant-specific estimates of ARV PK parameters AUC, clearance, C_{max} and C_{min}, estimated from nonlinear mixed-effect population PK models (see sections 10.2 and 10.3 for details)

9.2.3.2 Participant-specific estimates of DAA PK parameters AUC, clearance, C_{max} and C_{min}, estimated from nonlinear mixed-effect population PK models (see sections 10.2 and 10.3 for details)

9.3 Randomization and Stratification

There is no randomization in this study. Allocation to cohorts will be fully deterministic according to HIV-1 ART regimen, and for each ART regimen, assigned to duration of HCV treatment by the timing of accrual (longer duration cohorts first, followed by shorter duration cohorts), **and whether RBV is part of the HCV treatment is determined by the participant's HCV genotype**. Duration of (and inclusion of RBV in) HCV treatment will be necessarily open-label (ie, unblinded or unmasked) at the **participant** level, and at the team level **because of** the nature of the study design. The stratification factor (and levels) that will be used to control proportions of the following key subgroup within each cohort is cirrhosis (yes versus no). The enrollment to the strata level for cirrhosis=yes will be limited to no more than 30% (ie, no more than 7 **participants**) within any particular study cohort.

9.4 Sample Size and Accrual

The goal of this phase II study is to gather safety and efficacy data on the proposed HCV regimens in **HCV/HIV-1** coinfectd **participants** on certain HIV-1 ART regimens. The primary study objective is framed as a one-sample evaluation testing whether or not a fixed point estimate can be excluded.

To justify the sample size of **25 per cohort** for the primary efficacy outcome analysis SVR₁₂ is the dichotomous (Bernoulli distributed) outcome used, with assumptions of a one-sided significance level of 5% (compared to a standard one-sided type I error of 2.5%), and requiring at least 85% statistical power. The fixed point estimate to be excluded is 70% SVR₁₂, meaning that the alternative hypothesis will be accepted if the data support a conclusion of the SVR₁₂ rate being higher than 70%. This estimate of 70% comes from studies among HCV/HIV-1 coinfectd **participants** using the first approved DAAs [9, 10].

Power estimates given cohort size of 25 were calculated under various alternative hypotheses. With **25 participants**, there is **86%** power to conclude that SVR₁₂ is greater than 70% when the true SVR₁₂ rate is **92%**. Other alternative hypotheses are presented in the table below. **Note that these calculations use the exact binomial test, which differs from the proposed method for analyses (see section 9.6 below). However, this difference is motivated for being more conservative in calculations used for sample size estimates.**

True SVR ₁₂ Proportion	Power
.90	77%
.92	86%
0.94	94%
0.96	98%

Under Version 2.0, the anticipated accrual rate is approximately **10 to 15 participants** per month. **This rate would result in full accrual to a 25-person cohort in 1.67 to 2.5 months following implementation of Version 2.0.**

9.5 Monitoring

This study will be monitored at least annually by an ACTG -appointed SMC (via the standing committee for the HEPTSG). **This initial review will occur when the first of either 25 participants enrolled onto the study (irrespective of cohort) have at least 12 weeks of follow-up data available, or the 1-year anniversary of the first participant enrolling to the study (first participant enrolled September 16, 2015) occurs.**

Any/all SMC reviews will include administrative/conduct data as well as safety data **according the safety-related outcomes enumerated above**, and any data (**eg accrual, conduct, key specimen availability, and safety**) from substudies (if/as available).

Note that since efficacy outcomes in the substudies are not being assessed in real-time, but being performed in retrospective, batch testing, that efficacy outcome data from substudies will likely not be available at the time of A5329 interim reviews, and therefore no efficacy outcome data will be presented, even if initial batch testing has commenced.

For the main study, there are no plans for formal interim monitoring of the efficacy outcome of SVR₁₂ or related earlier HCV RNA outcomes. **However, HCV RNA descriptive summaries will be provided to the SMC. While HIV-1 VF has been removed as a safety event of interest in Version 2.0, HIV-1 RNA descriptive summaries will be provided to the SMC.**

The following routine monitoring reports are distributed to core team and are detailed in the study monitoring plan (SMP): screening, accrual, data delinquency,

study status, data and sample completeness. The routine safety monitoring report is distributed to the DAIDS Clinical Representative (separately by cohort) and a subset of the core team (collapsed over cohort) every 3 months.

Further details about monitoring of this study are available in the SMP.

9.6 Analyses

The analysis phase of this study will be initiated upon study completion (when the final participant has his/her final study evaluation visit and comes off study follow-up).

9.6.1 Primary Efficacy Analysis

The primary efficacy outcome (SVR₁₂) will be estimated within each study cohort, with a point-wise estimate as well as a 95%, one-sided lower confidence bound. The confidence bound will be calculated with exact binomial distribution according to the method of Clopper-Pearson. (Corresponding, two-sided, 90% confidence intervals may also be calculated). A one-sided exact test for a single binomial population will use the null hypothesis response rate of 70%, applied to each of the two analysis groups as defined above.

Those missing a HCV RNA result from the week 12 post-HCV therapy discontinuation visit (and missing all subsequent evaluations) will be considered as non-responders. However, if HCV RNA evaluations subsequent to week 12 PT are non-missing, then the first HCV RNA subsequent to week 12 PT will instead be used to define the primary outcome as per section 9.2.1.1.

As mentioned in the general statistical considerations section, the primary analyses of this study will be performed without regard to the protocol version under which participants enrolled or under which data were collected. The changes from Version 1.0 to Version 2.0 affected both ARV regimen and HCV study treatment. Due to sequential cohort enrollment these protocol version updates are anticipated to have differential implications by cohort; and cohort groups are expected to be heterogeneous, and some of this heterogeneity will have been caused by protocol version updates.

9.6.2 Secondary Analyses

Safety and tolerability outcomes will be summarized by cohort. Descriptions of the absolute and relative frequency and incidence of outcomes will also be summarized. The method of Kaplan-Meier can be used to estimate the cumulative probability of these outcomes (eg, time to first SAE, or time to first qualifying sign/symptom), at various **follow-up** times, but no comparisons to internal or external (ie, historical controls) groups is planned. Note that these analyses will be as-treated, as the outcomes are as-treated, where “as-treated” is defined as **participants** being evaluated for these outcomes only during receipt

of HCV therapy and for 30 days following HCV therapy discontinuation (including premature discontinuation).

PK outcome measures analyses are outlined in section 10 below.

The outcomes of HIV-1 VF and related outcome of presence of genotypic mutations (which are only measureable among those with VF) will be summarized and described (nature, timing, potential triggers, and supporting data). Because these outcomes are anticipated to be extremely rare (and maybe not ever observed), no formal statistical inference or comparisons are planned. Similar to safety and tolerability outcomes, HIV-1 VF outcome is evaluated only while HCV treatment is being received or within 4 weeks following permanent discontinuation (see section 7.3 for more details). Resistance outcome will consider whether observed mutations are associated with ARV drugs received in the past, currently, or never received. As noted in the definition of the outcome, resistance will be defined for mutations that confer major resistance of any HIV-1 PI. Resistance to other ARVs may also be described.

The distribution of baseline immune function markers (eg, sCD14 and IP-10) will be summarized and described as continuous outcomes (eg, key percentiles and graphics such as box-plots or dot-plots), and no transposition is anticipated. This will be repeated by cohort. To address the objective relating these markers to the outcome of SVR₁₂, a Wilcoxon Rank-Sum test where groups are defined by SVR will compare the distribution of baseline immune marker. If some signal is observed here, multivariable logistic regression for the outcome of SVR₁₂, and exploring the independent contribution of baseline immune markers when controlling for other factors prognostic for the SVR outcome will be fit.

HCV mutations among the subset who have this outcome defined (ie, non-responders for SVR₁₂ outcome) will be summarized by **participant** for patterns, and across **participants** by mutation location, for frequency. The list of relevant HCV mutations at the time of this protocol was provided by AbbVie and will be included on the PSWP or LPC. If additional relevant mutations are identified prior to analysis, these will be specified in the **study's** SAP. Baseline and follow-up samples will be compared for matching of genotype so that possible evolution (or selection of existing minor variants) of resistance can be described.

SVR₂₄ outcome will be summarized and described using methods parallel to the primary SVR₁₂ outcome as described above in section 9.6.1. The visit window for SVR₂₄ will start at the week 24 PT, and use imputation parallel to that for SVR₁₂ to account for missing data, if relevant, **and only as subsequent data are available during study follow-up for evaluation.**

Additional details regarding all analyses will be pre-specified in the study's SAP.

10.0 PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

(There are no primary objectives related to pharmacology)

10.1.1 Secondary objective: See section 1.3.4.

10.1.2 Exploratory objectives: See sections 1.4.3 to 1.4.5.

10.2 Pharmacology Study Design

10.2.1 PK Objectives

In the context of PK substudy A5334s, intensive PK sampling will be conducted prior to and 4 weeks (\pm 1 week) after initiation of HCV drugs, and **participant**-specific ARV and DAA PK parameters will be estimated using noncompartmental methods. Summary statistics for these parameters will be used as inputs to (prior information for) nonlinear mixed-effects population PK models, which will be fit to drug concentrations obtained from the sparse PK sampling conducted on all **participants** in A5329. For each **participant**, single samples (ranging from 2-10 hours after the preceding dose of both QD and BID drugs) will be collected at multiple occasions; see section 6.0 for details of sample collection.

The larger (compared to the substudy) number of **participants** available for these population models will provide: (1) an alternate assessment of the effects of the DAAs on ARV PK (via assessment of a covariate representing pre-HCV treatment (week 0) vs. post-HCV treatment (weeks >0), and (2) an alternate assessment of the effects of the ARVs on DAA PK (via comparison of A5329 **participant**-specific DAA estimates with external control group(s) of **participants** not taking ARVs (data from AbbVie). The larger number of **participants** will likely represent a wider and more representative distribution of factors that could affect PK such as age, sex, race, status of selected SNPs, and degree of cirrhosis, thereby providing an important alternative assessment of ARV-DAA DDIs.

10.2.2 PD Objectives

To examine the association of DAA systemic exposure with HCV treatment outcomes, **participant**-specific estimates (from the population PK models) of DAA clearance (or another PK parameter) will be used as independent variables in models of HCV treatment response as the dependent variable. Similarly, **participant**-specific estimates (from the population PK models) of ARV clearance (or another PK parameter) will be used to explain any observed cases of HIV-1 VF. Drug clearances will also be used as independent variables in models for the occurrence of selected toxicities.

10.3 Pharmacokinetics Analysis

PTV, OBT, DSV will be assayed at AbbVie **Bioanalysis** using mass spectrometry. **RAL, DTG, DRV, ATV**, and **RTV** will be assayed by the UB PSL. **RBV** plasma and dried blood spots will be assayed by the UCHS PSL.

For each drug, separate nonlinear mixed-effects population PK models will be fit, as described in section 10.2.1 above. Additional details will be specified in the Statistical Analysis Plan.

10.4 Anticipated Outcomes

We anticipate that **participants** taking both ARVs and DAAs will have similar or greater exposure to **RAL, DTG, DRV, ATV, PTV/r/OBT, and DSV**, compared to **participants** taking only ARVs or only DAAs. The proposed clinical pharmacology objectives will provide important data on possible PK changes that may occur in **participants** with HCV/HIV-1 coinfection. **However, since the number of participants taking individual ARVs within the same cohort regimen group is not controlled, there may be some ARVs for which there are too few observations in which to perform a population PK model, and therefore inference for those ARVs will not be possible because of sparse data.**

To provide context for these potential alterations to ARV and DAA exposure in **participants** treated for both infections, through PD models we will examine associations between altered drug exposure and treatment outcomes.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

CRFs will be provided for each **participant**. **Participants** must not be identified by name on any CRFs. **Participants** will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual **participant** records, including consent forms,

CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study **participants**, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

- 11.3.2 The site investigator will make study documents (eg, consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB/EC, the site monitors, the FDA, the NIAID, the OHRP, and the industry supporter or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 AE Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are:
 - **PTV/r/OBT**
 - **DSV**
 - **RBV**

11.4.3 Grading Severity of Events

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

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 PARTICIPANTS

12.1 Institutional Review Board Review and Informed Consent

This protocol and the informed consent document (Appendix II) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the **participant** (or legal guardian or person with power of attorney for **participants** who cannot consent for themselves). The consent form 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 **participant** or legal guardian and this fact will be documented in the **participant's** record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain **participant** confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the **participant**, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, or other government agencies as part of their duties, or the industry supporter or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, or the industry supporter, or other government agencies as part of their duties to ensure that research **participants** are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

14.0 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 and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

15.0 REFERENCES

1. Sherman KE, Rouster SD, Chung RT, Rajcic N. Hepatitis C virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2002 Mar 15;34(6):831–7.
2. Smith C. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. *AIDS Lond. Engl*. 2010 Jun 19;24(10):1537–48.
3. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, Koziel MJ. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001 Aug;33(4):562–9.
4. Chung RT, Andersen J, Volberding P, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med*. 2004 Jul;351(5):451–9.
5. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004 Jul;351(5):438–50.
6. Mehta SH, Lucas GM, Mirel LB, et al. Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic. *AIDS* 2006 Nov;20(18):2361–9.
7. Dieterich D, Soriano V, Sherman KE, et al. Telaprevir in combination with pegylated interferon-a-2a+RBV in HCV/HIV-co-infected patients: A 24-week treatment interim analysis. Seattle, WA USA: 2012.
8. Mallolas J, Pol S, Rivero A, et al. 50 Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV co-infected patients: end of treatment (week 48) interim results. *J Hepatol*. 2012 Apr;56, Suppl 2(0):S22.
9. Poordad F, Lawitz E, Kowdley KV, et al. 1399 12-Week interferon-free regimen of ABT-450/R +ABT-333 +ribavirin achieved SVR12 in more than 90% of treatment-naïve HCV genotype-1-infected subjects and 47% of previous non-responders. *J Hepatol*. 2012 Apr;56, Suppl 2(0):S549–S550.
10. Lawitz E, Poordad F, Kowdley KV, et al. 13 A 12-Week interferon-free regimen of ABT-450/R, ABT-072, and ribavirin was well tolerated and achieved sustained virologic response in 91% of treatment-naïve HCV IL28B-CC genotype-1-infected subjects. *J Hepatol*. 2012 Apr;56 Suppl 2(0):S7.
11. Kowdley KV, Lawitz E, Poordad F, et al. 3 Safety and efficacy of interferon-free regimens of ABT-450/r, ABT-267, ABT-333 +/- ribavirin in patients with chronic HCV GT1 infection: results from the AVIATOR Study. *J. Hepatol*. 2013 Apr;58, Supplement 1:S2.
12. Molla A, Korneyeva M, Gao Q, et al. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nat Med*. 1996 Jul;2(7):760–6.

REFERENCES (Cont'd)

13. Ferenci P, Bernstein D, Lalezari J, et al. **ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-1992.**
14. **Viekira Pak Prescribing Information. AbbVie Inc., North Chicago, IL. Revised April 2016.**
15. Feld JJ, Moreno C, Trinh R, et al. **Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. J Hepatol 2016;64:301-7.**
16. **AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. <http://www.hcvguidelines.org>. Accessed April 2016.**
17. Khakoo SI, Thio CL, Martin MP, et al. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science* 2004;305:872-4.
18. Golden-Mason L, Castelblanco N, Rosen HR. Pre-treatment activatory natural killer receptor (NKR) expression on natural killer (NK) and natural T (NT) cell subsets correlates with successful anti-viral therapy for chronic hepatitis C viral (HCV) infection. 15th International Symposium on Hepatitis C Virus and Related Viruses 2008:abstract 186.
19. Harrison B, Khakoo A. Natural killer cell phenotypes in chronic hepatitis C infection: correlation with genetics and the outcome of treatment. *Hepatol.* 2008;48 (Suppl):785.
20. Vidal-Castineira JR, Lopez-Vazquez A, Diaz-Pena R, et al. Effect of killer immunoglobulin-like receptors in the response to combined treatment in patients with chronic hepatitis C virus infection. *J Virol.* 2010;84:475-481.
21. Hu PF, Hultin LE, Hultin P, Hausner MA, Hirji K, Jewett A, et al. Natural killer cell immunodeficiency in HIV disease is manifest by profoundly decreased numbers of CD16+CD56+ cells and expansion of a population of CD16dimCD56- cells with low lytic activity. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;10:331-40.
22. Mavilio D, Lombardo G, Benjamin J, et al. Characterization of CD56-/CD16+ natural killer (NK) cells: a highly dysfunctional NK subset expanded in HIV-infected viremic individuals. *Proc Natl Acad Sci U S A* 2005;102:2886-91.
23. Gonzalez VD, Falconer K, Bjorkstrom NK, et al. Expansion of functionally skewed CD56-negative NK cells in chronic hepatitis C virus infection: correlation with outcome of pegylated IFN-alpha and ribavirin treatment. *J Immunol.* 2009;183:6612-18.
24. Anthony DD, Conry SJ, Medvik K, et al. Baseline levels of soluble CD14 and CD16+56-natural killer cells are negatively associated with response to interferon/ribavirin therapy during HCV-HIV-1 coinfection. *J Infect Dis.* 2012;206:969-73.
25. Conry SJ, Meng Q, Hardy GA, et al. Genetically associated CD16+56- NK-cell IFN α R expression regulates signaling and is implicated in IFN α -induced HCV decline *J Infect Dis.* 2012.
26. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* 2011;203:780-90.
27. Douek DC, Roederer M, Koup RA. Emerging concepts in the immunopathogenesis of AIDS. *Annu Rev Med* 2009;60:471-84.

REFERENCES (Cont'd)

28. De Maria A, Moretta L. NK cell function in HIV-1 infection. *Curr HIV Res* 2008;6:433-40.
29. Giorgi JV, Hultin LE, McKeating JA, et al. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis.* 1999;179:859-70.
30. Sandler NG, Koh C, Roque A, et al. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. *Gastroenterology.* 2011;141:1220-30.
31. Kovacs A, Karim R, Mack WJ, et al. Activation of CD8 T cells predicts progression of HIV infection in women coinfecting with hepatitis C virus. *J Infect Dis.* 2010;201:823-34.
32. Valdez H, Anthony D, Farukhi F, et al. Immune responses to hepatitis C and non-hepatitis C antigens in hepatitis C virus infected and HIV-1 coinfecting patients. *AIDS.* 2000;14:2239-46.
33. Gonzalez VD, Landay AL, Sandberg JK. Innate immunity and chronic immune activation in HCV/HIV-1 co-infection. *Clin Immunol.* 2010;135:12-25.
34. Marchetti G, Nasta P, Bai F, et al. Circulating sCD14 is associated with virological response to pegylated-interferon-alpha/ribavirin treatment in HIV/HCV co-infected patients. *PLoS One* 2012;7.
35. Harrington P, Zeng W, Naeger L. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. *Hepatology* 2012;55:1048-57.
36. Lontok E, Mani N, Harrington PR, Miller V. Closing in on the target: Sustained virologic response in hepatitis C virus genotype-1 infection response-guided therapy. *Clin Infect Dis.* 2013 Jan 29. [Epub ahead of print]
37. Wedemeyer H, Jensen DM, Godofsky E, Mani N, Pawlotsky JM, Miller V; Definitions/Nomenclature Working Group* of the HCV DrAG (HCV Drug Development Advisory Group), under the auspices of the Forum for Collaborative HIV Research. Recommendations for standardized nomenclature and definitions of viral response in trials of hepatitis C virus investigational agents. *Hepatology.* 2012 Dec;56(6):2398-403.
38. Iwamoto M, Wenning LA, Nguyen B-Y, et al. Effects of omeprazole on plasma levels of raltegravir. *Clin Infect Dis.* 2009 Feb 15;48(4):489-92.
39. Cahn P1, Fourie J, Grinsztejn B, et al. **Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients.** *AIDS* 2011;25:929-39.
40. Orkin C, DeJesus E, Khanlou H, et al. **Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial.** *HIV Med* 2013;14:49-59.
41. **Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. Section accessed March 2016.**

APPENDIX I: CONDITIONS INCLUDED IN THE 1993 AIDS
SURVEILLANCE CASE DEFINITION

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive *
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary * or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent *
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

*Added in the 1993 expansion of the AIDS surveillance case definition.

(<http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm>)

APPENDIX II: A5329 SAMPLE INFORMED CONSENT

DIVISION OF AIDS AIDS CLINICAL TRIALS GROUP (ACTG)

For protocol: A5329
Interferon-Free Therapy for Chronic HepAtitiS C Virus GENotype 1 InfecTion in **Participants**
with HIV-1 Coinfection Receiving Concurrent Antiretroviral Therapy
(**C_ASCENT**), **FINAL Version 2.0, 06/08/16**

SHORT TITLE FOR THE STUDY: Interferon-Free Therapy for HCV Genotype 1

ABBREVIATED TITLE: HCV GT 1 AbbVie

INTRODUCTION

You are being asked to take part in this research study because you are infected with the human immunodeficiency virus (HIV), the virus that causes AIDS and the hepatitis C virus (HCV). 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, the A5329 protocol team wants 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 take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

New drugs are being developed to treat people who are infected with the hepatitis C virus (HCV). These drugs are being tested as a part of drug regimens that do not contain the drug interferon (**IFN**). These regimens could be useful in treating people who are infected with both HCV and HIV because these people often do not respond well to interferon (it does not treat their HCV effectively and they may have complications from taking the drug, such as depression).

These new drugs have not yet been adequately tested in people who are infected with both HIV and HCV. These are the goals of this study:

1. To see if these drugs can effectively treat HCV in people who are infected with both HCV and HIV.
2. To see if these drugs are safe and well-tolerated in people who are infected with both HCV and HIV.

APPENDIX II (Cont'd)

The drugs used in this study are:

- Drug 1: **paritaprevir/ritonavir/ombitasvir (PTV/r/OBT) fixed-dose combination tablet** approved by the US Food and Drug Administration (FDA) **for the treatment of HCV**
- Drug 2: **dasabuvir (DSV) approved by the FDA for the treatment of HCV**
- Drug 3: **ribavirin (RBV) approved by the FDA for the treatment of HCV genotype 1a only**

Hepatitis C is divided into genotypes. A genotype is a way to describe the virus based on genetic material in the virus itself. This current study includes participants with HCV genotype 1a and 1b. Recent studies show patients with HCV genotype 1b do not have any added benefits when they take RBV as part of their HCV treatment regimen. Similar results have been seen in studies with patients who are infected with HIV and HCV.

Prior studies show patients with HCV genotype 1a do benefit from including RBV as part of an HCV treatment regimen.

Therefore, in the current study, RBV will be provided to you if you have HCV genotype 1a only.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Screening

After you read and sign the consent form, you will have a screening visit to make sure you are able to join the study. This visit will last about 1-2 hours.

- Your HIV infection will be confirmed. If there is no record available, you will have another HIV test. You may have to sign a separate consent form before having this test.
- You will have a physical exam and will be asked about your health and medicines you have taken in the past and are taking now. Also, an EKG (electrocardiogram, a recording of the heart's electrical activity) will be done at this visit.
- You will have about 3 tablespoons (**40 mL**) of blood drawn to measure your HCV viral load (the amount of HCV virus in your blood) and genotype (genetic makeup of the HCV virus), CD4+ cell counts (these are cells in your blood that fight infection), evidence of hepatitis B virus infection, and HIV viral load (the amount of HIV in your blood), and for routine safety tests. You will be told the results of these tests when they become available.
- You will have a blood test to look for Serum Alpha-Fetoprotein (AFP) in your blood. AFP is normally made by a fetus's liver and yolk sac. It's the main protein during the first three months of development. AFP greatly decreases by age 1 and should only be found in adults in very low levels. Some people with cirrhosis or chronic active hepatitis also have higher blood levels of AFP. You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will not be able to enroll in this study if you are pregnant. You will be told the result of the test when it becomes available.
- **If you are a male with a female partner who is able to become pregnant, you will be asked if your partner is pregnant. You will not be able to enter the study if you have HCV genotype 1a and your partner is pregnant.**

APPENDIX II (Cont'd)

- If you have been diagnosed with cirrhosis (a liver disease) and have not had imaging (CT, MRI, or ultrasound) of your liver in the last 6 months you will have an ultrasound of your liver. An ultrasound is a non-invasive procedure – waves of sound will pass through your skin and bounce off of your liver. You will not feel these waves. A computer will collect the waves that bounce back and make a picture of your liver. You will be told the results of these tests when they become available.

If you do not enroll into the study

If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of the screening visit, some demographic (age, gender, race), clinical (disease condition, diagnosis), and laboratory (CD4+ cell count, viral load) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Entry

If you are eligible for the study, you will come in for a study entry visit. At this visit:

- You will have a brief physical exam.
- Medical and medication history will be collected at the study entry visit.
- You will have about 6 tablespoons (90 mL) of blood drawn to measure HCV viral load, HIV viral load, CD4+ cell counts, and for some routine safety tests. You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will not be able to **enter the study** if you are pregnant. You will be told the result of the test when it becomes available.
- **If you are a male with a female partner who is able to become pregnant, you will be asked if your partner is pregnant. You will not be able to enter the study if you have HCV genotype 1a and your partner is pregnant.**
- You will have about 1 tablespoon (15 mL) of blood drawn for a genetic test to see if we can predict how well you will respond to HCV treatment (this is called an IL28B genotype test).
- You will have about 1 tablespoon (15 mL) of blood drawn and stored for future HCV/HIV studies, including resistance studies. A resistance test is used to determine the genetic makeup of your HCV virus. In addition, some of your blood will be stored for future testing required by the study.
- You will have to have IFN Gamma-Induced Protein 10 (IP-10) test to look at the protein levels in your **blood** that can become elevated in **people** infected with HCV genotype 1.
- You will have soluble CD14 (sCD14) plasma sample taken to see how well your body responds to treatment of your HIV and HCV. sCD14 is a biomarker (biological molecule such as proteins and DNA) found in your plasma (clear, yellowish, fluid part of the blood that carries the blood cells).

You will be assigned to a study group based on which medicines you take for your HIV and how long you take the study drugs. The study will require that you be on a specific antiretroviral therapy (ART) regimen containing either **integrase inhibitor (INI)** raltegravir (RAL) or **dolutegravir (DTG)** or **protease inhibitor (PI)** darunavir (DRV) or **atazanavir (ATV)**, but this regimen will not be provided by the study.

APPENDIX II (Cont'd)

The groups are described below. You and your study doctor will know the **study** drugs that you are taking. **You will have about 1 tablespoon (15 mL) of blood drawn after your first dose of study drugs to measure the drug levels in your blood.**

Group A

- Take study drugs for 24 weeks
- Take ART regimen containing raltegravir **or** dolutegravir

Group B

- Take study drugs for 12 weeks
- Take ART regimen containing raltegravir **or** dolutegravir

Group C

- Take study drugs for 24 weeks
- Take ART regimen containing darunavir **or** atazanavir

Group D

- Take study drugs for 12 weeks
- Take ART regimen containing darunavir **or** atazanavir

Study Visits While Taking Study Drugs (Weeks 2, 4, 6, 8, and 10) Group A, B, C, and D:

- You will have a brief physical exam.
- You will have about 3 tablespoons (45 mL) of blood drawn for routine safety blood tests and to measure your HCV and HIV viral loads. You will be told the results of these tests when they become available.
- You will have blood drawn to measure CD4+ cell counts (week 4). You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant (at week 4 **and** week 8). You will be told the result of the test when it becomes available.
- You will have about 1 tablespoon (15 mL) of blood drawn and stored for future testing required by the study.
- You will have about 1 tablespoon (15 mL) of blood drawn to measure the levels of study drugs in your blood.
- You will have to have an IP-10 test (at week 2 and week 4).
- You will have sCD14 plasma samples taken (at week 2 and week 4).

If you are assigned to Group B or D, you will stop taking study drugs at week 12.

If you are assigned to Group A or C, you will stop taking study drugs at week 24, so you will have three more study visits while taking study drugs.

Study Visits While Taking Study Drugs (Weeks 12, 16, and 20) Group A and C Only:

- You will have a brief physical exam.
- You will have an EKG (at week 12).

APPENDIX II (Cont'd)

- You will have about 3 tablespoons (45 mL) of blood drawn for routine safety blood tests, and to measure your HCV and HIV viral loads. You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will be told the result of the test when it becomes available.
- You will have about 1 tablespoon (15 mL) of blood drawn to measure the levels of study drugs in your blood (week 12 only).
- You will have about 1 tablespoon (15 mL) of blood drawn and stored for future testing required by the study.
- **You will have and IP-10 test and sCD14 plasma samples taken (week 12).**
- **You will have blood drawn to measure CD4+ cell counts (week 12). You will be told the results of these tests when they become available.**

Treatment Completion Visit (Groups A, B, C, and D)

When you are done taking your study drugs, you will have a treatment completion visit (at week 12 for Groups B and D; at week 24 for Groups A and C). At this visit:

- You will have a brief physical exam, including an EKG.
- You will have about 6 tablespoons (90 mL) of blood drawn to measure your HCV viral load, HIV viral load, CD4+ cell counts, and for some routine safety tests. You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will be told the result of the test when it becomes available.
- You will have about 1 tablespoon (15 mL) of blood drawn to measure the levels of study drugs in your blood. (Groups B and D only)
- You will have about 1 tablespoon (15 mL) of blood drawn and stored for future testing required by the study.
- You will have to have an IP-10 test.
- You will have sCD14 plasma samples taken.

You will not take any more study drug after this visit, but you will have study visits to follow your health.

Post-Treatment Visits (Post-treatment weeks 4, 12, and 24 for Groups A and C; Post-treatment weeks 4, 12, 24 and 36 for Groups B and D)

- You will have a brief physical exam.
- You will have about 6 tablespoons (90 mL) of blood drawn to measure your HCV viral load, your HIV viral load, your CD4+ cell counts (**at some visits**), and for some routine safety tests. You will be told the results of these tests when they become available.
- If you are a woman able to become pregnant, you will be asked to give a urine or blood sample to see if you are pregnant. You will be told the result of the test when it becomes available.
- You will have about 1 tablespoon (15 mL) of blood drawn and stored for future testing required by the study.

APPENDIX II (Cont'd)

- **You will have and IP-10 test and sCD14 plasma samples taken (at some visits).**

If you are assigned to Group A or C, you will have 3 post-treatment visits and be done with the study after your post-treatment week 24 visit.

If you are assigned to Group B or D, you will have 4 post-treatment visits and will be done with the study after your post-treatment study visit week 36 visit.

If You Have to Stop Taking the Study Drugs Early or You Have to Stop the Study Early

If you have to stop taking the study drugs early, you will come to the clinic for an additional visit. This visit will last about 1 hour. At this visit:

- You will have a brief physical exam.
- You will have about 5 tablespoons (75 mL) of blood drawn to measure HCV viral load, HIV viral load, CD4+ cell counts, and for some routine safety tests.
- If you are a woman able to become pregnant, you will be asked to give a urine sample or blood sample. You will be told the result of the test when it becomes available.
- You will have about 1 tablespoon (15 mL) blood drawn to measure the level of study drugs in your blood.
- You will have about 1 tablespoon (15 mL) of blood drawn and stored for future testing required by the study.
- You will have an EKG test.
- You will have to have an IP-10 test.
- You will have sCD14 plasma samples taken.
- **You will have about 1 tablespoon (15 mL) of blood drawn to measure the study drug levels in your blood.**

After this visit, you will either: continue “on study/off study drugs,” if you agree and it is safe for you to continue; or you will be taken off the study altogether. If you continue “on study/off study drugs,” you will have the post-treatment visits as described above for your group.

Virologic Failure

If you experience HCV virologic failure (when your HCV worsens) or HIV virologic failure (when your ART fails to suppress and sustain your viral load to less than 200 copies/mL), a blood sample (1 teaspoon) will be collected to confirm this result. This **collection** may be combined with another study-scheduled visit. **You will also have these tests done:**

- You will also have about 1 tablespoon (15 mL) of blood drawn to measure the levels of study drugs in your blood.
- **You will have about 1 tablespoon (15 mL) of blood drawn and stored for future testing required by the study.**
- **You will have routine safety labs done (for HCV virologic failure).**
- **You will have and IP-10 test and sCD14 plasma samples taken (for HCV virologic failure).**
- **You will have about 1 teaspoon of blood drawn for HIV-1 resistance testing (for HIV virologic failure).**

APPENDIX II (Cont'd)

Your study doctor will talk to you about the plan for future treatment.

For HCV virologic failure: You must stop taking HCV study drugs right away. You will continue “on study/off study drugs” and have the post-treatment visits as described above for your group.

For HIV virologic failure: You may or may not need to stop taking HCV study drugs. Your study doctor will discuss this with you. If it is safer for you to stop taking HCV study drugs, you will continue “on study/off study drugs” and have the post-treatment visits as described above for your group.

Other

Some of your blood that is left over after all required study testing is done may be stored (with the usual protectors of your identity) and used for ACTG-approved HIV-related research. Refusing to have your blood stored will not affect your participation in this study. We will not store your samples with any information that will identify you. These samples may be stored for an indefinite period. You might not receive the results of testing performed on these samples.

Please indicate now if you agree to allow your leftover blood to be used for future ACTG-approved HIV-related research. You may still change your mind at any time and we will destroy your samples.

_____ YES, I AGREE _____ NO, I DO NOT AGREE

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 100 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for up to 11 months.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- the study is cancelled
- a Study Monitoring Committee (SMC) recommends that the study be stopped early (An SMC is an outside group of experts who monitor the study.)
- you are not able to attend the study visits as required by the study
- your primary care provider or investigator thinks the study is no longer in your best interest

APPENDIX II (Cont'd)

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

- continuing the study drugs may be harmful to you
- you need a treatment that you may not take while on the study
- you are not able to take the study drugs as required by the study
- **you miss 3 or more clinic visits in a row**
- **you experience** HCV virologic failure
- **you become** pregnant or breast-feed (**for females on study**)
- **your female partner becomes pregnant (for males on study)**

If you must stop taking the study drugs before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED DRUGS OR ONCE I LEAVE THE STUDY, HOW WOULD DRUGS BE PROVIDED?

During the study:

If you must permanently stop taking study-provided drugs before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

After you have completed your study participation, the study will not be able to continue to provide you with the drugs you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

Risks of Social Harm

Although the study site staff will make every effort to protect your privacy and confidentiality, it is possible that other people could find out that you are in a study and this could cause problems for you. For example, other people might figure out that you are infected with HIV. If this happens, people could treat you unfairly or family members, friends, and/or the community might not accept you.

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.

Risks of EKG

An EKG has no serious risks and does not give off electrical charges, such as shocks. You may develop a mild rash where the electrodes (soft patches) were attached. This rash often goes away without treatment.

APPENDIX II (Cont'd)

Risks of Study Drugs

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of **paritaprevir/r/ombitasvir** and **dasabuvir**

- Abnormal EKG (the changes may be associated with abnormal heart rhythms)
- Fatigue
- Headache
- Abnormal liver tests (inflammation of the liver)
- High bilirubin level, may cause yellowing of the skin and eyes
- High alkaline phosphatase level in the blood (may be associated with gall bladder disease)
- **Headache: 7.3%, about 7 in 100 participants**
- **Diarrhea: 3.6%, about 4 in 100 participants**
- **Nausea: 2.9%, about 3 in 100 participants**
- **Dizziness: 2.9%, about 3 in 100 participants**
- **Constipation: 2.5%, about 3 in 100 participants**
- **Common cold symptoms: 2.2%, about 2 in 100 participants**

More than 5,000 HCV-infected patients have been treated with a paritaprevir/r-based interferon-free, combination DAA HCV treatment regimen during phase II/III and currently ongoing clinical trials.

Side effects which were considered related to the 3-DAA+ ribavirin (RBV) medications are listed below from most frequent to least frequent. These events occurred at least 5% more often in patients receiving 3-DAA + RBV medications than with patients who received a sugar pill (placebo) in the placebo-controlled phase III studies.

- **Very common ($\geq 1/10$): tiredness (34.2%, about 34 in 100 patients), nausea (22.3%, about 22 in 100 patients), itching (15.7%, about 16 in 100 patients), trouble sleeping (14.0%, about 14 in 100 patients), weakness (13.5%, about 14 in 100 patients)**
- **Common ($\geq 1/100$ to $< 1/10$): low blood count (5.3%, about 5 in 100 patients)**
- **The side effect that was considered related to the 3-DAA medications alone (without RBV) was itching (6%, in about 6 of 100 patients)**

Risk of liver problems and failure

A small number of patients have experienced severe liver problems while on the 3-DAA medicines, some of whom died or required liver transplantation. These liver problems

APPENDIX II (Cont'd)

included confusion, abdominal fluid accumulation and swelling, bleeding, and changes in blood tests that measure the function of the liver.

It is unknown whether these liver problems were directly caused by the 3-DAA medicines or were a result of their advanced liver disease. Most patients who died or needed a liver transplant already had advanced disease before starting the 3-DAA medicines. Blood tests that measure your liver function will be performed during the study, and your doctor will monitor you for signs of severe liver problems. Let your doctor know if you have swelling of the stomach area, bleeding, or are feeling confused.

Risk of ALT elevations

About 1 in 100 patients (1%) being treated with 3-DAA medicines experienced an increase in ALT (a blood test that increases when your liver is inflamed) levels. Increased levels of ALT happened more often in patients receiving medicines containing ethinyl estradiol, which many birth control pills contain. These increased ALT levels did not cause symptoms, usually happened during the first 4 weeks of treatment, and got better with continued treatment with the 3-DAA medicines.

Patients who are taking ethinyl estradiol-containing medicines will be asked to stop taking these medicines before starting treatment with the 3-DAA medicines. Ethinyl estradiol-containing medicines include pills, patches, or rings that deliver ethinyl estradiol for the purpose of contraception or for other clinical indications, including some hormone replacement therapy. Estrogens used to treat symptoms of menopause like vaginal creams do not typically contain ethinyl estradiol. If you are using an estrogen, it is important for your physician to check what type of estrogen it contains. (FOR STUDY M13-101 ONLY: The dose of paritaprevir is <200 mg in both the approved HCV medication as well as in most of the clinical trials, except for the study M13-101 in which the dose administered is 200 mg. If you are in this M13-101 study and receiving paritaprevir at the 200mg dose, the risk of ALT elevations is increased when compared with participants receiving paritaprevir at <200 mg dose.)

If you are taking an ethinyl estradiol-containing medication for birth control, your doctor may switch you to a different method of birth control (for example, a progestin-only containing contraceptive or non-hormonal form of birth control). You may restart your ethinyl estradiol-containing medicine about 2 weeks after your 3-DAA medicine treatment is completed. Your blood levels of ALT will be measured during this study. Let your doctor know if you have new onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces.

Increased bilirubin levels

Some patients taking the 3-DAA medicines, especially those who were also taking ribavirin or the HIV medicine ATV, had increased levels of bilirubin (a substance measured in your blood that is produced when red blood cells are broken down) that can cause yellowing in the eyes or under the tongue in a small number of people. These bilirubin increases can be temporary and may not be caused by damage to the liver.

APPENDIX II (Cont'd)

Increases in bilirubin usually reach their highest level in the first week after starting the 3-DAA medicines and get better with continued 3-DAA treatment.

In some cases, increases in bilirubin can get worse. If bilirubin increase occurs with other signs such as swelling of the stomach area, vomiting of blood, or confusion, it may be a sign of a severe liver problem.

Hemoglobin decreases

RBV is known to cause anemia (low hemoglobin levels from having low red blood cell counts). See RBV-related risks. In studies in which patients received the 3-DAA medicines with RBV, hemoglobin levels decreased during treatment and got better after treatment was finished. Low hemoglobin levels were usually treated by decreasing the dose of RBV given. Patients rarely required blood transfusions or other medicines to increase hemoglobin levels.

General information

The study medications may interfere/interact with some medications. One such interaction is with a type of blood pressure medicine called calcium channel blockers. In studies done in Japanese patients, 5% of patients taking calcium channel blockers developed leg swelling, a known side effect of calcium channel blockers, after starting DAA (study medications).

Some drug interactions may be serious or life-threatening. You must let your doctor know about any medications (oral, inhaled, topical, or other), including herbals or vitamins that you are taking.

In addition, as with any medicines, the 3-DAAs may cause unexpected allergic reactions. Allergic reactions, including lip and tongue swelling, have been observed in patients taking the 3-DAA medications.

Information about pregnancy

The risks of AbbVie's 3-DAA medicines in pregnancy are not known.

Risks of Ribavirin (RBV)

- **Anemia (decreases in your red blood cells caused by breakdown of your red blood cells). Anemia can worsen existing heart and pulmonary conditions.**
- **Temporary changes in blood platelet levels**
- **Temporary changes in liver function tests (a measure of your liver activity)**
- **Stomach and intestinal**
 - **Nausea**
 - **Vomiting**
 - **Indigestion**
 - **Stomach discomfort**
 - **Skin disorders**
- **Upper respiratory tract inflammation**
- **Teratogenicity (risk to an unborn baby)**

APPENDIX II (Cont'd)

- Nervous system
 - Depression
 - Insomnia (inability to sleep)
 - Nervousness
 - Skin tingling
 - Drowsiness
 - Light-headedness
- Hyperuricemia (excess of uric acid in blood which can lead to gout, a painful swelling of joints and may lead to kidney disease).

NOTE: There are reports indicating that HIV-infected people taking treatment for HIV and HCV have developed high lactate (an acid that can build up in the bloodstream and cause life-threatening illness) levels with worsening liver disease. It is not clear if ribavirin is the cause. This may be more common if ribavirin is taken with didanosine (ddl, Videx) for HIV infection. There may be an increased risk of inflammation of the pancreas when didanosine is taken with ribavirin. Because of these risks, didanosine use is not allowed in this study.

RBV is associated with birth defects and should not be taken by pregnant women or men with pregnant sexual partners.

ARE THERE RISKS RELATED TO PREGNANCY?

The drug or drug combinations in this study are unsafe for unborn babies. The risks to unborn babies for each drug are listed in the section called "What Are The Risks Of The Study?"

If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant.

Because of the risk involved, **if you are participating in sexual activity that could lead to pregnancy**, you and your partner must use two methods of birth control that you discuss with the study staff. You may choose two of the birth control methods listed below:

- Condoms (male or female) with **or without** a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)

You and your partner must use two reliable methods of birth control simultaneously while receiving study drugs. If you will be taking RBV on study, then you must continue to use two reliable methods of birth control at the same time for 6 months after stopping study drugs. Ribavirin is known to cause birth defects and can lead to the death of an unborn child. If you will not be taking RBV on study, then you must continue to use two reliable methods of birth control at the same time for 30 days after stopping study drugs.

If you **are a woman who** can become pregnant, you must have a pregnancy test within **24** hours prior to starting the study drugs. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits. If you think you may be pregnant at

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any time during the study, tell your study staff right away. The study staff will talk to you about your choices.

If you are a man on study and you think your female partner may be pregnant at any time during the study, tell your study staff right away.

For participants with HCV genotype 1a who are receiving RBV:

Pregnancy (either women or men whose female partners become pregnant) at any time during the study will result in immediate discontinuation of RBV and counseling on ribavirin teratogenicity (ability to cause birth defects). **You will continue on DAAs. You will continue to be followed on study and have the visits as described above for your group until study completion.**

For participants with HCV genotype 1b:

Women or men with women partners who become pregnant at any time during the study will continue on DAAs. You will continue to be followed on study and have the visits as described above for your group until study completion.

All participants:

You will be contacted by the study staff 6 months after the end of the pregnancy to follow up on any side effects. In addition, the study staff will report pregnancies to the Ribavirin Pregnancy Registry (if you were taking RBV) and the Antiretroviral Pregnancy Registry. These are websites housing information about any side effects seen in babies who were exposed to RBV or anti-HIV drugs during pregnancy.

Breastfeeding

It is unknown whether the study drug or study drug combinations pass through the breast milk and may cause harm to your infant. You will not be allowed to participate in the study if you are breastfeeding.

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. 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 and HCV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

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

- treatment with prescription drugs available to you
- treatment with experimental drugs, if you qualify
- no treatment

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

APPENDIX II (Cont'd)

WHAT ABOUT CONFIDENTIALITY?

The A5329 team will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. 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 ACTG, Office for Human Research Protections (OHRP) or other government agencies as part of their duties, Food and Drug Administration (FDA), (insert name of site) institutional review board (IRB) (a group that protects the rights and well-being of people in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, the A5329 team will be required to tell the proper authorities.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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 study.

WILL I RECEIVE ANY PAYMENT?

(Sites: please indicate whether you will provide payment to participants.)

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. You will not be giving up any of your legal rights by signing this consent form.

APPENDIX II (Cont'd)

WHAT ARE MY RIGHTS AS A RESEARCH **PARTICIPANT**?

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

The A5329 protocol team 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:

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

For questions about your rights as a research **participant**, contact:

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

APPENDIX II (Cont'd)

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 Representative (print)
(As appropriate)

Legal Representative's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff's Signature and Date

Witness's Name (print)
(As appropriate)

Witness's Signature and Date