This is ACTG A5348 SAP Version 2.0 with names of authors, names of publication writing team members and analysis timeline redacted.

ACTG A5348

Phase II Trial of Retreatment Strategies for Difficult-to-Treat Hepatitis C Virus (HCV)-infected Individuals Who Have Failed Prior Direct Acting Antiviral (DAA)-based Regimens

ClinicalTrials.gov Identifier: NCT02605304

Statistical Analysis Plan

Version 2.0

Version 1.0 December 18, 2015

Version 2.0 January 19, 2017

Table of Contents:

1 Introduction

This document describes the proposed content for the interim review reports and the primary statistical analysis report for ACTG study A5348, focusing on analyses that address the safety and HCV virologic outcome measures. The plan includes the key analyses that will form the core of any presentation or publication used to disseminate the primary conclusions of the study. It also includes analyses in interim reports for the Study Monitoring Committee (SMC) while the study is ongoing and describes the components shared with the Study Chairs in open interim reports. It is recognized that this statistical analysis plan (SAP) may be modified by the Study Team as new information becomes available or to reflect recommendations made by the SMC.

SAP Version 2.0: The study closed to accrual prematurely on July 21, 2016 due to the enrollment challenges. The SAP version 2.0 removes analysis components that are no longer feasible or applicable based on 7 study participants, and it updates planned analyses. The final analysis report will be descriptive, with the goal of contributing to the sponsor company's (Gilead's) manuscript on a similar clinical trial.

2 Study Overview

2.1 Study Design

A5348 is a prospective, phase II, open-label study to evaluate 12-week and 24-week regimens of ledipasvir(LDV)/sofosbuvir(SOF) for retreatment of HCV among individuals with prior treatment failure, with the addition of ribavirin (RBV) to the 12-week regimen.

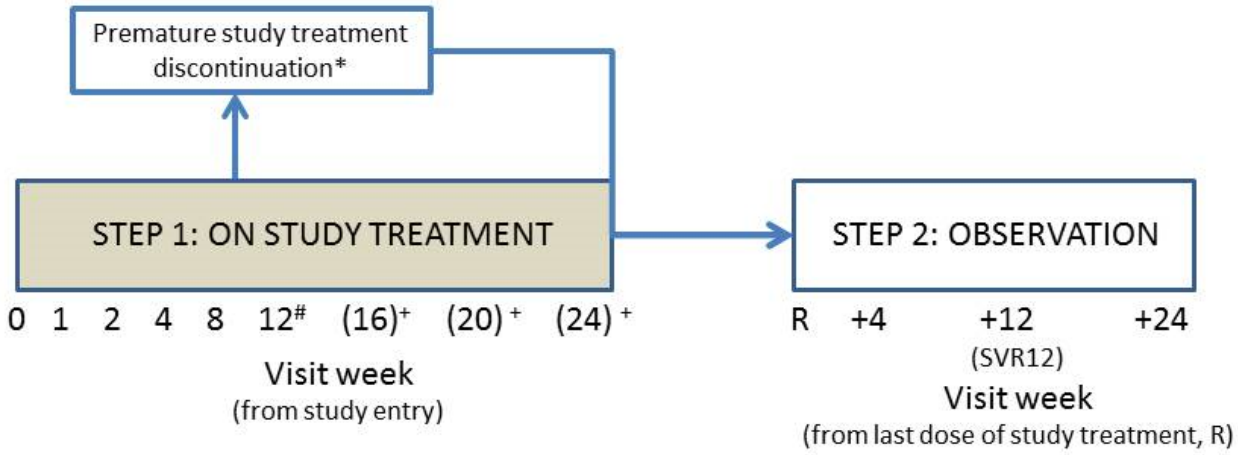
Study population is HCV genotype 1 infected participants, co-infected with HIV, who have previously experienced HCV virologic failure on SOF-based treatment, including SOF/RBV +/- pegylated interferon (PEG) and SOF/simeprevir (SIM). For the HIV infection, the participants can be on a stable protocol-approved ARV regimen (efavirenz, rilpivirine, raltegravir, dolutegravir, tenofovir, abacavir, 3TC/FTC, RTV-boosted atazanavir, RTV-boosted darunavir), or they may not be on ARVs.

Participants will be randomized (1:1) to the two study arms, stratified by cirrhosis status.

Arm A: 12 weeks of LDV/SOF with RBV (N=20)
Arm B: 24 weeks of LDV/SOF (N=20)

The study is randomized because there is clinical equipoise on the benefits and drawbacks in the two study regimens. The study is not designed to be powered for comparison between the randomized arms.

All participants receive study treatment for up to 12 or 24 weeks (Step 1) depending on the study arm and HCV virologic response (Section 2.3). The treatment period (Step 1) is followed by 24 weeks of observation (Step 2).



* Includes discontinuation due to confirmed HCV virologic failure (VF).
# Arm A participants complete study treatment at Week 12 and register to Step 2.
+ Step 1 visits at Weeks 16, 20 and 24 are for Arm B participants only. Arm B participants complete treatment at Week 24 and register to Step 2.

SAP Version 2.0: The study closed to accrual after 7 participants in the study. All 7 participants will complete follow-up as described in the protocol.

2.2 Study Treatment

Arm A: LDV 90 mg/SOF 400 mg fixed dose tablets QD with weight-based RBV (1000 mg/day for weight < 75 kg, 1200 mg/day for weight ≥ 75 kg) for up to 12 weeks depending on the HCV virologic response

Arm B: LDV 90 mg/SOF 400 mg fixed dose tablets QD for up to 24 weeks, depending on the HCV virologic response

2.3 Study Treatment Discontinuation According to HCV Virologic Response

Study treatment will be discontinued in participants who experience confirmed HCV virologic failure (VF) defined as follows.

a) Confirmed increase in HCV RNA to ≥LLOQ if HCV RNA previously declined to <LLOQ (target detected or not detected).
b) Confirmed ≥1 log10 IUmL HCV RNA increase from HCV viral load nadir.
c) Confirmed HCV RNA ≥LLOQ at week 8 visit.

Confirmatory HCV RNA sample should be obtained as soon as possible and no more than 2 weeks after receiving initial HCV RNA result. HCV RNA measurement to confirm failure will be performed in

real time at the designated laboratory and the results will be provided to the site investigators within two weeks of specimen receipt. Participants who experience confirmed HCV VF will discontinue study treatment and are followed on-study/off-treatment for 24 weeks post treatment discontinuation (Step 2).

2.4 Hypotheses

1. The study regimens (12 weeks of LDV/SOF/RBV and 24 weeks of LDV/SOF) will each result in estimated SVR12 of 90%, when used for HCV retreatment after sofosbuvir failure.
2. Twelve weeks of LDV/SOF/RBV and 24 weeks of LDV/SOF will be safe and well-tolerated.

2.5 Study Objectives

2.5.1 Primary Objectives

1. To assess the proportion of participants who attain SVR12 in each study arm
2. To evaluate safety and tolerability of each study regimen

2.5.2 Secondary Objectives

1. To assess the impact of LDV/SOF and HIV PI/r coadministration on the pharmacokinetics (PK) of tenofovir.
2. To assess the impact of LDV/SOF and RTV-boosted HIV PI coadministration on any associated clinical events attributed to elevated tenofovir levels, including renal toxicity (defined as the development of ≥Grade 2 renal dysfunction or development of new or worsened proteinuria or glucosuria).
3. To assess the proportion of participants who attain SVR4 (i.e., SVR 4 weeks after stopping HCV antiviral therapy) and SVR24 (i.e., SVR 24 weeks after stopping HCV antiviral therapy) in each study arm.
4. To evaluate baseline predictors of SVR12, including cirrhosis, prior treatment response (relapse, partial response, null responder), HCV genotype 1a vs. 1b, race, and IL-28B status.
5. To evaluate the association between LDV/SOF adherence and SVR12 in both study arms.
6. To evaluate the impact of baseline HCV resistance mutations on the SVR12 attained with retreatment with LDV/SOF (+/- RBV).
7. To evaluate emergence of HCV resistance mutations in participants who fail to attain SVR12 with retreatment with LDV/SOF (+/- RBV).
8. To evaluate kinetics of HCV RNA during treatment (weeks 1, 2, 4, 8, 12, and in Arm B weeks 16, 20, and 24) and 4, 12, and 24 weeks after treatment discontinuation.
9. To assess the influence of LDV/SOF based retreatment on HIV-specific parameters, including maintenance of HIV-1 RNA < 50 copies/mL for participants on antiretrovirals and CD4+ cell count during treatment.
10. To evaluate the differences in SVR12 among participants receiving specific antiretroviral therapy (ARV) regimens compared to those taking no ARV.
11. To compare the SVR12 proportions, safety, and tolerability in the two study arms.

SAP Version 2.0: As a result of the early enrollment closure, the final analysis report will be descriptive and consist primarily of listings of endpoints related to each objective. Secondary Objective 1 will not be included in the primary analysis report, because the PK data will be analyzed separately by the study pharmacologist, who may develop a joint report with PK data obtained outside of A5348.

2.6 Visit and evaluation schedule

Analyses by study week will use the visit windows provided in the protocol schedule of events (Protocol Section 6.1 Schedule of Events).

Arm A

		Step 1: On-Treatment Visit Week					Step 2: Post-Treatment Visit Week		
	Entry	1	2	4	8	12	R+4	R+12	R+24
Days	0	4-10	11-17	21-35	49-63	77-91	R+23 to R+35	R+79 to R+98	R+161 or later

R= Date of Last Dose of Study Treatment from the Study Treatment Record CRF

Arm B

		Step 1: On-Treatment Visit Week								Step 2: Post-Treatment Visit Week		
	Entry	1	2	4	8	12	16	20	24	R+4	R+12	R+24
Days	0	4 - 10	11 - 17	21 - 35	49 - 63	77 - 91	105 - 119	133 - 147	161 - 175	R+23 to R+35	R+79 to R+98	R+161 or later

R= Date of Last Dose of Study Treatment from the Study Treatment Record CRF

2.7 Monitoring

The study is monitored by the core team (study chairs and medical officer) to review the renal toxicity events and HCV RNA results for evidence of virologic breakthrough, and by the ACTG Hepatitis Study Monitoring Committee (SMC) to conduct full reviews of study data. The SMC review is planned to occur at least annually, or upon request by the SMC or the study team. A formal interim review of SVR12 by the SMC is not planned, because much of study follow-up will be complete before participants reach SVR12, especially in Arm A, due to the anticipated accrual rate (5-10 per month to complete enrollment under 6 months) and the small study sample size.

2.7.1 Ongoing Team Monitoring

The core study team will review the renal toxicity events and HCV RNA results on a frequent, routine schedule. The core team will also review routinely availability of data samples for key objectives and planned assays. The study team will monitor accrual. The Study Monitoring Plan (SMP) describes team monitoring reports.

2.7.2 SMC Reviews

The SMC will review the study six months after the study enrolls its first participant, or when about 40% of the study participants (about 16 participants) have the week 16 data, whichever occurs earlier. Because Arm A treatment duration is shorter at 12 weeks, the data will include the end of treatment

data and potentially some SVR4 data from Arm A participants. The components of the SMC Review Reports as described in the SMP are outlined in Section 3.1.

2.8 General Data Analysis Considerations

- Data summaries and analyses will be completed by study arm, unless specified otherwise. They will be collapsed across treatment arms for open interim reports.
- All participants who met the study eligibility criteria and received any study treatment will be included in the planned analyses, unless specified otherwise. The participants who are found to have been ineligible for the study after enrollment occurred will not be part of the planned analyses; if any of such participants received any study treatment, their safety profiles will be described separately in an appendix to the report.
- Participants are instructed to discontinue the study prior to initiation of non-study provided HCV treatment during follow-up after discontinuation of the study-provided treatment. If they remain on study in error, the data are censored at the time of alternative HCV treatment initiation.
- For the summaries on evaluations by study visits, calculated visit weeks will be used according to the tables shown above in Section 2.6. Entry value is defined as the evaluation from the day of treatment dispensation or the closest preceding evaluation. For the post-entry values, the evaluations conducted closest to the targeted dates will be used.
- For the summaries of AEs, diagnoses and opportunistic infections, events with the onset date on or after the study treatment initiation date will be summarized.
- In data lists, study participants will be identified by an anonymous patient identifier generated at the statistical center (publicID). Dates will not be shown, but converted to time (e.g. weeks) since randomization.
- Each Table/Figure/Listing will be annotated with the name and location of the program used to create it, including its location directory.
- Key outcome measures for which analysis programs require validation and the level of validation that is required are noted throughout the plan in Section 4.

2.9 Statistical Methods

For binary or categorical measures, number of participants and percent will be provided.

SAP Version 2: Two-sided 90% Wilson confidence intervals are provided for the key HCV virologic endpoints, per protocol. In addition, two-sided 95% Clopper-Pearson confidence intervals will be provided for SVR12, as suggested by the Gilead statistician on the Jan 6, 2017 manuscript call. For the continuous measures, median, lower and upper quartiles (Q1 and Q3), min, max will be provided. Additional summary statistics, such as mean with standard deviation (SD) may also be included for some measures, if noted below.

3 Components in the Reports

The listed components are described in Section 5.

3.1 SMC Review Reports

The purpose of SMC review reports is to provide data summaries relevant for interim reviews to ensure participant safety and to review data quality and study conduct. As described in the Study Monitoring Plan (SMP), the Open Report will be pooled across study arms, and the Closed Report will be by study arm.

SAP Version 2: There was one SMC review on August 18, 2016. The SMC became aware of the early enrollment closure. An abbreviated SMC report was generated and distributed, in consideration of only 7 participants in the study.

5.1.1 Study History
4.1.2 Accrual
4.1.3 Eligibility Violations and Registration Errors
4.1.4 Baseline Characteristics
4.1.5 Study Treatment Status and Duration of Treatment (Only in the Closed Report)
4.2.1 Adverse Events and Protocol-Required Laboratory Tests
4.2.2 Pregnancy
4.2.3 Deaths
4.2.4 HIV-Related Measures and Changes in ARV Regimen (Only in the Closed Report)
4.2.5 Virologic Failures (Only in the Closed Report)
4.3.1 SVR12
4.4.2 HCV Virologic Responses

- The Open Report will be limited to on-treatment HCV RNA. Only the following component will be provided in the Open Report.
  a) Listing of each participant's HCV RNA results will be provided with calculated visit weeks.

3.2 Final Primary Analysis Report and SVR24 Supplement

The purpose of the final analysis report is to complete the main analyses as described in the protocol, including the analysis of the primary endpoint SVR12.

SAP Version 2.0: The final primary analysis report for the study will occur when SVR12 data are complete. All the components of this plan in Section 4 will be included in the Final Primary Analysis Report, except for SVR24 results which will not yet be available. See Appendix Table B for the timetable. Once the study is complete, SVR24 data table will be generated and distributed to the study team as a supplement to the final primary analysis report.

4 Description of Components

SAP Version 2: Components have been updated.

4.1 Administrative and Baseline Characteristics

4.1.1 Study History

Purpose: To provide a summary of the protocol, any clarification memos and amendments and key events during the study that may be relevant to the study conduct.

a) A summary of changes to and clarifications of protocol.
b) A summary of recommendations from SMC reviews.
c) Description of the accrual process and progress.

4.1.2 Accrual

Purpose: To give a summary of accrual and the distribution of enrollment across sites.

a) Table of number (%) enrolled by site and month/year
b) Table of number (%) enrolled by the stratification factor
c) Number of participants on each regimen with ritonavir-boosted HIV protease inhibitor and tenofovir who participated in the PK sample collection*
d) Dates of first and last enrollments

* In consideration of the secondary objective on tenofovir PK.

4.1.3 Eligibility Violations and Registration Errors

Purpose: To document any participants who were accrued to the study but were subsequently excluded from analyses due to errors in screening procedures.

a) Description of each eligibility or screening error and exclusion from analyses.

4.1.4 Baseline Characteristics

Purpose: To describe the study population.

Notes: For all variables, the numbers of participants with available data will be provided. For the lab measures, the values up to and including treatment initiation date will be considered, and the value closest to treatment initiation date will be chosen.

a) Demographic and health variables: race/ethnicity, sex, age, IVD history, BMI.
b) Liver-related variables: HCV RNA, APRI, FIB-4, FibroSure, cirrhosis status, method used to determine cirrhosis status, HCV genotype 1 subtype, liver function tests. Listing of HCV resistance mutations detected at study baseline.
c) HIV-related variables: HIV viral load and CD4 count by ARV receipt.
d) ARV regimen.
e) Other: prior HCV treatment (e.g. SOF/PEG, SOF/PEG/RBV, SIM/SOF) and response (relapse, partial response, null response), IL28B.

- ✓ SDAC Validation: All programs generating variables as study-specific will be validated (e.g. APRI, FIB-4).

4.1.5 Study Treatment Status and Duration of Treatment

Purpose: To summarize completeness of study treatment

a) Study Treatment Status
   - Total number of participants who met the eligibility criteria and initiated study treatment
   - Number of participants who initiated study treatment regimen
   - Number of participants who completed study treatment regimen
   - Summary of reasons for treatment discontinuation, including categories for: completion of prescribed treatment duration, HCV virologic failure (as protocol-defined clinical event), lost to follow-up, adverse events, consent withdrawal, non-adherence, other. For reasons coded as "other", a listing will be provided.
b) Summary statistics (median, Q1, Q3) on time on treatment

- ✓ SDAC validation: All programs generating variables as study-specific will be validated (e.g. treatment regimen, time on treatment).

4.2 Safety

Purpose: To address the safety objectives of the study.

4.2.1 Adverse Events and Protocol-Required Laboratory Tests

a) Descriptive tables summarizing the adverse events and the number of participants experiencing the events will be provided by grade and by the site report on relationship to study treatment.
b) Summary table of all diagnoses reported.
c) Listing of participants with renal toxicity events (defined as Grade ≥2 creatinine clearance post-entry or new proteinuria or glucosuria, an increase from entry glucosuria or proteinuria by ≥1+).
   - baseline characteristics: age, sex, race/ethnicity, ART regimen, study treatment, cirrhosis status
   - all available results on: urinalysis protein and protein, creatinine clearance (CrCl), spot protein and creatinine (and protein/creatinine ratio)
   - study treatment modifications
   - study treatment adherence
   - ARV modifications

Notes:

1. The protocol requires grading of events according to The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, which is available on the RCC website: http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx
2. The protocol requires the collection of signs and symptoms, diagnoses, laboratory events that
    a. are Grade ≥3 post-entry
    b. that led to a change in treatment (excluding indications for RBV dose modification) regardless of grade, or
    c. that met ICH, EAE or SAE guidelines regardless of grade.

    In addition, all creatinine, creatinine clearance (CrCl) and urinalysis results are required. Urine spot protein and creatinine are repeated in participants who develop new proteinuria or glucosuria, an increase from entry glucosuria or proteinuria by ≥1+, or who develop an increase in creatinine of 0.4 from entry or CrCl <50, until resolution.
3. Summary tables are based on events reported on the following forms: EVW0314, EVW0315, F2860 (Hematology), F2861 (Chemistry), LBW0144 (Creatinine Clearance) and will not explicitly include events reported on EAEs to DAIDS. Before the database is finalized, the data manager will ensure that all EAE events deemed 'reportable' and included in the SDMC AR001AES table are reflected on the study CRFs.
4. Events with date of onset or specimen date prior to the first study treatment dose will be excluded.
5. Deaths will be described separately and not included in the safety summary tables.

✓ SDAC validation: All programs generating variables as study-specific will be validated (e.g. variable to indicate participants who experienced a renal toxicity event). User-specific inputs in standard programs will also be validated.

4.2.2 Pregnancy

a) List and outcome, if any.

4.2.3 Deaths

a) List and description, if any.

4.2.4 HIV-Related Measures and Changes in ARV Regimen

a) A summary of CD4 cell count and percent CD4 and changes from baseline at study visits.
b) A summary of HIV RNA detection status at study visits.
c) A listing of changes in HIV regimens during the study.

✓ SDAC validation: All programs generating variables as study-specific will be validated (e.g. CD4 and HIV RNA categories, changes over time).

4.2.5 Virologic Failures

a) HIV Virologic Failure

- Details on participants on ART with undetectable HIV RNA at entry who experience HIV-1 virologic failure (as defined in the protocol), including adherence to study regimen and ARV medications, and dose modifications to study medications and ARVs.

b) HCV Virologic Failures

- Details on participants who experience HCV virologic failure (as defined in the protocol), including ARV regimen, adherence to study regimen and ARV medications, dose modifications to study medications and ARVs, and the following baseline information: HCV RNA, cirrhosis status, race and ethnicity, HCV genotype, development of resistance-associated variant at the time of virologic failure.

✓ SDAC validation: All programs generating variables as study-specific will be validated (e.g. HIV breakthrough, HCV breakthrough).

4.3 Primary Objectives

4.3.1 SVR12

Purpose: To address the primary HCV virologic response objective to assess the proportion of participants who attain SVR12 in each study arm.

a) Two-sided 90% confidence interval around the observed SVR proportion using the Wilson confidence limits, per protocol.
b) Two-sided 95% confidence interval around the observed SVR proportion using Clopper-Pearson limits, to line up with the Gilead study (in consideration of joint manuscript).
c) For the non-SVRs, reasons for failure will be provided: detectable HCV RNA after treatment discontinuation, HCV virologic failure (VF) as determined by the site, unavailable HCV RNA result, other.

Note on the primary HCV virologic endpoint:

1. SVR12 is defined in the protocol as HCV RNA < lower limit of quantification (LLOQ), either target detected (TD) or target not detected (TND), at 12 weeks after treatment discontinuation. The sample within the week R+12 visit window, as described in Section 2.6, which is closest to the targeted time will be used. If there is no HCV RNA sample within this window, then the participant will be considered SVR12 failure, unless there are preceding and subsequent HCV RNA measurements that are both <LLOQ (either TD or TND).
2. Participants not providing SVR data (e.g. due to early study discontinuation) will be included and counted as SVR failures.

✓ SDAC Validation: Derivation of SVR12 variable will be validated. The analysis program that summarizes SVR12 and calculates confidence intervals will also be validated.

✓ Data sources for the primary endpoint SVR12: HCVRNALDMS (LDMS data table), F1601 (off study CRF table), F4003 (off treatment CRF table), F0010 (patient visit CRF data table),

STATUS (data table on key patient characteristics and date variables including date of last dose of study treatment), CMW0029 (concomitant medication CRF table to censor data at initiation of alternate HCV treatment in case any participants erroneously remained on study when alternate HCV treatment was initiated), SPW0455 (HCV RNA specimen tracking CRF table).

4.3.2 Safety

Purpose: To address the primary safety objective.

a) Number of participants meeting the criteria noted below. The worst graded event per person over time will be used.
b) Summaries on all reported adverse events and laboratory events and listings described in Section 4.2.1 provide supplemental information on safety.

Notes on the primary safety endpoint:

1. Occurrence of Grade ≥3 or higher adverse event (diagnosis, sign, symptom or laboratory event), SAE according to ICH criteria, or AE reported as the reason for permanent discontinuation of study treatment during study treatment and up to 30 days after study treatment discontinuation.
2. Event that is ongoing at the same grade from prior to study treatment initiation will be excluded.

- ✓ SDAC Validation: The program deriving the indicator variable on meeting the safety endpoint criteria as described above will be validated.
- ✓ Data sources for the primary safety endpoint: EVW0314, EVW0315, F2860 (Hematology), F2861 (Chemistry), HXW0148 (Signs and Symptoms History), LBW0144 (Creatinine Clearance), STATUS (data table on key patient characteristics and date variables including date of last dose of study treatment), CMW0029 (concomitant medication CRF table to censor data at initiation of alternate HCV treatment in case any participants erroneously remained on study when alternate HCV treatment was initiated).

4.4 Secondary Objectives

4.4.1 Tenofovir PK

Purpose: (Secondary Objective 1) To assess the impact of LDV/SOF and HIV PI/r co-administration

Note: The tenofovir PK analysis will be described and conducted by the study pharmacologist separately.

4.4.2 HCV Virologic Responses

Purpose: (Secondary Objective 3 and 8) To assess the proportion of participants who attain SVR4 and SVR24 in each study arm. To evaluate kinetics of HCV RNA during treatment and after treatment discontinuation.

a) Listing of each participant's HCV RNA results will be provided with calculated visit weeks.
b) Number and percent of participants with SVR4 with a two-sided 90% confidence interval.
c) Number and percent of participants with SVR24 with a two-sided 90% confidence interval. (SAP Version 2: This will be provided as part of SVR24 supplement to the Primary Final Analysis Report.)
d) Number of participants with relapse.

Notes:

1. SVR4 is defined in the protocol as HCV RNA < LLOQ (either TD or TND) at 4 weeks after treatment discontinuation. The sample within the week R+4 visit window, as described in Section 2.6, which is closest to the targeted time will be used. If there is no HCV RNA sample within this window, then the participant will be considered SVR4 failure, unless there are preceding and subsequent HCV RNA measurements that are both <LLOQ (either TD or TND).
2. SVR24 is defined in the protocol as HCV RNA <LLOQ (either TD or TND) at 24 weeks after treatment discontinuation. Sample after 20 weeks after treatment discontinuation that is closest to the targeted, not followed by any result ≥LLOQ, will be used.
3. Relapse is defined as <LLOQ (either TD or TND) for the latest HCV RNA result prior to the end of study treatment and HCV RNA ≥LLOQ after treatment at a subsequent visit.

✓ SDAC validation: All programs generating variables as study-specific will be validated (e.g. HCV RNA variable for each study visit, HCV relapse, SVR4 and SVR24).

4.4.3 Development of HCV Resistance Mutations

Purpose: (Secondary Objective 7) To evaluate emergence of HCV resistance mutations in participants who fail to attain SVR12 with retreatment with LDV/SOF (+/- RBV).

- Listing of participants with any targeted HCV resistance mutations detected in any sample tested with the SVR12 outcome.

✓ SDAC Validation: Programs that generate variables as study-specific will be validated (e.g. indicator variable on HCV resistance mutation).

4.4.4 HIV RNA and CD4+ Cell Counts

Purpose: (Secondary Objective 9) To assess the influence of LDV/SOF-based retreatment on HIV-specific parameters, including maintenance of HIV-1 RNA < 50 copies/mL for participants on antiretrovirals and CD4+ cell count during treatment.

This is addressed in Section 4.2.4.