General Instructions

The Visit Evaluation form should be completed at every protocol treatment and follow-up visit. Note that Follow-Up Weeks 196, 200, 204, 208, 212, 216, 228, and 240 correspond to 4, 8, 12, 16, 20, 24, 36, and 48 weeks post treatment. Per protocol the laboratory testing (liver panel) plus telephone assessment can replace outpatient visit at weeks 208 and 212 if ALT at the preceding assessment (week 204 and 208 respectively) is <300 U/L for men or <200 U/L for women and bilirubin is normal (total bilirubin < 1.5 mg/dL or direct bilirubin < 0.5 mg/dL).

This form captures information on adverse effects, concomitant medications, study medications, and minimal physical assessment items obtained via patient interview and medical record review. When information in the medical record conflicts with information provided by the patient, the medical record is normally considered to be the accurate source, although there may be instances when the information provided by the patient is more up to date or accurate. In this instance, the information from the patient may be used.

The coordinator is responsible for obtaining the information recorded on this form. In non-English speaking patients, the interview may be performed through a certified interpreter. While a trained translator is preferred, a family member or friend of the patient (who speaks fluent English and the native language of the patient) may be acceptable for this role as determined on an individual basis.

Specific Instructions

Patient ID**:**	Record the Patient ID in the top right hand corner of each page.
Date of Evaluation:	Record the date (month/day/year) that corresponds to the protocol visit.
Protocol Timepoint:	Record the timepoint associated with the treatment or follow-up visit.
Last Protocol Visit:	Record the date of the last protocol visit for a treatment or follow-up timepoint. This date will be used as a reference when asking the patient to provide information since the last protocol visit.

Section I: Adverse Effects

Check “Yes” or “No” for each adverse effect listed to indicate whether or not the patient reports that he/she has had any of the signs, symptoms, or conditions, or has been told by a doctor that he/she has the condition, since the last protocol visit.

Adverse Effects:

Fatigue: Defined as a lack of energy, weariness, or chronically tired. Characterized as prolonged weakness or tiredness that is not relieved by adequate rest, sleep or by the removal of other stressful factors. The patient may feel rested but with daily activity feel tired or feel tired after awakening and throughout the day a lack of energy or weariness or chronically tired.

Trouble sleeping: The inability to fall asleep, remain asleep throughout the night, or awake feeling refreshed.

Headache: Pain in the head that requires medical intervention and medication on a regular basis, such as migraines.

Dizziness: Refers to an impairment in spatial perception and stability, including but not limited to vertigo, disequilibrium, or lightheadedness.

Depression: Defined as having extreme feelings of sadness, dejection, lack of worth, and emptiness. There may be a loss of sense of pleasure in normal activities, decreased energy, change in sleeping habits, and feelings of hopelessness. Clinical definition of depression is the presence of these symptoms for at least a two week period. Information provided by the patient should be used in conjunction with results from the CES-D.

Weight loss: **Unintentional** loss of weight.

Decreased appetite: a loss of desire to eat even though you may not have eaten enough to supply your body with its basic caloric requirements.

Vision problems: Any type of visual disturbance including but not limited to blurred vision, halos, blind spots, or floaters.

Nausea: Uncontrolled persistent nausea and needed to seek medical intervention.

Upper abdominal pain: Pain in the upper abdominal area.

Breathing problems: Difficult or uncomfortable breathing.

Joint aches: Characterized as pain or stiffness in one or more joints.

Diarrhea: Frequent or loose bowel movements of unformed, watery stools

Vomiting: Uncontrolled or persistent vomiting.

Upset stomach: An unsettled stomach, indigestion, or a condition of impaired digestion.

Muscle pain: Any pain in the muscles. Do not include pain that is due to recent overuse or exercise.

Rash: eruption or breaking out of the skin, an inflammation of the skin.

Skin irritation: Skin redness or any other type of irritation of the skin, not including rash.

Flu-like symptoms: These may include but are not limited to fever, cough, headache, muscle aches, chills, sweating, fatigue, congestion, sore throat, nausea, diarrhea, and loss of appetite.

Hair loss: temporary or permanent loss of hair not associated with hereditary loss of hair that occurs with aging.

Other: any other sign, symptom, or condition that the patient reports as currently experiencing.

Adverse Events: Check “Yes” or “No” to indicate if the patient experienced any adverse events since the last protocol visit. If “Yes”, also report the event on the Adverse Event Log. At a minimum, the following criteria should be used as a guide for recording events on the Adverse Event Log. These guidelines are not all inclusive and the recording of events remains at the discretion of the investigator. A symptom or

condition that is present but does not reach one of these levels may still be recorded as an adverse event.

1) A symptom or event that requires discontinuation of study medication.
2) A newly diagnosed symptom or event that requires a written prescription for treatment.
3) A newly diagnosed symptom or event that results in a referral to another provider.
4) Any grade 3 or 4 event according to the NCI Common Toxicity Criteria.

If the adverse event meets the criteria of a Serious Adverse Event then complete the MedWatch form too.

Section II: Concomitant Medications

Prescription Medications: Check "Yes" or "No" to indicate if the patient has started a new medication or stopped taking a medication since the last protocol visit. If Yes, update the Concomitant Medication Log. Prescription medications are defined as those medications prescribed by the patient's medical provider(s). Instruct the patient to bring a complete list of medications or the prescription pill bottles to all protocol visits.

Herbal/natural medications: Check "Yes" or "No" to indicate if the patient is currently taking any herbs, herbal or natural medicines. Check "Unknown" if it is not known whether the patient is taking any herbs, herbal or natural medications.

Vitamins and minerals: Check "Yes" or "No" to indicate if the patient is currently taking any vitamins or minerals. Items are to be taken as a separate supplement and may be in pill or liquid form. If yes, check the appropriate type. Check "Unknown" if it is not known whether the patient is taking any vitamins or minerals.

Multi-vitamin: a supplement containing three or more vitamins or minerals but no herbs, hormones, or drugs. Common brand names include but are not limited to Centrum or One-a-Day. There are also multi-vitamins available as generic and store brands or prenatal vitamins.

Vitamin D: supplement specific to vitamin D and may be in combination with calcium. Do not include if part of a multi-vitamin supplement. Common vitamin D and calcium combinations include but are not limited to Os-Cal, Viactive, and Caltrate+D. Record vitamin D and calcium combinations as both Vitamin D and Calcium supplements.

Vitamin E: supplement specific to vitamin E. Do not include if part of a multi-vitamin supplement.

Folate: supplement specific to folate. May also be referred to as folic acid or vitamin B_9. Do not include if part of a multi-vitamin supplement.

Iron: supplement specific to iron. Do not include if part of a multi-vitamin supplement.

Calcium: supplement specific to calcium and may be in combination with Vitamin D. May be noted as calcium citrate, calcium carbonate, or calcium lactate. Do not include if part of a multi-vitamin supplement. Common vitamin D and calcium combinations include but are not limited to Os-Cal, Viactive, and Caltrate+D.

Record vitamin D and calcium combinations as both Vitamin D and Calcium supplements.

Other: a vitamin or mineral other than those listed, and not part of a multi-vitamin supplement.

HBV Antivirals: Check "Yes" or "No" to indicate if the patient is currently taking any antiviral therapy for hepatitis B, other than the study drugs.

If Yes, record the following information for each treatment the patient received:

Antiviral therapy: Record the appropriate code for the treatment. If you know that the patient received interferon or an oral antiviral but do not know the specific agent, record -3 (Unknown) for the antiviral therapy code.
Note: Tenofovir (TDF) = Tenofovir disoproxil fumarate
Tenofovir (TAF) = tenofovir alafenamide fumarate

Date started: Record the month, day, and two digit year that the treatment was started. If any piece of the date is not known, record "Unk" [-3].

Date stopped: Record the month, day, and two digit year that the treatment was stopped. If any piece of the date is not known, record "Unk" [-3]. If the patient is currently on this treatment, do not complete the date stopped fields and check "Currently on Therapy".

Section III: Study Medication

This section applies to when the participant is on treatment. Study drug should be dispensed at every protocol visit and patients should be instructed to return unused tablets of tenofovir and used vials of peg-interferon at every protocol visit.

Patients should be encouraged to keep a diary to track doses of study drug. Pill/vial counts along with the diaries should be used to monitor compliance and to facilitate adherence counseling.

Study medication: Check "Yes" or "No" to indicate whether or not the patient has taken study medication since the last study visit.

If Yes, record the following information:

Return tenofovir: Check "Yes" or "No" to indicate whether or not the patient returned the bottle of tenofovir along with any unused tablets of tenofovir. Complete the Study Drug Log.

Return peg-interferon: Check "Yes" or "No" to indicate whether or not the patient returned the used vials of peg-interferon. Complete the Study Drug Log. If timepoint is after week 24 or the patient was randomized to tenofovir alone, check "N/A".

Return diary: Check "Yes" or "No" to indicate whether or not the patient returned a completed diary that was used to track doses of study drug since the last protocol visit.

Interview questions: Ask the patient the 4 general questions about how well they are able to adhere to the study drug regimen and then record their responses.

Change in dose: Check "Yes" or "No" to indicate whether or not there was a prescribed change in dose (decrease or increase) of either study medication since the last protocol visit. If Yes, complete the Dose Change Log. A prescribed change in dose is defined as a decrease or increase in study drug dose as prescribed by a medical health care provider. A skipped/missed dose of study drug is not considered to be a change in dose.

Adherence counseling: Check "Yes" or "No" to indicate whether or not the patient was counseled on the importance of adherence to the study drug regimen, including the discussion of barriers to adherence, strategies to overcome barriers, and goals for adherence to therapy.

Section IV: Physical Assessment

Height: **A height measurement must be obtained at Weeks 192 and 240.** Record the patient's height at the time of the physical exam. Ask the patient to remove shoes prior to obtaining the measurement. Check "inches" or "cm" (centimeters) to indicate which unit of measure was used. If for any reason (e.g. wheelchair-bound, equipment failure, etc.) a standing measurement is not obtained, record "Not done".

Weight: Record the patient's weight at the time of the physical exam. Check "lbs" (pounds) or "kg" (kilograms) to indicate the unit of measure used. If weight was not measured then check "Not done".

Blood pressure: Record the patient's systolic and diastolic blood pressure in mmHg. Blood pressure should be obtained after the patient has been seated with both feet flat on the floor for at least 5 minutes. If blood pressure was not measured then check "Not done".

Current conditions: Indicate whether or not the following conditions are present at the time of the evaluation and calculate the CTP score if appropriate.

Ascites: Defined as an excess of fluid in the peritoneal cavity that is mild, moderate or marked on ultrasound (ultrasound report of minimal fluid around the liver does not meet the definition) or is progressive on serial physical examinations or requires diuretic therapy. ***The physician investigator should determine the degree of ascites for study purposes.***

Hepatic encephalopathy: Characterized by recurrent disturbances of consciousness, impaired intellectual function, neuromuscular abnormalities, metabolic slowing on EEG and elevated serum ammonia levels. Symptoms include changes in mental state, consciousness, behavior and personality, decrease in performance of simple self-care tasks, and muscle spasms or rigidity. Also known as portal-systemic encephalopathy.

Medical record must indicate one of the following:

- Asterixis
- Clinical alteration in mental status with reversibility with therapy
- Two or more episodes of confusion consistent with encephalopathy

Grades *(to be determined by the physician investigator)*:

1 = Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition or subtraction

2 = Lethargy or apathy, minimal disorientation for time or place, subtle personality change, inappropriate behavior
3 = Somnolence to semi-stupor, but responsive to verbal stimuli; confusion, gross disorientation
4 = Coma

Hepatic hydrothorax: ascites associated pleural effusion.
Medical record must indicate the presence of ascites or diuretic usage and one of the following:

- Paracentesis lab report
- Liver ultrasound report
- Liver CT report
- Liver MRI report

Variceal bleeding: Defined as GI bleeding from varices present in the esophagus or stomach based on an endoscopy showing either:

- Direct evidence of variceal bleeding (bleeding varix, red wale sign)
- Moderate varices with no other site of bleeding identified and historical evidence for clinically significant upper GI bleeding.

Portal hypertensive bleeding: gastrointestinal bleeding associated with portal hypertension.

Medical record must include an endoscopy report showing evidence of active or recurrent bleed within 48 hours of an episode.

Gilbert's Syndrome: a condition in which the liver doesn't properly process bilirubin, and is the result of an inherited gene mutation. Also known as constitutional hepatic dysfunction and familial nonhemolytic jaundice.

Hemolytic disease: a disorder in which the red blood cells are destroyed prematurely (e.g. hemolytic anemia).

Fanconi syndrome: a disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine, instead of being reabsorbed. **NOTE: If the following tests are performed as standard of care, results should be reported to the Nephrotoxicity Monitoring Group: aminoaciduria or beta-2 microglobulin.**

CTP (Child-Turcotte-Pugh):

CTP score is calculated using the algorithm below.

		Number of points		
Items	**Units**	**1**	**2**	**3**
Serum albumin	g/dL	>3.5	2.8-3.5	<2.8
Serum total bilirubin No Gilbert's Syndrome No hemolytic diseases Not receiving Ribavirin	mg/dL	<2.0	2.0-3.0	>3.0
Serum total bilirubin Presence of Gilbert's Syndrome Hemolytic disorder such as patients receiving Ribavirin*	mg/dL	<4.0	4.0-7.0	>7.0
INR		<1.7	1.7-2.3	>2.3
Ascites		None	Mild^ or Moderate (diuretic responsive)	Severe‡ (diuretic refractory)
Encephalopathy		None	Mild^ (Grade 1-2; precipitant induced)	Severe‡ (Grade 3-4; chronic)

Note that if, in the opinion of the investigator, the patient has Gilbert's syndrome or a hemolytic disorder (e.g., patients receiving ribavirin) the level of the serum total bilirubin may be increased to as high as 3.99 mg/dL without considering the total bilirubin to be sufficiently elevated for the patient to receive a score of 2 in the CTP scoring system.

^ Mild means readily controlled by standard medical therapies.

‡ Severe means difficult to control or uncontrollable by optimal, maximally tolerated medical therapies.

The score is the sum of the scores for albumin, bilirubin, INR, ascites and encephalopathy (range 5-15)**.**

Class A = 5-6
Class B = 7-9
Class C = 10-15

Section V: Abdominal Imaging

Tests performed: Check "Yes" or "No" to indicate whether or not the patient has had any liver related imaging tests such as MRI, CT, or ultrasound since the last protocol visit.

If Yes, complete the following information.

Date of test: Provide the date of the most recent test performed since the last protocol visit, regardless of the type of imaging. If any piece of the date is unknown, record "Unk" [-3] in that field.

Tests performed: Check all liver related imaging tests (CT, MRI, ultrasound) that were performed since the last protocol visit. If another type of imaging test was performed, check "Other" and specify the test in the space provided.

Evidence of HCC: Check "Yes" or "No" to indicate if there was any evidence of HCC on any of the imaging test reports. If Yes, complete the HCC form.

Refer to the AASLD guidelines for HCC surveillance on the HBRN Study website: http://www.hepbnet.org/research/docsharing/?startFolder=%5CReference+Documents

Section VI: Bone Mineral Density

Test performed: Check "Yes" or "No" to indicate whether or not the patient has a bone mineral density test performed since the last protocol visit. Bone density tests should be performed according to standard of care when clinically indicated. Potential indications for testing include:

- history of osteopenia or osteoporosis
- history of prior fracture
- history of malabsorption
- thyrotoxicosis, anorexia nervosa
- hyperparathyroidism
- women ≥65 years of age
- men ≥70 years of age
- postmenopausal women under age 65 with risk factors for osteoporosis
- women with premature menopause (<50 years) or long periods of amenorrhea
- vitamin D level < 30 ng/mL
- Asian race
- Type 2 diabetes
- tobacco use
- BMI < 23
- family history of osteoporosis, medications
- alcohol excess (≥2 drinks per day)
- minimal weight-bearing exercise.

If Yes, complete the following information.

Date of test: Provide the date of the most recent test performed since the last protocol visit. If any piece of the date is unknown, record "Unk" [-3] in that field.

Evidence of Osteopenia: Check "Yes" or "No" to indicate if there was any evidence of osteopenia, defined as a decrease in the amount of calcium and phosphorus in the bone that can cause bones to be weak and brittle, and increases the risk for broken bones.

Evidence of Osteoporosis: Check "Yes" or "No" to indicate if there was any evidence of osteoporosis, defined as the thinning of bone tissue and loss of bone density over time.

Section VII: Biospecimens

Samples obtained: Check "Yes" or "No" to indicate if blood samples were obtained at this visit.

If yes, check "NIDDK Repository", "Central lab", "Genetics", or "Immunology study" to indicate which samples were obtained.