Protocol

Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand.

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Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand.

Short title:

HCV-HIV co-infected patient cohort in Thailand.

2. Protocol team and investigators' names and contact information

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3. Project Summary

Title: **Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand**

This is a study of HCV treatment using the standard regimen of pegylated-interferon plus ribavirin in HIV co-infected patients participating in the PHPT cohort study. The treatment will be implemented in conjunction with gastro-enterologists/hepatologists by the internists responsible for the HIV treatment.

Chronic hepatitis C virus (HCV) infection is responsible for several severe and life threatening complications, which are worsened by HIV co-infection. HIV-HCV co-infected patients are at a higher risk of death compared to HIV mono-infected individuals, even if HIV replication is suppressed on antiretroviral treatment.

The goal of HCV antiviral treatment is to cure HCV infection. Curing HCV infection allows fibrosis regression, improved clinical outcomes. In addition, individuals who have been cured are no longer contagious to other individuals, therefore widespread access to HCV treatment may contribute to the control of the HCV epidemic.

A combination of injectable pegylated-interferon with oral ribavirin is currently the recommended regimen for the treatment of hepatitis C in the setting of HIV co-infection. They are administered for 24 weeks in HCV mono-infected patients but need to be administered for one year in HIV-HCV co-infected patients. Newer drugs, such as the first generation HCV protease inhibitors (boceprevir, telaprevir), administered concomitantly, are used in patients who have not been cured using peg-interferon + ribavirin, or may allow for a shorter treatment.

PRIMARY OBJECTIVE

1. To determine the percentage of patients according to genotypes with sustained virological response 6 months after treatment discontinuation (SVR).

HCV TREATMENT

- Peg-interferon alpha 2-b (a subcutaneous injection of 1.5 micrograms/kg once a week)
- Ribavirin dosing according to HCV genotype and bodyweight; dose adjustment in case of anemia.

SAMPLE SIZE

A total of 60 patients will be enrolled in the study: 15 HCV-HIV co-infected patients in a first part and 45 patients in a second part, if funding is obtained from the GFATM and/or other funding sources.

STUDY POPULATION

Screening: HIV infected patients with a positive anti-HCV test will be approached for screening if they are at least 18 years old, participate in the PHPT cohort study, have evidence of control of HIV replication and have a CD4 cell count ≥200 cells/mm^3 if currently receiving antiretroviral HIV treatment (on the same anti-HIV regimen for at least 12 weeks); or HIV RNA load ≤5000 copies/ml CD4 cells ≥500 cells/mm^3if not receiving antiretroviral treatment.

Inclusion Criteria

- Evidence of chronic HCV infection for at least 6 months before study entry (at least one detectable HCV viral load, i.e. ≥17 IU/mL, with an antibody test positive at least 6 months before the HCV RNA load result)
- Fibrosis Stage F2-3-4 determined by transient elastography (Fibroscan or other similar equipment). During the first part of the study, priority will be given to patients with Fibrosis Stage F2-3.
- Negative pregnancy test (on the day of inclusion).

Main exclusion criteria (see complete list in the protocol)

- Anemia and thrombocytopenia

- Severe liver damage, advanced stage cirrhosis or cancer
- Uncontrolled diabetes, Uncontrolled thyroid dysfunction
- Retinopathy
- Creatinine clearance <50 mL/min (Cockcroft)
- Disease associated with the immune system
- Significant heart problems
- Severe neuropsychiatric conditions Contra-indication to study treatment (including pregnancy or lack of effective contraception in the participant or female partner)
- Other exclusion criteria related to the use of ribavirin and peg-interferon
- Any conditions that, in the investigator's judgment, may compromise the follow up.

FOLLOW UP AND STUDY PROCEDURES

During the screening process, the following assessments will be performed in this order to determine eligibility for HCV treatment:

- HCV RNA load (if undetectable, the screening process will be terminated)
- Fibrosis assessment by transient elastography
- SGPT/ALT, SGOT/AST, gamma glutamyl transferase (GGT), conjugated and unconjugated bilirubin, albumin, alkaline phosphatase, glucose, triglycerides, prothrombin time (PT), HDL & LDL cholesterol, alpha fetoprotein (AFP), thyroid-stimulating hormone (TSH), vitamin D plasma level, abdominal sonogram
- Ophthalmologic examination if diabetes mellitus or hypertension
- CBC
- Electrocardiogram
- Chest X-ray
- Creatinine, urine protein
- Beck's Depression Inventory
- Pregnancy test (for female participant or partner of male participant) if childbearing age
- IL28B polymorphism.

After HCV treatment initiation, patients will be monitored for safety and antiviral efficacy at 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 weeks (end of treatment) and 6 months after treatment discontinuation.

Treatment will be discontinued earlier in patients who do not achieve early viral response, i.e. a decrease of at least 2 $\log_{10}$ HCV RNA IU/mL after the first 12 weeks of HCV therapy.

DURATION OF THE STUDY

First enrollment: April 2014

Planned enrollment duration: until April 2015

Planned date of last visit completed: November 2016

Biological analyses completed: November 2017

Final analyses and submission of manuscripts: November 2018

STATISTICAL CONSIDERATIONS

It is expected that up to two thirds of the patients will be cured of their HCV infection. With 60 subjects, there would be 71% power to conclude that an observed SVR rate of 66% is significantly greater than 50% in a two-sided exact binomial test of nominal type I error of 5%.

All patient characteristics recorded at baseline will be summarized using frequencies, medians and confidence intervals. All endpoints will be summarized using appropriate statistical methods. Details on these analyses will be further provided in the statistical analysis plan before their initiation.

4. Background information

4.1. Epidemiology

It is estimated that up to 160 million individuals or 3% of the global population are chronically infected with Hepatitis C virus (Lavanchy, 2011)

In Thailand, about 0.5% of new blood donors were carriers of HCV antibodies in 2009, a prevalence that has been declining since 1995. A study among military conscripts between 2005 and 2008 found that the HCV prevalence was 2.2% among 5,246 young Thai men and 8.4% in 500 HIV-1 sero-positives (Jatapai et al., 2010).The prevalence of HCV infection in the HIV population seems higher than in non-HIV populations. Among HIV-infected patients participating in the PHPT cohort study (NCT00433030), 1,956 were tested and 105 patients (5.4%) were found HCV antibody positive (data as of July 1, 2013). Of 1,435 HIV-infected pregnant enrolled in a PMTCT trial conducted between 1996 and 2000 (PHPT-1,NCT00386230), 69 women (4.9%) were HCV antibody positive (Ngo-Giang-Huong et al., 2010).

The main route of HCV transmission is the exposure to infected blood. Common routes of transmission include, through blood transfusion, intravenous drug use, high risk sexual activity, solid organ transplantation from an infected donor, occupational exposure, hemodialysis, household exposure, birth to an infected mother and intranasal cocaine use.

4.2. Hepatitis C virus and genotypes

HCV is a positive single-strand RNA *Hepacivirus*, a member of the family *Flaviviridae*. Its 9.6 kb genome consists of 5' and 3' untranslated regions flanking a single open reading frame (ORF) encoding structural and non-structural proteins. Structural proteins include the capsid or core and 2 envelope glycoproteins, E1 and E2. Among the 6 non-structural proteins, NS3 is the protease; NS5A is an RNA binding phosphoprotein involved in RNA replication and virus assembly; and NS5B is the viral RNA-dependent RNA polymerase.

HCV genotypes. HCV replicates using error-prone polymerases that lack proofreading activity. For this reason, HCV exists in an infected individual as a mixture of closely related viruses or quasi species. Phylogenetic analysis of HCV nucleotide sequences showed that HCV variants fall into 6 major genotypes with specific geographic distributions. The highest diversity is found in sub Saharan Africa and in South and Southeast Asia. In western countries, HCV genotype 1 is the most prevalent genotype. HCV genotypes 1 and 4 are predominant in central Africa while genotype 2 is predominant in western Africa. In Southeast Asia, genotypes 3 and 6 are predominant. In western countries, genotypes 1 and 2 are predominant. In Egypt, where HCV epidemic is related to injections for the treatment of bilharzia using non sterile equipment, genotype 4 is predominant. HCV genotypes 1 and 4 are intrinsically more resistant to interferon-alpha treatment than genotypes 2 and 3. The determination of HCV genotype helps determine the optimal dose and duration of treatment. Several recombinants of HCV genotypes have also been reported. Subtypes have also been described and found relevant to treatment, for example subtype 1a is more difficult to treat than 1b.

4.3. Natural history

Acute infection. The majority of acute infections are asymptomatic (70% to 80%). If symptomatic, the clinical characteristics of acute HCV infection are similar to those of other acute viral hepatitis and may appear3 to 12 weeks after contamination. The virus can be detected in the serum within1 to 2 weeks after contamination (Thimme et al., 2001) (Farci et al., 1991). The level of HCV RNA rises rapidly during the first few weeks, and then peaks between 10^5 to 10^7 IU/ml (Chen & Morgan, 2006). Specific serologic testing is required to identify the etiologic cause but up to 30% of patients test negative for anti-HCV at onset of their symptoms. Antibodies to HCV are detectable by enzyme immunoassay approximately 1 to 3 months after contamination. Serum alanine aminotransferase (ALT/SGPT) levels rise 2 to 8 weeks after exposure (often >10 times the upper limits of normal). Symptoms can last several weeks. Fulminant liver failure is rare. (Chen & Morgan, 2006)

Some patients with acute HCV infection clear the virus spontaneously within a mean time of about 10 weeks from diagnosis to spontaneous clearance.(Corey, Mendez-Navarro, Gorospe, Zheng, &

Chung, 2010)Predictors of spontaneous viral clearance include: HCV genotype 3, low HCV RNA load, female sex, and IL28B CC allele (SNP rs12979860 at the IL28B locus).

Chronic HCV infection. 50% to 80% of acute infections are not cleared and become chronic. Even if the risk of progressive hepatic injury from HCV infection varies with some patients showing slower progression and others progressing rapidly to cirrhosis, the risk of cirrhosis increases with the duration of infection, and becomes significant after 20 years. Patients with cirrhosis may develop HCC (1–7% per year). Increased alpha-fetoprotein levels are predictive of HCC. Risk factors of disease progression include duration of infection, age at the time of acquiring infection, sex, alcohol consumption, immunosuppression, obesity, insulin resistance, co-infection with hepatitis B virus (Imazeki, Yokosuka, Fukai, Hiraide, & Saisho, 2003), elevated aminotransferase, and genetic factors (Asian Pacific Association for the Study of the Liver (APASL) Hepatitis C Working Party et al., 2007). An assessment of the degree of fibrosis is thus an important information to decide as when treatment should be started.

Co-infection with HIV. Specific issues are related to HIV co-infection. In HIV infected patients with significant immunodeficiency, the diagnosis of infection may require the use of virologic tests (HCV RNA assay), as anti-HCV antibodies may not appear or become undetectable. Thus, a negative serologic test in a patient with a low CD4 cell count cannot rule out chronic HCV infection. Each infection (HIV and HCV) has a negative impact on the progression of the other. The prognosis of each infection is worsened by the other and co-treatment can be challenging.

4.4. Treatment of HCV infection

Currently, pegylated interferon (peg-interferon) plus ribavirin combination therapy is the standard of care recommended by the 2012 Thailand Practice Guideline for management of chronic hepatitis C (Thai Association for the Study of the liver.Thailand practice guideline for management of chronic hepatitis B and C, 2012) as well as the Asian Pacific Association for the Study of the Liver (APASL) (Asian Pacific Association for the Study of the Liver (APASL) Hepatitis C Working Party et al., 2007) and the Guide for Evaluation and Treatment of Hepatitis C in Adults Coinfected with HIV (U.S. Department of Health and Human Services, Health Resources and Services Administration, Last Updated: January 14, 2011).

According to the Thai Guidelines, the treatment should be administrated to HIV-HCV co-infected patients at least aged of 18 years old, with confirmed chronic HCV infection. The pegylated interferon and ribavirin treatment should be continued for 48 weeks.

Off note, access to HCV treatment is currently limited in Thailand, not included in the universal coverage system and the number of physician trying to deliver this treatment is very limited.

Treatment response monitoring. The hepatitis C virus load (HCV RNA load) is used to monitor the efficacy of the treatment. HCV RNA load is usually measured before treatment begins (at baseline) and at week 4, week 12, at the end of treatment (week 24 or 48), and then 24 weeks after the end of treatment (week 48 or 72). At baseline, a high HCV RNA load indicates that the viral cure (see SVR below) may be less likely to occur. A rapid virological response (RVR), i.e. if the HCV RNA is undetectable after 4 weeks of treatment predicts a high likelihood of achieving viral cure. Early virological response (EVR) is achieved when HCV RNA cannot be detected after 12 weeks of treatment (complete EVR) or when HCV RNA drops by at least 2 $\log_{10}$IU from the baseline level by Week 12 (partial EVR). However, SVR does not occur in all patients achieving EVR. Failure to achieve an EVR predicts a low likelihood of achieving viral cure in patients treated with pegylated interferon alfa and ribavirin. Studies have shown that only 1% of patients who do not achieve an EVR will achieve an SVR. Failure to achieve an EVR is therefore used as a criterion to discontinue HCV treatment (Davis, 2002). End of treatment response (ETR) is achieved when HCV RNA is not detected at the end of treatment. Finally, sustained virological response (SVR) indicates viral cure. It is achieved when HCV RNA is not detected six months after treatment discontinuation.

Pegylated versus standard interferon. Treatment with peg-interferon alfa-2b has been found more effective than standard interferon alfa-2b,with ribavirin, for HCV infection in HIV-infected patients (Carrat et al., 2004).

Role of viral and host factors. Response to interferon-alpha depends on both viral and host related factors. Interferon alfa inhibits HCV replication by inducing host interferon-stimulated genes (ISG)

involved in antiviral functions. It is not associated with viral resistance but chronic HCV infection confers resistance to exogenous interferon alfa in the liver by interfering with host interferon response and ISG expression. Ribavirin enhances hepatic gene responses to peg-interferon (Feld et al., 2007). Pegylated Interferon alfa (peg-interferon) and ribavirin (RBV) remains the standard of care in patients infected with genotype 2/3 although recently developed direct-acting antiviral drugs (DAAs) may allow for interferon-free treatment in the near future.(Liang & Ghany, 2013)

The response rate to peg-interferon + ribavirin combination varies according to ethnicity, some host genetic characteristics and viral genotypes. Single nucleotide polymorphisms (SNPs) within or adjacent to the IL28B gene have been associated with a better response to peg-interferon + ribavirin therapy in patients infected with genotypes 1 and 4, but less strongly in patients with genotypes 2 and 3. For example, SNPs coding for IFN lambda-3, strongly correlate with spontaneous clearance of hepatitis C virus HCV (about 30% of acute infections with viral genotypes 1 and 3) (Pedergnana et al., 2012; Rao et al., 2012) as well as a better response to peg-interferon + RBV in individuals infected with genotype 1 HCV (Ge et al., 2009). However, the effect of the IL28B polymorphism in patients infected with Genotypes 2, 3 is attenuated when compared to Genotype 1 (Mangia et al., 2010) or 1 and 4 (Jiménez-Sousa, Fernández-Rodríguez, Guzmán-Fulgencio, García-Álvarez, & Resino, 2013). The IL28B rs12979860 SNP is the strongest predictor of an SVR to peg-interferon + ribavirin therapy in HCV Genotype 4 patients (De Nicola et al., 2012). The prevalence of IL28B CC polymorphism is high in Thailand and South East Asia (Thomas DL et al., 2009). Also female sex may play a favorable role in HCV clearance (Rao et al., 2012).

Tolerance and safety aspects. Anemia is the main adverse effect associated with the use of ribavirin. The risk of ribavirin-induced anemia may be dependent on some inosine triphosphate pyrophosphatase (ITPA) gene polymorphisms (Domingo et al., 2012). Genetic variants leading to ITPA deficiency protect against hemolytic anemia in hepatitis-C-infected patients (Fellay et al., 2010; Naggie et al., 2012). Associations between risk of anemia and ribavirin trough concentrations have also been reported (Arase et al., 2005).

Specific treatment issues in HIV-HCV co-infection. The recommended duration of HCV treatment in HIV co-infected patients is 48 weeks, when using peg-interferon and ribavirin. Possible drug-drug interactions between HIV and HCV drugs need to be considered. No significant pharmacokinetic interactions occur between pegylated interferon alfa and ribavirin. However, several antiretrovirals are metabolized via the cytochrome (CYP) P450 enzyme pathway and interferons are known to down-regulate CYP P450 enzymes. A study in healthy volunteers showed that pegylated-interferon alfa-2a had no effect on CYP2C9, CYP2C19, CYP2D6 or CYP3A4, while there was a small inhibitory effect on CYP1A2 (Brennan, Xu, & Grippo, 2013). Ribavirin inhibits inosine-5'-monophosphate (IMP) dehydrogenase and *'in vitro'* reduces phosphorylation of certain NRTIs, suggesting a potential antagonism between ribavirin and formation of intracellular NRTI-triphosphate moieties. Within the multinational AIDS PEGASYS Ribavirin International Co-infection Trial (APRICOT) the impact of ribavirin on the intracellular phosphorylation and plasma pharmacokinetics of NRTIs were investigated in in 56 HIV/HCV co-infected patients. Ribavirin (800 mg/day) did not significantly affect the intracellular phosphorylation or plasma PK of 3TC, d4T, and ZDV in HIV/HCV co-infected patients (Rodriguez-Torres et al., 2005). Increases in the certain drug toxicity can also occur with HIV-HCV co-treatment. For example, it is recommended to avoid the combination of ddI with ribavirin and/or pegylated interferon alfa-2b, which could cause or worsen clinical toxicities (i.e. increased risk of mitochondrial toxicity) ("PI ribavirin 2011.pdf," n.d.) (Merck, 2013).

4.5. The PHPT Cohort:

A cohort study is currently conducted in the PHPT hospital network in Thailand (PHPT Cohort NCT00433030) to document the outcomes of the national program for access to antiretroviral treatment. Adult patients enrolled in this cohort are followed and treated for HIV infection according to the standard of care. They are screened for co-infections including Hepatitis C infection. XXX adult patients have been enrolled, 74% are female, current median age is 41.8 years-old. The HIV treatment outcome is assessed regularly; results have been published (Fregonese et al, 2012). This HCV treatment study will be conducted in this context.

5. Study specific objectives and design

5.1. Study objectives

Primary objective

1. To assess the percentage of patients according to genotypes with sustained virological response 6 months after treatment discontinuation (SVR).

Secondary objectives

2. To assess the safety of treatment: incidence of serious adverse events associated with study treatment (peg-interferon and ribavirin) as defined by ICH GCP (International conference on harmonization (ICH) Good Clinical Practice or GCP), 1996).

3. To report on operational issues to serve as a source of information for further HCV treatment implementation within the existing health care system.

4. To assess the percentage of patients with early virological response (EVR) at week 12 of treatment.

5. To assess the risk of premature treatment discontinuation for tolerance or safety reasons.

6. To assess the plasma concentrations of ribavirin in Thai patients and its relationship with the occurrence of anemia.

7. To assess the impact of HCV treatment on HIV replication.

8. To assess the quality of life of patients at baseline, during and after treatment.

5.2. Study Design

Phase IV, prospective, observational, multicenter, single group, cohort study of HCV chronic infection treatment in HIV co-infected patients in Thailand using the standard treatment of peg-interferon and ribavirin.

6. Study sites and duration of the study

6.1. Study sites

All sites are currently participating in the PHPT cohort study. Staff at the Internal Medicine Departments are highly trained in conducting clinical research on HIV care. Each site is regularly monitored by a PHPT clinical research assistant to ensure that study procedures are implemented according to the protocol and regulations.

Based on the data currently available regarding prevalence of HCV chronic infection at each site, the approximate number of patients to be enrolled per site is listed in Table 1 below:

Table 1: Sites and planned number of subjects

Site	Estimated number of patients to be enrolled	
	First part	Second part
Phayao Provincial Hospital	2	4
Chiangrai Prachanukroh Hospital	2	5
Nakornping Hospital	3	6
Sanpatong Hospital	2	3
Lampang Hospital	-	3
Bhumibol Adulyadej Hospital	-	3
Samutsakhon Hospital	2	3
Chonburi Hospital	2	6
Rayong Hospital	2	3
Hat Yai Hospital	-	3
Maharaj Nakhonratchasima Hospital	-	3
Mahasarakam Hospital	-	3
Total	15	45

6.2. Duration of the study

First enrollment: April 2014
Planned enrollment duration: until April 2015
Planned date of last visit completed: November 2016
Biological analyses completed: November 2017
Final analyses and submission of manuscripts: November 2018

7. Workplan

7.1. Study population

7.1.1 Pre-screening

The study can be proposed to individuals who meet the criteria listed in Table 2.

Table 2: Criteria to select subjects for screening

1	Documentation of a positive HCV antibody test at least 6 months before starting study screening.
2	Current participation in the PHPT HIV cohort study (NCT00433030).
3	Age ≥18 years
4	Two most recent HIV RNA loads ≤400 copies/ml if receiving HIV antiretroviral treatment or HIV RNA loads ≤5000 copies/ml if not receiving antiretroviral treatment.
5	Either two CD4 counts ≥200 cells/mm^3 within 1 year before screening if receiving antiretroviral treatment (lower CD4 cell count is acceptable if attributed to hypersplenism); or CD4 cells ≥500 cells/mm^3 if not yet receiving antiretroviral treatment.
6	Have been on the same anti-HIV drugs and doses, for 12 weeks or longer, and intend to stay on these drugs the first 24 weeks of the study or Not yet treated for their HIV infection because they do not need it and intend not to start HIV treatment for the first 24 weeks of the study No use of didanosine, zidovudine or stavudine (adjustment of antiretroviral treatment should be completed at least 12 weeks before starting treatment)

Subjects who meet all criteria listed in Table 2 will be approached, informed about the study and proposed participation. Before any study procedures, they must formally consent for participation in the study (see Patient Information Sheet and Informed Consent form in Appendix 1, 2).

7.1.2. Inclusion and exclusion criteria

The population enrolled in the study will be HIV infected individuals meeting all screening and inclusion criteria, and none of the exclusion criteria listed in Tables 3 and 4.

Only patients who meet all the following selection criteria can be enrolled in the study.

Table 3: Inclusion Criteria

HCV RNA loads	Have evidence of chronic HCV infection for at least the last 6 months before study entry (at least one detectable HCV viral loads, i.e. ≥17 IU/mL, with an antibody test positive at least 6 months before the HCV RNA load).
Liver	Fibrosis Stage F2-3-4 as determined by transient elastography (Fibroscan or other similar equipment). During the first part of the study, priority will be given to patients with Fibrosis Stage F2-3.
Contraception	Negative pregnancy test (on the day of inclusion).

Table 4: Exclusion criteria

Hematology	Anemia (hemoglobin level <10 g/dL) Platelets <50,000 /mm^3
Liver	Evidence of decompensated liver disease manifested by presence or history of ascites, variceal bleeding, or hepatic encephalopathy or Child-Pugh score greater than A (Participants with documented or suspected hepatic cirrhosis must have either serum alpha-fetoprotein level of 50 ng/ml or less within 24 weeks prior to study entry; or serum alpha-fetoprotein greater than 50 ng/ml but no greater than 400 ng/ml with an imaging procedure that shows no evidence of a hepatic tumor, both obtained within 24 weeks prior to study entry.) Suspicion or evidence of liver cancer. Hepatitis B (this exclusion criteria will be applied only to the first part of the protocol).
Endocrinology	Uncontrolled diabetes. Uncontrolled thyroid dysfunction (thyroid-stimulating hormone, TSH).
Ophthalmology	Retinopathy.
Kidney function	Creatinine clearance <50 mL/min (Cockcroft).
Immunology	Disease associated with the immune system (such as Crohn's disease, ulcerative colitis, active rheumatoid arthritis, lupus, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, cryoglobulinemia with clinical manifestations including leukocytoclastic vasculitis, scleroderma, or severe psoriasis).
Cardiology	Significant heart problems, such as active symptomatic coronary artery disease.
Neurologic and psychiatric conditions	Have uncontrolled seizures. Have a history of severe mental problems. Uncontrolled depression or other psychiatric disorder, such as untreated Grade 3 psychiatric disorder, Grade 3 disorder not amenable to medical intervention. Both selective serotonin reuptake inhibitors and other classes of antidepressants are allowed. Active drug or alcohol abuse or dependence that, in the opinion of the study investigator, could interfere with adherence to study requirements.

Other exclusion criteria related to the use of ribavirin and peg-interferon	Pregnancy or no contraception if participant is a woman. Pregnancy or no contraception in the female partner of a male participant. No use of condoms, sperm donation or participation in any other fertilization procedures if participant is a man. Breastfeeding. Other contra-indications to ribavirin (see Package Insert). Allergy to peg-interferon or ribavirin. Current administration of didanosine, zidovudine or stavudine. Have taken the following drugs within 6 weeks before study entry: rifampin, rifabutin, pyrazinamide, isoniazid, G-CSF (filgrastim), GM-CSF (sargramostim), or ganciclovir.
Others	Have taken any of the following drugs within 6 months before study entry: interleukins, interferons, therapeutic HIV vaccine, thalidomide, pentoxifylline, dinitrochlorobenzene (DNCB), thymosin alpha, thymopentininosiplex, polyribonucleoside, ditiocarb sodium, hydroxyurea, systemic corticosteroids, azathioprine, 6-mercaptopurine, cyclosporin A, or any investigational drug. Any conditions that, in the investigator's judgment, may compromise the follow up.

7.1.3. Discontinuation criteria

Participation in the study. A study site co-investigator may decide to end a subject's participation in the study if, in his/her own judgment, such a participation would be detrimental to a subject's health or well-being. However, all efforts should be made to inform the study team and discuss options prior such a decision.

Discontinuation of treatment. For the discontinuation of therapy prior to week 48, the protocol will follow the recommendations of the "Guide for evaluation and treatment of Hepatitis C in adults co-infected with HIV" (See Figure 1) (Sulkowski, Cheever, & Spach, 2011), i.e.:

"*HCV treatment should be stopped earlier than 48 weeks if on-treatment HCV RNA response futility criteria are met at treatment week 12 or 24.*

Treatment should be discontinued in patients who at week 12 do not achieve an early partial virologic response (≥ 2 log_{10} decline in HCV RNA level from baseline) or complete virologic response (undetectable HCV RNA at treatment).

Patients who have an early virologic response, but do not achieve an undetectable HCV RNA at treatment week 12, should be re-tested at week 24. If HCV RNA levels remain detectable at week 24, treatment should be discontinued.

In addition, treatment may need to be discontinued in patients who develop severe adverse effects to treatment or intolerable treatment-related side effects."

These patients will then continue to receive the standard of care, off treatment.

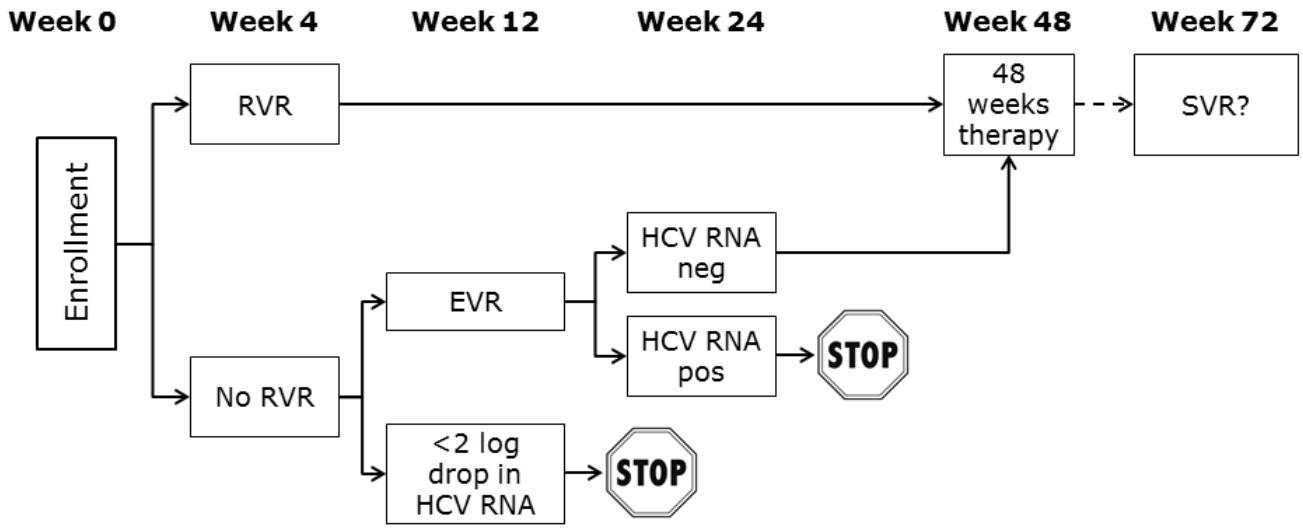

Figure 1: Decision tree for discontinuation of treatment

Discontinuation of the study. The study could be discontinued if required by Thailand health authorities or sponsors.

7.2. Implementation, data collection and monitoring procedures

7.2.1. Assessments

7.2.1.1 Screening Assessments

The assessments listed in Table 5 will be performed to determine if a subject can participate in the study.

The **first investigation** performed will be the measurement of HCV RNA load to assess the need for treatment. Only patients with detectable HCV RNA load will continue to be assessed for potential participation in the study.

Table 5: Screening assessments

Category	**Examination**
Virology	HCV RNA load
Medical history	Interview and/or chart review
Liver imaging	Fibrosis assessment by transient elastography Liver ultrasound exam
Clinical chemistries	SGPT/ALT, SGOT/AST, gamma glutamyl transferase, bilirubin (conjugated, unconjugated), Albumin, Alkaline phosphatase, glucose, triglycerides, prothrombin time (PT), HDL & LDL cholesterol, alpha fetoprotein (AFP), creatinine, urine protein, thyroid-stimulating hormone (TSH), vitamin D level
Hematology	CBC including platelets
Ophthalmology	Ophthalmologic examination (fundus) if diabetes mellitus or hypertension
Central nervous system	Beck Inventory Depression scale (nurse, counselor)

Heart, lungs	Electrocardiogram, chest X-ray,
Contraception	Pregnancy test (for female participant or partner of male participant) if childbearing age
Host genetic	IL28B polymorphism

7.2.1.2 Assessments during the study

The detailed assessments are listed in Table 6.

Fibrosis assessment. For enrollment, fibrosis assessment will be performed using the transient elastography ultrasound based technique. It measures the stiffness of the liver, which is well correlated with the fibrosis stage assessed by liver biopsy. It has been extensively used as a non-invasive method for detection of cirrhosis in patients with chronic liver disease (Foucher et al., 2006). In addition, to further characterize patients enrolled in this study, two scores will be calculated:

- the AST to platelets ratio index (APRI score) will be calculated at baseline as it has been shown to predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C (Wai et al., 2003).
- The FIB4 score (Bruno et al., 2011), which has also been used for the evaluation of fibrosis. A cut-off value >3.25 is consistent with significant (F2–F4) fibrosis; its sensitivity was 70%and specificity 86–97% in a study conducted in HIV/HCV co-infected persons(Sterling et al., 2006). It is calculated using the following formula:

  (age [years]×AST [U/L])/(platelet count [×109/L])×(ALT [U/L]1/2))

Depressive symptoms will be screened using the Beck Depression Inventory (Thai version). This auto-administered scale, which consists of 21 questions to assess the severity of depression, has been extensively used in various studies related to HCV treatment.

Table 6: Follow up Assessments

	Scr.	Baseline	Wk2	Wk4	Wk8	Wk12	Wk16	Wk20	Wk24	Wk28	Wk32	Wk36	Wk40	Wk44	Wk48	6 months post-Treatment
HCV RNA load	X			X		X			X						X	X
Counseling	X	X	X	X					X						X	X
Beck's Depression Inventory scale (more often if necessary, see Section 7.2.2.2, page 20)	X			X		X			X			X			X	
SF-36 Scale (quality of life)		X							X						X	X
Pregnancy test (for female participant or partner of male participant) if childbearing age	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with differential	X	X	X	X	X	X	X		X		X		X		X	X
SGPT (ALT)	X	X		X		X		X		X		X		X	X	X
Alkaline phosphatase, albumin, bilirubin (conjugated, unconjugated), gamma-glutamyl-transferase (GGT), HDL, LDL cholesterol, triglyceride, prothrombin time, SGOT (AST), proteinuria (random)	X														X	X
Electrolytes (Na+, K+, Cl-, HCO3-)		X				X			X						X	
Creatinine	X	X		X	X	X		X		X		X			X	X
Glucose	X	X				X			X						X	
TSH	X	X							X						X	
Alpha fetoprotein (AFP), Vitamin D, IL28B polymorphism, HCV genotype	X															
Chest X-Ray, Electrocardiogram, Abdominal sonogram, Ophthalmologic examination (fundus) if diabetes mellitus or hypertension, Fibrosis assessment	X															
Ribavirin plasma level (further assessments as needed)			X	X												
Plasma and cell pellets collection & storage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRF completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total blood volume (mL)	20	8	6	9	6	18	3	3	18	3	3	3	3	3	20	18

7.2.2. Safety procedures

7.2.2.1 Anemia

Monitoring

Anemia, the most frequent side effect of ribavirin, will be carefully monitored (see Table 6).

Grade 4 will be immediately reported to the PHPT coordination center.

Management

The principles for the management of anemia will be based on "Guide for evaluation and treatment of Hepatitis C in adults co infected with HIV" (Sulkowski, Cheever, & Spach, 2011).

"The initial and primary management of symptomatic anemia (hemoglobin level below 10 g/dL) is ribavirin dose reduction. The ribavirin dose reduction most often consists of a gradual two-step process:

- ***Step 1**: reduce by 200 mg for patients receiving 800-1200 mg/day or reduce by 400 mg for patients receiving 1400 mg/day;*
- ***Step 2:** reduce by another 200 mg if the hemoglobin level has not improved 2 weeks after step 1 reduction (and if the patient's current dose is 800 mg or greater). If the patient has a sharp decline in hemoglobin, particularly during the first 4 weeks of therapy, or the patient has moderate to severe symptoms from the anemia, most experts would recommend immediately reducing the ribavirin dose to 600 mg/day (without a step-wise reduction).*
- *The ribavirin dose should not be reduced to lower than 600 mg/day.*
- *Patients undergoing ribavirin dose reduction should have close monitoring of hemoglobin level levels, typically every 1-2 weeks; the frequency of monitoring can decrease when the hemoglobin level improves and stabilizes. Ribavirin should then remain at the reduced dose."*
- *Treatment discontinuation should be considered in case of persisting severe anemia or major clinical consequences of anemia."*

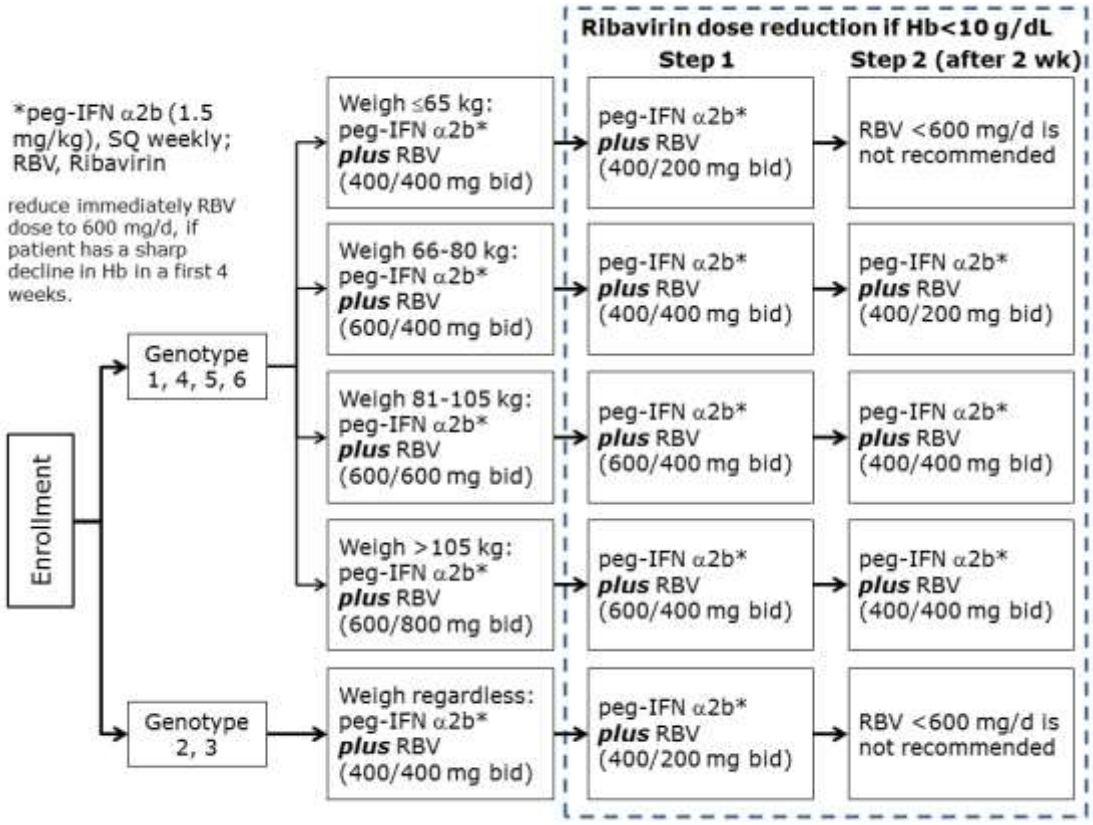

Figure 2: Dose reduction for the management of anemia

7.2.2.2. Depression

Monitoring

A common side effect of peg-interferon is depression. The study nurse will be trained before the beginning of the study to specifically search for signs and/or symptoms of depression. The screening for depression and other side effects will be performed at every visit. In addition, the Beck's Depression Inventory (BDI) will be used to screen for depression at the screening visit, 4, 12, 24, 36 and 48 weeks after the beginning of treatment and more frequently if needed.

A BDI score greater than 20 should be immediately reported to the PHPT coordination center.

Management

Mild depressive symptoms during treatment do not typically require peg-interferon dose reduction or treatment discontinuation. In case of any mild depressive symptoms, more frequent monitoring of depression severity will be implemented, typically once weekly by visit or phone. Antidepressants, such as selective serotonin re-uptake inhibitors, will be prescribed and specialized advice sought as necessary.

Moderate or severe depression mandates an evaluation by a mental health professional (e.g., psychiatrist, clinical psychologist) and dose reduction of peg-interferon (peg-interferon alfa-2b from 1.5 to 1.0 mcg/kg). In some cases, a larger initial peg-interferon dose reduction may be needed (reduce peg-interferon alfa-2b from 1.5 to 0.5 mcg/kg). Importantly, all persons found to have moderate or severe depression should be evaluated for suicidal ideation. For patients suffering from severe depression or active suicidal ideation, peg-interferon injection (and ribavirin treatment) will be discontinued and the patient will be explained that this treatment cannot be administered in his/her case. Medical follow up will continue. For the study, the evolution of depression will be documented as completely as possible but study procedures will be adapted to the case. In some cases, patients may require hospitalization for management.

7.2.2.3. Other potential adverse events

Monitoring

Numerous other adverse events are expected. Specific symptoms and lab abnormalities likely to occur will be systematically monitored at each visit using detailed questions in the CRF.

Management

They will be managed according to guidelines by the site investigators. Multiple resources are available on the internet, for example "Hepatitis C Treatment Side Effects Management Chart" of the US Department of Veterans Affairs (http://www.hepatitis.va.gov/products/patient/side-effects-chart.asp). The protocol team, including experienced hepatologists from Thailand and France, will be consulted if necessary. Recommendations for the management of clinical side effects of the treatment are described in the Appendix 4.

7.2.3. Implementation

Roles of protocol team members, investigators and co-investigators

The PHPT Clinical Trial Unit (CTU) team is responsible for the overall organization and monitoring of the study, as well as data entry, data management and statistical analysis in compliance with Good Clinical Practices and, as necessary, reporting to sponsors. The technical team in charge of the study at the CTU will be composed of 1 physician, 1 coordinator, 1 nurse in charge of the safety monitoring, at least 4 clinical research assistants, 1 data manager, 3 data entry technicians, 1 laboratory technician, 1 logistician, 1 translator and 1 secretary. In addition, the PHPT CTU pharmacist will oversee the management of study drugs.

The protocol team is responsible for the design of the study, the preparation of the study and its monitoring. Members of the protocol team are not involved in the day to day patient management but may provide suggestions to site investigators in relation with the conduct of the study.

Site co-investigators are responsible for the medical management of the patients, the implementation of the study interventions according to the protocol and the completion of the Case Report Forms (CRFs). At each site, the study teams consist of internists who will implement the study in close collaboration with gastroenterologists, nurses, laboratory technicians, pharmacists and counselors. Study co-investigators and study staff will be trained before the beginning of and during the study to the specific aspects of Hepatitis C treatment management.

The PHPT laboratory staff also monitors the quality control of the site laboratories.

7.2.4. Data collection

The completed CRFs are reviewed and signed by the site co-investigator, then forwarded to the CTU. Upon arrival at the CTU, they are immediately recorded in a tracking database and filed. The tracking database provides updated information on each patient every week, as well as the total number of patients at each stage of follow-up.

Data will be keyed using a double data entry system, and programs check the datasets for range checks on each field within a form, consistency checks between fields on the same form, and between fields on different forms. The data managers generate queries as necessary until final validation of the CRFs. Validated CRFs serve as evidence that the history and clinical data has been recorded, and that all lab tests and procedures have been completed. All serious adverse events will be reported according to GCP. As required by GCP, any change made to an original CRFs/data set is documented. The databases are stored in My-SQL format in central computers with restricted access and regular backups are made and stored in another place to prevent accidental loss of data. All important operations are described in procedures within our IRD UMI 174 quality management system, accredited according to the standard of ISO 9001:2008.

As for previous studies conducted by our group, investigators and co-investigators will facilitate any audit of the data, procedures at study sites and at the laboratory by independent external monitors sent by sponsors.

The PHPT laboratory staff also monitors the quality control of the site laboratories.

7.2.5. Laboratory assessments

The PHPT laboratory is responsible for the centralized laboratory exams, i.e., HCV RNA quantification, IL-28 polymorphism, ribavirin level, HIV viral load, and samples repository. The blood samples will be stored until the completion of the study, two years after the date of last study visit for repeated/confirmation assessments if needed. The PHPT laboratory is located in Chiang Mai, under the Faculty of Associated Medical Sciences, Chiang Mai University.

The PHPT laboratory has received the laboratory accreditation by the Association of Medical Technologists of Thailand (AMTT) and the ISO 15189 accreditation by the DMSc, MoPH, Thailand.

HCV RNA load will be measured at the central PHPT laboratory using the commercial Abbott RealTime HCV (Abbott Laboratories) assay. Performance will be controlled through participation in the Quality Control for Molecular Diagnostics (QCMD, Scotland, UK) external quality assessment program for HCV RNA. Other laboratory evaluations will be performed at the site laboratories.

7.3. Study drugs

<u>Peg-interferon alpha 2-b</u>

First dose: 1.5 micrograms/kg (subcutaneous injection)

Mode of administration:

The study nurse will read with each patient the booklet ‘Patient diary for PEG-INTRON monotherapy or PEG-INTRON and Rebetol’ in Thai language (MSD), which provides information on peg interferon and ribavirin and specific instructions for the preparation and injection of peg-interferon. The nurse will give each patient this booklet.

For the first injection, the study site nurse at the hospital will prepare the syringe and proceed to the injection, observe and record the occurrence of side effect for at least the first 3 hours after administration. The second injection, one week later, can be done by the patient, under supervision of an experienced nurse at the hospital. The nurse will evaluate if the patient is able and willing to perform following injections by him/herself. As long as the patient does not appear able or willing to perform injections, he/she will be welcome to return to the hospital for injections.

The patient will be provided with an Injection Card, reporting all the injections received with date, time and person who administered the dose. During the first weeks, the nurses will regularly call the patient to make sure that the drugs are correctly administered and how to deal with adverse events.

Ribavirin

First dose:

- For genotypes 2, 3: ribavirin 400 mg in the morning and in the evening (i.e. 800 mg daily).
- For genotypes 1, 4, 5 and 6: the ribavirin dose is
    - 800 mg/day, if bodyweight <65 kg,
    - 1000 mg/day, if bodyweight between 66–80 kg,
    - 1200 mg/day, if bodyweight between 81–105 kg,
    - 1400 mg/day, if bodyweight >105 kg.

Mode of administration:

Ribavirin should be given in two divided doses (e.g. 400/400 mg bid, 600/400 mg bid, 600/600 mg bid, or 800/600 mg bid) at the end of the meals, in the morning and evening.

At each visit, patients will be asked to bring back the remaining study drug's vials or bottles (Peg-interferon alpha 2-b and ribavirin) even if they are empty to assess adherence.

The study site pharmacist will be responsible for storage, dispensation including drug counseling, and drug accountability.

7.4 Statistical considerations

Considering the proportion of HCV circulating genotypes in Thailand and the high proportion of Asian people with IL28B CC polymorphism, it is expected that up to two thirds of the patients may be cured of their HCV infection.

7.4.1. Endpoints

For each objective, the following definitions of endpoints will be used:

Primary objective 1: To assess the percentage of patients according to genotypes with sustained virological response 6 months after treatment discontinuation (SVR).

The SVR is the percentage of patients with sustained virological response among the patients who have taken at least one dose of HCV treatment.

Secondary objective 2: To assess the safety of HCV treatment: incidence of serious adverse events as defined by ICH GCP ("International conference on harmonization (ICH) Good Clinical Practice (GCP)," 1996).

The cumulative risk of any serious adverse event will be assessed 6, 12 and 18 months after HCV treatment initiation using a Kaplan-Meier curve. The distribution of serious adverse events will be provided by type of events (in particular hematology, central nervous system).

Secondary objective 3: To report on operational issues.

Operational issues will be described and documented to serve as a source of information for further HCV treatment implementation. Specific endpoints will include: the proportion of patients screened and enrolled in the study who have completed the first 24 and 48 weeks of treatment, incidence of adverse events by severity grade, compliance with study visit schedule, adherence to HCV and HIV

treatment (peg-interferon injections, number of missed doses of oral treatment during the last week, pill count), number/percentage of patients able to perform self-injections.

Secondary objective 4: To assess the percentage of patients with early virological response at week 12 of treatment (EVR).

The EVR is the percentage of patients with early virological response among the patients who have taken at least one dose of HCV treatment.

Secondary objective 5: To assess the risk of premature treatment discontinuation for tolerance or safety reasons.

The cumulative risk of premature HCV treatment discontinuation will be assessed using a Kaplan-Meier curve.

Secondary objective 6: To assess the plasma concentrations of ribavirin in Thai patients. The analysis will be descriptive. Ribavirin trough plasma concentration will be determined and compared to published data in non-Asian populations.

Secondary objective 7: To assess the impact of HCV treatment on HIV infection. HIV viral load will be monitored.

Secondary objective 8: To assess the effect of the treatment on quality of life. The score provided by SF-36 will be used as a measure of the quality of life.

7.4.2. Sample size

We recognize that the small number of study participants, i.e. 15 in a first part and, if possible, an additional 45 patients in a second part, is due to funding considerations rather than statistical considerations. The precision of the estimate will be limited. For example, the 95% confidence interval (CI) of a 60% SVR rate in a group of 60 patients is 47% to 72%. Higher rates would have a narrower CI. With 60 subjects, there would be 71% power to conclude that an observed SVR rate of 66% is significantly greater than 50% in a two-sided exact binomial test of nominal type I error of 5%.

However, no data are currently available on HCV treatment in the HIV infected population in Thailand, and data carefully collected from this relatively small number of patients undergoing treatment will help better understand feasibility issues

7.4.3. Progress reports

To inform the co-investigators about the study and its progress, a meeting will be held before the beginning of the study, then every year. In addition, a monthly progress report, prepared by the data management team at the PHPT CTU, will be provided to all co-investigators, including the Program Scientists during the trial.

7.4.4. Monitoring of the study

The protocol team will conduct a formal review of the study progress 3, 6, and 12 months after the first enrollment and then every year until completion of the study. At each meeting, the progress of the study will be presented by the principal investigator including safety profiles. More meetings may be organized by the principal investigator as necessary.

7.4.5. Analyses

All patient characteristics recorded at baseline will be summarized using frequencies, medians and confidence intervals.

All endpoints will be summarized using appropriate statistical methods.

Details on these analyses will be further provided in the statistical analysis plan before their initiation.

8. Ethical considerations

8.1 Possible risks including preventive or alleviative measures

8.1.1. Potential Risks to Participants

All patients may experience side effects of the treatments used in the study. Although there are no preventive measures for most side effects of the drugs, in particular anemia and depression, the protocol include close follow up of the patients with regular and systematic monitoring of hemoglobin, signs of depression and other likely adverse effects as detailed in Section 7.2.2, to alleviate the consequences of these adverse effects.

The study involves collection and analysis of data from consenting patients receiving antiretroviral treatment, anti HCV treatment approved and recommended by the Thai FDA, and laboratory monitoring including repeated blood draws that may cause pain, swelling, bruising, and phlebitis.

8.1.2. Potential benefits

Patients may benefit from participating in this study. This study cannot guarantee the success of treatment but it can be beneficial to the patient once HCV viral load decreases, reducing the hepatitis risks and complications caused by hepatitis C infection.

8.2. Recruitment and informed consent (see Patient Information Sheet and Informed Consent Form in Appendix 1, 2)

All co-investigators have passed a training curriculum course on Human Subjects Protection. Specific training will be provided to co-investigators, nurses and counselors prior to the implementation of the study. Training will address the specific aspects of the study, the Good Clinical Practice (GCP) requirements, and procedures for protection of human subjects in clinical research.

Consent form

Written informed consent must be obtained from the subject before any screening procedures. The consent form has been drafted in as practical and non-technical language as possible to ensure that it is understandable to all study subjects. The information included in the consent form has been reviewed by members of the PHPT Community Advisory Board. The informed consent describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The consent document specifies the subject's freedom to withdraw his/her participation at any time without compromising access to future medical care. Any changes to the consent document will be submitted to the relevant Ethical Committees.

Consent process

All nurses/counselors who will provide counseling have received training for counseling as well as for Protection of Human Subjects in clinical research and Good Clinical Practice (GCP).

At each site, the nurses/counselors will individually discuss with each potential participant the information included in the consent. Consenting subjects will provide written informed consent for their participation in the study after receiving specific information and counseling. A copy of the consent form will be given to the subject.

The consent form will include names and contact details of the site co-investigator and local Ethic Committees. A copy of the consent document will be given to the patient. In addition, study participants may contact personnel from the Clinical Trial Unit 24 hours a day by phone. The original consent forms will be kept in a locked cabinet at the site. If new information relevant to the patient's consent or her willingness to continue participation in the trial becomes available, the participants and potential participants will be informed.

A notation that written informed consent has been obtained will be made on the patient's case report form. A copy of the consent document will made available to the patient.

- Step 1: The nurses/counselors explain the study to the potential subject verbally, providing relevant information (purpose, procedures, risks, benefits, alternatives). The potential subject is provided ample opportunity to ask questions.

- Step 2: Following this verbal explanation, the potential subject will be provided with a study informed consent form and sufficient time to consider whether or not to participate in the

research. "Sufficient time" can range from minutes to hours or days. The potential subject may discuss their participation with relative, contact the local ethics committee for this study (named in the informed consent form) or the hospital director to ask questions about the study, their rights and study-related injury.

- Step 3: After allowing the potential subject time to read the study informed consent form, the nurses/counselors answer any additional questions, propose the subject to consent to participate in the research and sign the consent form.

- Step 4: The nurses/counselors will provide the subject with any significant new findings which may modify the subject's willingness to continue participation.

To prevent a possible risk of a conflict of interest and reduce the risk that patients do not enroll in this cohort under undue influence, the consent process will be primarily performed by the nurses/counselors

8.3. Protection against risk

8.3.1 Institutional Review Board

Prior to the initiation of the study, the protocol and patient consent documents will be reviewed and approved by a national ethics committee at the Thai Ministry of Public Health, the Ethics Committee at the Faculty of Associated Medical Sciences, Chiang Mai University, and at each local hospital site. Subsequent modifications will be submitted for approval before implementation.

8.3.2 Expedited Adverse Experience Reporting

Some adverse events are expected, such as anemia and depression. The protocol includes specific evaluations (hemoglobin level, depression scale) to detect such events so adequate action will be taken to correct these effects (see section 7.2.2). Patients will be informed during the counseling process. In some cases, treatment will have to be interrupted. All clinical adverse events and abnormal laboratory values will be recorded and graded. For severe toxicity and serious adverse events, as defined by International conference on harmonization (ICH) GCP ("International conference on harmonization (ICH) Good Clinical Practice (GCP)," 1996) possibly related to drugs, an Expedited Adverse Experience Report (EAE) will be sent to the Ethics Committees, and program scientists, within three business days of awareness. If a subject dies, events prior to and at the time of death will be transcribed from hospital records, and possible cause(s) of death will be investigated. Management of toxicities and dose modifications for patients will be managed with experts' advice.

8.3.3 Confidentiality

Every effort will be made to maintain the confidentiality of the study participants. All site staff receives initial and ongoing training on Human Subjects Protection and confidentiality. To minimize this risk, study participants will not be identified by name on any study documents but will be identified by the provided patient identification number. All evaluation forms, laboratory specimens, reports and other records will be identified only by the patient identification number to maintain subject confidentiality. All records will be kept in a locked file cabinet in the clinical research unit. All computer entry and networking programs will be processed with patient identification number only. Clinical information will not be released without the written permission of the patient except when necessary for monitoring by the PHPT Clinical Trial Unit (CTU) monitoring staff or the Ministry of Public Health.

8.3.4 Biohazard Containment

As the transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be used by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US Centers for Disease Control. All infectious specimens will be transported using requirements for shipping infectious substances.

8.3.5 Compensation

Compensation, medical care and other services to be provided to the subjects who may be affected by any complication and policy regarding research related Injuries.

Immediate necessary care is available free of charge to mothers and her infant in the case of medical problems related to participation in this study. However, the study is not responsible for treatments unrelated to the study and no financial compensation will be provided (see Patient Information Sheet Appendix 1).

8.3.6 Other related ethical aspects

The subject information sheet is written in Thai language, and physician or hospital's names, contact address and telephone number have been included.

9. References

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Appendices

Appendix 1: Patient Information Sheet (English Language)

Patient Information Sheet

Title of Study: Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand

Short title: HCV-HIV co-infected patient cohort in Thailand

Purpose

You are currently followed within the "Observational cohort of HIV infected adults and children in the PHPT network hospital" for your HIV infection. It was determined that you have antibodies against the virus that causes Hepatitis C (HCV). When such antibodies are detected, this is usually because the person has been infected with this virus. Some people infected by this virus can clear the infection. However, in others, the infection becomes chronic and a specific treatment is needed to clear the infection. The measure of HCV-RNA load can determine if the virus is still present and replicating. You may need a treatment if the virus is detectable and replicating.

You are being asked to participate in a research study "Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand". This form, along with discussions with your physician, will provide you with detailed information about the study so that you can decide if you want to participate. Your participation in this research study is voluntary. You may discontinue your participation at any time. Refusal to participate will not involve any loss of benefits to which you are otherwise entitled.

Nature of the Study

Chronic Hepatitis C infection is caused by a virus, "Hepatitis C virus" (HCV). It is responsible for various severe and life threatening complications, which are worsened by HIV co-infection.

The goal of HCV antiviral treatment is to cure HCV infection, and it is expected that more than 50% of the patients will be cured of their HCV infection. The cure allows better clinical outcomes and quality of life. Moreover, individuals who achieve viral clearance are no longer contagious for other individuals.

This study is supported by the Global Fund. During the first year of this study, 15 Hepatitis C chronically infected patients will be proposed enrollment for treatment. If funding is available, in a second time an additional 45 patients will be enrolled.

The treatment proposed is the currently recommended regimen for the treatment of hepatitis C in the setting of HIV co-infection, i.e. a combination of injectable pegylated-interferon with oral ribavirin.

12 sites will participate in the study. They will be provincial/regional hospitals throughout Thailand: Phayao hospital, Chiang Rai Prachanukroh Hospital, Nakornping Hospital, Sanpatong hospital, Lampang Hospital, Chonburi Hospital, Maharaj Nakhonratchasima Hospital, Samutsakhon Hospital, Rayong Hospital, and Hat Yai Hospital, Bhumibol Adulyadej Hospital and Mahasarakam Hospital.

Study Procedures for You.

Prior to entry into this study, you will undergo specific tests to see if you qualify for the study. This includes medical history taking, physical examination, liver imaging, and blood tests.

Before starting treatment, we will need to determine if you can safely benefit from the treatment proposed in this study. You will have the following exams: fibrosis assessment, liver ultrasound exam, complete cell blood count (CBC), SGPT, SGOT, bilirubin (conjugated, unconjugated), albumin, alkaline phosphatase, glucose, triglycerides, prothrombin time, HDL and LDL cholesterol, a test to look for liver cancer (alpha fetoprotein), a test to look at your thyroid function (thyroid-stimulating hormone or TSH), vitamin D plasma level and ophthalmologic examination if you suffer from diabetes

mellitus or hypertension, an electrocardiogram (EKG), chest x-ray, creatinine, urine protein, a pregnancy test (if you are or if your partner is a woman of childbearing age), Hepatitis C viral load and HCV genotype (if not done before). For all these tests, a total amount of 20 mL or 4 teaspoons of blood will be drawn.

Your physician will give you the results of the tests and, according to these results, explain whether you need treatment and you are entitled to participate in the study. If you can enroll, you can begin therapy.

HCV treatment

According to the current recommendations, you will receive 2 different drugs.

Peg-Interferon 2-b injections, once every week for 48 weeks, the dose will depend on your weight and will be modified if you experience side effects.

The study nurse will provide and read with youthe booklet 'Patient diary for PEG-INTRON monotherapy or PEG-INTRON and Rebetol' in Thai language (MSD), which provides information on peg interferon and ribavirin and specific instructions for the preparation and injection of peg-interferon. The nurse will give each patient this booklet.

For the first injection, the study site nurse at the hospital will prepare the syringe and proceed to the injection, observe and record the occurrence of side effect for at least the first 3 hours after administration. The second injection, one week later, can be done by you, under supervision of an experienced nurse at the hospital. The nurse will evaluate if you are able and willing to perform following injections by him/herself. As long as you do not appear able or willing to perform injections, you will be welcome to return to the hospital for injections."

Ribavirin pills that you will have to take every morning and evening for 48 weeks. The number of pills will depend the type of the Hepatitis C virus you are infected with. It will also depend on you weight and will be modifies if you experience side effects.

The study treatment will be stopped if you experience severe side effects or if the virus is still replicating despite the treatment after the 12 or 24 weeks visits.

Study visits

Each monthly visit will include a physical examination, counseling, adherence and tolerance evaluation, review of lab results, and drug supply renewal. In addition to the routine visits needed for treatment follow up, you will be asked at some visits to complete some questionnaires about the impact of the disease and treatment on your daily life. You may be seen more often if required, in particular for side effects, intolerance, or management of therapy.

A plasma sample will be collected at treatment initiation, 2 weeks later, every 4 weeks until 48 weeks and 6 months after treatment discontinuation.

Assessments

List of assessments:

- Complete Cell Blood Count (CBC) at treatment initiation, 2 weeks later, every 4 weeks until Week 16, every 8 weeks until Week 48 and 6 months after treatment discontinuation.
- Liver inflammation test (SGPT) at baseline, Week 4, every 8 weeks until Week 44, at Week 48 and 6 months after treatment discontinuation.
- Electrolytes at baseline, Week 12, Week 24 and Week 48
- Creatinine at baseline, Week 4, every 4 weeks until Week 12, and then every 8 weeks until Week 36, Week 48 and 6 months after treatment discontinuation.
- Alkaline phosphatase, albumin, bilirubin (conjugated, unconjugated), gamma glutamyl transferase (GGT), HDL, LDL and total cholesterol triglyceride, prothrombin time, SGOT (AST), Proteinuria (random urine protein) at Week 48 and 6 months after treatment discontinuation.
- Thyroid function test (TSH) at baseline, Week 24, and Week 48.
- Glucose at baseline, Week 12, Week 24, and Week 48.

- IL28B CC polymorphism (hereditary characteristic that helps clear the virus).
- Hepatitis C viral load at 4, 12, 24, 48 weeks after HCV treatment initiation and 6 months after discontinuation.
- Depression scale at treatment initiation, Week 4, Week 12, Week 24, Week 36, Week 48 and any visit in case of depression signs.
- Quality of life questionnaire at baseline, Week 24, Week 48 and 6 months after treatment discontinuation
- Pregnancy test (for female participant or partner of male participant) if childbearing age at baseline, Week 4, every 4 weeks until Week 48 and 6 months after treatment discontinuation
- Plasma and cells collection at baseline, Week 2, Week 4, and every 4 weeks until Week 48 and 6 months after treatment discontinuation.
- Amount of HIV in your blood before starting treatment and 6 months after treatment discontinuation.

In case you do not achieve early virological response (a decrease of at least 2 $\log_{10}$ HCV RNA IU/mL after the initial 12 weeks of therapy), it is not recommended to continue the treatment because this means that the treatment is probably not efficacious for you. Thus, HCV treatment will be discontinued but you will continue to receive HIV treatment and care as previously.

During all the study, you should call right away your doctor or the nurse in charge of the study (see contact numbers at the end of this form) if you suffer from any conditions.

The amount of your blood that will be drawn during the study is as follows: about 2 teaspoons at treatment initiation and Week 4 1 teaspoon at Week 2 and Week 8. 1/2 teaspoon at Week 16, Week 20, Week 28, Week 32, Week 36, Week 40, Week 44 and about 4 teaspoons at Week 12, Week 24 and Week 48 and 6 months post treatment.

Table: Planned blood draws

Visit	Screening	First day	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20
Blood draws (teaspoon)	4	2	1	2	1	4	1/2	1/2

Visit	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	6 months post treatment
Blood draws (teaspoon)	4	1/2	1/2	1/2	½	1/2	4	4

	Total
Blood draws (teaspoon)	29 + ½

Known side effects of the treatment used in this study

For peg-interferon alfa-2b:

- Pain (You will be explained in details how to perform the injection of peg-interferon but they may cause pain)
- Fatigue
- vision problems
- fast heart rate, feeling like you might pass out
- fever, chills, body aches, flu symptoms, pale skin, easy bruising or bleeding, unusual weakness
- high fever with severe stomach pain and bloody diarrhea
- pain or burning when you urinate

- severe pain in your upper stomach spreading to your back, nausea and vomiting, fast heart rate
- cough with mucus, feeling short of breath, chest pain, uneven heartbeats
- sudden numbness or weakness, problems with vision, speech, or balance; or
- new or worsening liver symptoms (upper stomach pain, dark urine, jaundice)
- severe depression, hallucinations, thoughts of suicide or hurting yourself

For ribavirin

- problems with your vision
- fever, chills, body aches, flu symptoms
- severe pain in your upper stomach spreading to your back, nausea and vomiting, fast heart rate
- stabbing chest pain, wheezing, feeling short of breath
- chest pain or heavy feeling, pain spreading to the arm or shoulder, nausea, sweating, general ill feeling
- Pale (a sign of anemia) or yellowed skin, dark colored urine, easy bruising or bleeding, confusion, or unusual weakness.

If you experience any side effect you will be given immediate care and treatment and the cost for this treatment will be covered by the study. The study is not responsible for treatments unrelated to the study and no financial compensation will be provided.

A common side effect of peg-interferon is depression. The study nurse will be trained before the beginning of the study to specifically search for signs and/or symptoms of depression. The screening for depression and other side effects will be performed at every visit. In addition, the Beck's Depression Inventory (BDI) will be used to screen for depression at the screening visit, 4, 12, 24, 36 and 48 weeks after the beginning of treatment and more frequently if needed.

In case of any mild depressive symptoms, more frequent monitoring of depression severity will be implemented, typically once weekly by visit or phone. Antidepressants, such as selective serotonin re-uptake inhibitors, will be prescribed and specialized advice sought as necessary. The cost for this treatment will be covered by the study.

Moderate or severe depression mandates an evaluation by a mental health professional and dose reduction of peg-interferon. Importantly, if you experience moderate or severe depression, you will be evaluated for suicidal ideation. If you suffer from severe depression or active suicidal ideation, the treatment will have to be discontinued. Medical follow up will continue. For the study, the evolution of depression will be documented as completely as possible but study procedures will be adapted to the case. If you require to be hospitalized for management of severe depression, the costs will be covered by the study.

Safeguards for Your Health. You will undergo careful check-ups throughout the study. It is very important that you keep all study appointments and take treatments as instructed. At each visit, you will be asked if you have suffered from any other condition, are taking any other medicines or have experienced any adverse events. A treatment for any side effect will be provided to you by your physician whenever needed. If you need to, you may contact us or come to the clinic at any time, even if no visit is planned.

Costs to You for Participation. There is no cost to you for the medication, extra clinic visits or laboratory tests associated with this study. All study participants will receive 300 Baht at each visit to compensate for transportation costs (if justified, the research team at site will compensate for higher transportation costs).

Significant New Findings. Any significant new findings that develop during the study that could affect you or your willingness to continue participation will be made available to you as soon as possible.

Withdrawal from the Study. Your physician could recommend that you withdraw from the study if any condition or severe adverse event developed that would make continued participation harmful to you. In such a case,

- immediate care and treatment will be provided and covered by the study.
- HCV treatment will be discontinued
- your HIV treatment will continue as before.

Alternatives to Participation. You are completely free to choose not to participate in or to withdraw yourself from this study at any time. Your alternative to participation in this study is the usual care available to Hepatitis C co-infection in HIV infected patient at your health care facility.

Confidentiality. Your participation in this study will be kept confidential and will not be communicated to anyone without your written permission.

Confidentiality of Records. Efforts will be made to keep your personal information confidential. Your medical records will be kept confidential. They will be disclosed to you, to those health care providers directly involved in your care. Your record may also be disclosed to the members of the research team, the Thai Food and Drug Administration (FDA), The Ethical Review Committee for Research in Human Subjects at The Ministry of Public Health, local Ethics Committee in your hospital, study staff, study monitors, and study sponsors for study monitoring or auditing purposes. All study forms will be coded by number and your name will not be recorded on these forms. Only these code numbers will be kept in the study database that will be used for analysis. Any publication of this study will not use your name or identify you personally. However, we cannot guarantee absolute confidentiality and your personal information may be disclosed if required by law.

Repository of Blood Specimens. Blood samples taken as part of the study, identified by code, will be kept for confirmation of results, which will be of two years after the last study visit (until November 2018). Blood samples will be stored at the IRD-PHPT Laboratory under Faculty of Associated Medical Sciences, Chiang Mai University, where only approved researchers and staff will have access to them. People who work at the facility will also have access to your samples to keep track of them, but these people won't be able to directly identify you. Blood samples will not be sold or directly used to produce commercial products. You can withdraw your blood samples from the sample repository at any time, and they will be immediately destroyed by autoclave following the standard procedure at the Faculty of Associated Medical Sciences, Chiang Mai University.

You may approve or refuse the use of your sample by ticking the right box in the informed consent form that selects your choice of sample storage. If other studies were deemed necessary, we would request additional consent and this would be submitted to the Ethics Committee as a specific study.

Policy Regarding Research Related Injuries. Immediate necessary care is available free of charge to you should you have a medical problem related to participation in this study. However, the study is not responsible for treatments unrelated to the study and no financial compensation will be provided.

Risks to You. You may experience some adverse effects of the treatments used in this study, as described above for Peg-interferon and ribavirin. In addition, participation in this research study involves some additional blood draws that may cause pain, swelling, bruising, and phlebitis (inflammation or infection of veins). You will receive the appropriate care from your physician.

Benefits to You. The drug combination used in this study is a combination that is currently used for the treatment of hepatitis C in the setting of HIV co-infection. This study cannot guarantee the success of treatment but it can be beneficial to you once HCV viral load decreases, reducing the hepatitis risks and complications caused by hepatitis C infection.

Further Questions. At any time, if you have further questions about this study or your rights and benefits as a participant, you may contact:

The Ethical Review Committee for Research in Human Subjects

3rd floor, Department of Medical Services Building, The Ministry of Public Health
88/21 M.4 Tivanond Road, Muang Nonthaburi 11000
Tel: 02-5906171-2 Fax: 0 2591 8251

Or the your hospital's Ethics Committee

___[completed at site]_____ Telephone # _____,
(Representative of your hospital's Ethics Committee)

For questions about the research project, your rights, and research-related injuries, you may contact a doctor independent from the research team:

Name: Dr. Sorakij Bhakeecheep
Address: National Health Security Office (NHSO)
The Government Complex Commemorating His Majesty the King's 80th Birthday Anniversary 5th December, B.E. 2550 (2007) Building B
120 M. 3 Chaengwattana Road, Lak Si District, Bangkok 10210
Tel: +66 2141 4000 Fax: +66 2143 9730-1

The investigator responsible for safeguarding your welfare (available 24 hours/day):

Principal Investigator:

Dr. Kanawee Thetket
Medical Department, Nakornping Hospital
159 M.10 Chotana Rd., T. Don Keaw, Mae Rim Chiang Mai 50180
Telephone: 053 999 200 – Mobile phone: 081 888 3037

Dr. _____ [Principal investigator name at each site]
Address: _____
Telephone # Office:_____ Home: _____Mobile: _____
Fax: #_____

Appendix 2: Informed Consent Form (English Language)

Informed consent Form

For the study: Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand Version 1.0 dated 17 June 2014

Date of consent: _____Month_____ Year_____

The investigator has explained the purpose of the project, methods, risks/side effect of the study and study agents, and benefits in detail before signing this assent form and I understand.

The investigator has agreed to honestly answer all of my questions until I am satisfied.

I have the right to withdraw from this study at any time. My participation in the study is completely voluntary and my withdrawal would not affect any other care to which I am entitled.

The investigator ensures that he/she will keep my personal information confidential and will only be disclosed as part of the summary results or disclosed to the people who support or monitor the study.

The investigator ensures that any damages related to the study will be treated at no cost to me.

Name of the Investigator (available 24 hours/day):

Kanawee Thetket, MD
Medical Department, Nakornping Hospital
159 M.10 Chotana Rd., T. Don Keaw, Mae Rim Chiang Mai 50180
Telephone: 053 999 200 – Mobile phone: 081 888 3037

Dr. _____ [Principal investigator name at each site]
Address: _____
Telephone # Office: _____ Home: _____
Mobile: _____ Fax: #_____

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 (Typed or print)	Signature	Date
_____	_____	_____
Investigator/Counselor's Name (Typed or print)	Signature	Date
_____	_____	_____
Witness' Name (Typed or print)	Signature	Date
_____	_____	_____
Witness' Name (Typed or print)	Signature	Date

Appendix 3: Informed consent form for specimen storage (English Language)

Informed consent form for specimen storage

For the study: Response to peg-interferon and ribavirin for the treatment of HCV infection in HIV co-infected patients, implemented in public hospitals in Thailand Version 1.0 dated 17 June 2014

Date of consent: _____Month_____ Year_____

Prior to signing this informed consent, the study investigators provided me with a detailed explanation about blood draws and about the risks or symptoms that could result from the process as well as the possible benefits. I understand the information thoroughly.

> Blood samples taken as part of the study, identified by code, will be kept for tests, which will be of two years after the last study visit (until November 2018). If other studies related to this study were deemed necessary, we would request additional consent and this would be submitted to The Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health and the local Ethics Committee as a specific study.

A plasma sample will be collected at treatment initiation, 2 weeks later, every 4 weeks until 48 weeks and 6 months after treatment discontinuation.

You can withdraw your blood samples from the sample repository at any time, and they will be immediately destroyed by autoclave following the standard procedure at the Faculty of Associated Medical Sciences, Chiang Mai University.

Consent for blood storage: I will tick in the check box □ of my decision

□ I give my permission for the storage and use of my stored specimens for test(s) as discussed in the information sheet.

□ I do not permit to store my blood for test(s) as discussed in the information sheet.

I have read all the above and clearly understand. I sign this informed consent voluntarily and will have a copy of this consent to keep.

_____	_____	_____
Participant's Name (Typed or print)	Signature	Date
_____	_____	_____
Investigator/Counselor's Name (Typed or print)	Signature	Date
_____	_____	_____
Witness' Name (Typed or print)	Signature	Date
_____	_____	_____
Witness' Name (Typed or print)	Signature	Date

Appendix 4: Clinical side effects management:

Side Effect	Recommendations and prescription for the patient
Fever/chills	• Injecting interferon at bedtime if fever/chills develop 1-3 hours after the interferon injection • Prescribe acetaminophen about 30-60 minutes before weekly interferon injection • Prescribe acetaminophen 1-2 tablets prior to interferon injection and 4-6 hours later if needed up to a maximum of 2,000 mg/day. Thus, do not exceed 6 tablets/day of 325 mg or 4 tablets/day of 500 mg acetaminophen. • Prescribe ibuprofen or naproxen is possible if no other contraindication • Prescribe physical recommendations as: cool sponge bath, ice pack or cold pack when a fever occurs or extra blankets and clothes when chills occur • Encourage notifying the provider if temperature is above 38.5°C for more than 24-48 hours
Muscle and body aches	• Injecting interferon at bedtime if body aches develop 1-3 hours after the interferon injection • Prescribe acetaminophen about 30-60 minutes before weekly interferon injection • Prescribe acetaminophen 1-2 tablets prior to interferon injection and 4-6 hours later if needed up to a maximum of 2,000 mg/day. Thus, do not exceed 6 tablets/day of 325 mg or 4 tablets/day of 500 mg acetaminophen. • Prescribe ibuprofen or naproxen is possible if no other contraindication • Recommend trying low-impact exercise such as walking or low-impact aerobics if possible • Recommend maintaining adequate fluid intake (at least six to eight non-caffeinated glasses/day) • Recommend applying warm moist heat or massaging areas
Headaches	• Recommend maintaining adequate fluid intake • Prescribe acetaminophen or ibuprofen is possible if no other contraindication • Recommend keeping lights dim, wearing sunglasses or staying in darkened rooms • Recommend getting plenty of rest
Fatigue	• Recommend trying low-impact exercise such as walking or low-impact aerobics if possible • Recommend maintaining adequate fluid intake (a caffeinated beverage in the morning is acceptable) • Recommend taking a short nap during the day • Recommend lessening your work schedule if possible • Recommend eating well-balanced meals every day

Depression	• **If mild depression symptoms (according to the Back scale):**
	  ○ Encourage patients to talk about their symptoms and to take medications that might help (if indicated)
	  ○ Encourage discussion about thoughts of harming him/herself or someone else
	  ○ Encouraging patients to go to the nearest emergency room if feeling in danger of harming him/herself or others
	  ○ Advising to do mild to moderate exercises at least 3 times/week as directed by your provider
	  ○ **Increase monitoring frequency of depression evaluation**
	  ○ **Prescribe antidepressant if necessary and seek for specialized advice**
	• **If moderate to severe depression symptoms (according to the Beck scale):**
	  ○ **Evaluate for suicidal ideation and seek specialized advice**
	  ○ **Decrease the dose of peg-interferon from 1.5 to 1.0 mcg/kg or less**

Side Effect	Recommendations and prescription for the patient
	○ **If, severe depressive symptoms or suicidal ideation: discontinue HCV treatment**
Anxiety and irritability	• Recommend talking to healthcare personnel about symptoms and medications that might help • Recommend always discussing with healthcare personnel thoughts of harming him/herself or someone else • Recommend going to the nearest emergency room if in danger of harming him/herself or others • Recommend doing mild to moderate exercises at least 3 times/week if possible • Recommend trying relaxation techniques such as deep breathing, taped exercises, yoga, Tai Chi or meditation • Recommend avoiding stimulants like caffeine and maintaining adequate fluid intake
Insomnia	• Recommend going to sleep and waking up at the same time every day • Recommend to not read or watch TV in bed • Recommend limiting daytime naps • If experiencing anxiousness after ribavirin intake, recommend taking at 4-5 pm instead of before bedtime • Recommend limiting fluid intake for 2 hours before bedtime to avoid having to get up to go to the bathroom • Recommend avoiding caffeinated products, especially in the afternoon and at night • Recommend avoiding heavy meals close to bedtime • Recommend taking warm baths, reading or listening to music, getting a massage • Recommend trying a glass of warm milk (contains tryptophan, a natural sleep agent) • Prescribe diphenhydramine or other medications if indicated
Dry mouth or mouth ulcers	• Recommend ○ brushing teeth frequently, especially after eating ○ Avoiding mouthwash containing alcohol ○ Drinking plenty of water or use ice chips or sugar-free lemon drops • Other medications may be needed for mouth sores/ulcers
Bad taste in mouth	Recommend: • Using sugar-free lemon drops or real lemon wedges • Eating a small amount of yogurt, 1/2 hour before meals • Drinking lemonade or cranberry juice (monitor glucose levels if diabetes) • Eating food cold or at room temperature • Brushing teeth frequently, especially after eating, to eliminate metallic taste • Using plastic utensils if experiencing metallic taste
Poor appetite	• Eating smaller, more frequent (4-6) meals throughout the day • Drinking protein drinks (Carnation Instant Breakfast*, Ensure* or Boost*) • Eating snacks with protein (cheese, peanut butter, eggs) • Eating whatever is appealing even without hunger. Eating a variety of foods • Walking before a meal
Nausea and vomiting	• Taking ribavirin with food • Eating small meals • Avoiding foods or smells that trigger nausea • Eating healthy foods. Avoiding greasy, spicy, acidic or sweet foods • Eating ginger in ginger tea, ginger ale or gingersnaps • Eating some crackers or dry white toast if feeling sick in the morning • Prescribe antacids or other medications may be helpful
Diarrhea	• Eating more soluble fiber like Bananas, white Rice, Applesauce and white Toast (the "BRAT" diet) • Avoiding foods that are spicy or acidic (like citrus)

Side Effect	Recommendations and prescription for the patient
	• Avoiding dairy products up to several days after diarrhea resolves • Maintaining adequate fluid intake (at least six to eight glasses/day) • Prescribe loperamide, methylcellulose or psyllium if needed
Dehydration	• Increasing intake of water or non-caffeinated beverages • Avoiding caffeinated beverages
Cough	• Increasing intake of water or non-caffeinated beverages • Trying sugar-free hard candy or cough drops
Dry skin/ rashes	• Avoiding long, hot showers or baths • Using moisturizing soaps • Using moisturizing lotion after showers • Using mild unscented laundry detergents and avoiding fabric softeners • Using sunscreen • Trying rubbing or pressing on the itchy areas rather than scratching • Prescribe petroleum jelly or other agents on dry, itchy areas
Hair thinning or hair loss	• Avoiding harsh hair products such as dyes, perms, gels, sprays and mousses • Using a mild shampoo such as baby shampoo • Avoiding braiding hair; using a wide-tooth comb or soft brush • Wearing a cap, scarf, turban or wig
Injection site reactions	• Before injecting, warming the medicine by gently rolling the syringe in the hands for a minute • Rotating/alternating the injection site - thigh, upper arm and abdomen. If thin, using the thigh area might help • Not doing injection into an area that is irritated, bruised or red • Not doing rub injection site • Applying a cold pack • Hydrocortisone cream or other medications can be prescribe to help

Modification of treatment in case of laboratory abnormality:

Peg-interferon alfa-2b must be **stopped** if:**Laboratory exam**	**Value**	**Yes**	**Dose modification**
Hemoglobin	< 8.5 g/dL	1☐	➔ **STOP Peg-interferon** in case of any of these events
Hemoglobin if history of stable cardiac disease * 4 weeks of a dose reduction	< 12 g/dL*	1☐	
WBC	< 1000/mm^3	1☐	
Neutrophils	< 500/mm^3	1☐	
Platelets	< 25000/mm^3	1☐	

Laboratory exam	**Value**	**Yes**	**Dose modification**
Hemoglobin if history of stable cardiac disease	≥ 2 g/dL decrease since the last visit	1☐	➔ **Reduce dose of Peg-interferon of 0.5 mcg/kg** If one of these events is verified
WBC	< 1500/mm^3	1☐	
Neutrophils	< 750/mm^3	1☐	
Platelets	< 50000/mm^3	1☐	

Ribavirin dose reduction

Laboratory exam	**Value**	**Yes**	**Dose modification**
Hemoglobin	< 10 g/dL	1☐	➔ **Reduce dose of Ribavirin** If one of these events is verified
Hemoglobin if history of stable cardiac disease	≥ 2 g/dL decrease since last visit	1☐	

Dose reduction:

If previous dose = 400 mg morning/200 mg evening → ✋**STOP Ribavirin and contact ☎**

If previous dose = 400 mg morning/400 mg evening → Decrease to 400 mg morning/200 mg evening

If previous dose = 600 mg morning/400 mg evening → Decrease to 400 mg morning/400 mg evening

If previous dose = 600 mg morning/600 mg evening → Decrease to 600 mg morning/400 mg evening

If previous dose = 600 mg morning/800 mg evening → Decrease to 600 mg morning/400 mg evening

☎**:** If Ribavirin dose has already been reduced two times but the listed laboratory abnormalities persist, please contact: 053 819 125-9 #631, 08 1884 7786

Appendix 5: Cockcroft-Gault formula

For men:

$$\frac{(140\text{-age [in years]}) \times \text{weight [in kg]}}{(72 \times \text{creatinine [in mg/dL]})}$$

For women

$$\frac{(140\text{-age [in years]}) \times \text{weight [in kg]} \times 0.85}{(72 \times \text{creatinine [in mg/dL]})}$$

Calculation on line at: http://nephron.com/cgi-bin/CGSI.cgi