Clinical Study Protocol

Cardiovascular disease in HIV and Hepatitis C: Risk Outcomes after hepatitis C Eradication (CHROME)

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Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
ART	Antiretroviral Therapy
CCMD	Critical Care Medicine Department
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CD38	Cluster of Differentiation 38
CHROME	Study short name
Co-Infection	Identifier for those with both HIV and hepatitis C
CXCL 9	Chemokine ligand 9
CXCL 10	Chemokine ligand 10
CXCL 11	Chemokine ligand 11
DAA	Directly Acting Antiviral
DC PFAP	DC Partnership for HIV/AIDS Progress
EDTA	Ethylenediaminetetraacetic acid
ELISPOT	Enzyme-Linked Immunospot assay
HCV	Hepatitis C Infection
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA-DR+	Human Leukocyte Antigen-antigen D related
HRPP	Human Research Protection Program
hsCRP	High Sensitivity C-reactive protein
hsTRP	High Sensitivity Troponin
IFN-γ	Interferon-gamma
IHV	Institute of Human Virology
IL-6	Interleukin 6
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
MTA	Materials Transfer Agreement
N	Number (typically refers to number of subjects/sample size)
NIH	National Institutes of Health
NK	Natural Killer (cells)
PD-1	Programmed Cell Death Protein 1
PEG-IFN-α	Pegylated interferon-alpha
PWID	People who inject drugs
PI	Principal Investigator
PRO	Patient Reported Outcomes
RNI	Reportable New Information
SAE	Serious Adverse Event/Serious Adverse Experience
SOC	Standard of Care
SOM	School of Medicine
SVR	Sustained Virologic Reponse
TIM-3	T Cell Immunoglobulin and Mucin Domain 3
TNF-α	Tumor Necrosis Factor alpha
UP	Unanticipated Problem

UPnonAE	Unanticipated Problem that is not an Adverse Event

Protocol Summary

Full Title:	*Cardiovascular disease in HIV and Hepatitis C: Risk Outcomes after hepatitis C Eradication*
Short Title:	*CHROME*
Conducted by:	*Institute of Human Virology, University of Maryland*
Principal Investigator:	*Poonam Mathur, DO*
Sample Size:	N= 90; 60 on hepatitis C treatment; will consent up to *200 for screening*
Study Population:	*Adults infected with HIV and/or HCV*
Accrual Period:	*12 months*
Study Design:	*This is a pilot, intervention, non-randomized, controlled prospective study. We will enroll 90 patients into 3 groups. Patients with HCV mono-infection (Group 1) or HIV/HCV co-infection (Group 2) will receive therapy with DAAs. Patients with HIV mono-infection (Group 3) will be followed throughout the study and laboratory work and imaging will be obtained.*
Study Duration:	*Start Date: September 2018* *End Date: July 2021*

Primary Objective: Determine the change in cardiovascular risk from baseline to after functional cure of hepatitis C among HCV monoinfected and HIV/HCV-coinfected patients, using high-sensitivity C-reactive protein.

Secondary Objectives:1) Determine the difference in change (pre vs. post functional cure) in cardiovascular risk among HCV monoinfected and HIV/HCV coinfected patients compared to HIV monoinfected patients, using high-sensitivity C-reactive protein.

2) Compare the difference in levels of cardiac biomarkers between HCV monoinfected, HIV/HCV coinfected, and HIV monoinfected patients at baseline.

3) Determine the difference in change (pre vs. post functional cure) in cardiac biomarkers among HCV monoinfected and HIV/HCV coinfected patients, compared to HIV moninfected patients.

Exploratory Objectives:

1) Compare the difference in cardiac MRI between HCV monoinfected, HIV/HCV coinfected, and HIV mono-infected subjects at baseline. MRI parameters that will be assessed

are the native myocardial T1, myocardial T2, and myocardial extracellular volume fraction (to look for myocardial inflammation and small vessel disease). Gadolinium enhacement will be used to look at macroscopic fibrosis.

2) Determine the difference in change (pre vs. post functional cure) in cardiac MRI in HCV monoinfected and HIV/HCV coinfected patients, compared to HIV monoinfected patients. MRI parameters that will be assessed are listed in objective 1.

3) Determine the relationship between immune markers of activation, cardiac biomarkers, and MRI in HIV positive and negative subjects. MRI parameters that will be assessed are listed in objective 1.

4) Compare the difference in levels of cellular and soluble immune markers of activation between HCV monoinfected, HIV/HCV coinfected, and HIV monoinfected subjects at baseline.

5) Determine the difference in change (pre vs. post functional cure) in cellular and soluble immune markers of activation HCV monoinfected and HIV/HCV coinfected patients, compared to HIV moninfected patients.

Précis

Among people living with HIV (PLWH), there is a 50% increased risk of acute myocardial infection compared to the general population(1). Although the advent of highly active antiretroviral therapy (HAART) has had several benefits for PLWH, including increased life expectancy(2), the longer life span has also made this population apt to develop comorbidities seen in age-matched individuals without HIV, including cardiovascular disease. In addition, HAART itself is a risk factor for cardiovascular disease (CVD)(3), and persistent inflammation and chronic immune activation caused by HIV and ART results in a proinflammatory state that also increases the risk for cardiovascular disease(4).

Hepatitis C (HCV) is another chronic viral infection with significant morbidity and mortality. The development of directly acting antivirals (DAAs) has dramatically improved the cure rate of HCV treatment. However, besides the effects on the liver, chronic infection with HCV leads to numerous extrahepatic manifestations that are associated with morbidity and mortality, including cardiovascular disease(5, 6). Therefore, patients co-infected with HCV and HIV have a magnified cardiovascular risk than that of the general population (7). If treatment of HCV can lower the risk of CVD among HIV and HCV co-infected patients, then this would provide an indication for early HCV treatment in this population.

As such, we propose a pilot, intervention, non-randomized, controlled prospective study to treat HCV in mono-infected and HIV co-infected individuals and compare cardiovascular risk outcomes to HIV mono-infected controls. This pilot study will demonstrate whether functional cure of HCV reduces myocardial injury and risk of cardiovascular disease.

1 Background Information and Scientific Rationale

1.1 Background Information

Rates of cardiovascular disease (CVD) are over twice as high in HIV-infected individuals compared to matched uninfected controls, with rates anticipated to increase as this population ages(8). Factors contributing to increased risk of CVD in HIV-infected patients remain unclear, but there is considerable evidence suggesting that concurrent viral disease, especially HCV, is an important contributing factor. With the advent of direct acting antivirals (DAA), HCV is now a factor that can be easily eliminated. Hepatitis C (HCV) co-infection occurs in approximately one-third of all patients infected with human immunodeficiency virus (HIV) in the U.S(9). The early treatment of HCV in this population could be an important intervention to reduce the burden of liver disease; thus far, early treatment has been a controversial intervention in patients with no fibrosis given the cost of HCV treatment. Moreover, chronic HCV is an important model for understanding the role of chronic viruses in accelerating inflammation and organ dysfunction in multiple anatomic sites.

While some studies have strongly suggested that hepatitis C (HCV) co-infection is associated with increased rates of CVD in HIV-infected patients, results in all studies have not been consistent. However, several of these larger cohort studies included predominantly Caucasian and male participants in the pre-antiretroviral therapy era(8). Given that HIV, HCV, and atherosclerosis are all associated with chronic inflammation and immune activation, it can be challenging to understand relative disease pathogenesis when found concurrently in individual patients. Identifying predictors of CVD progression from overlapping pathways has the potential to suggest novel preventive and therapeutic intervention strategies to mitigate CVD progression. If HCV confers additional risk for CVD among HIV-infected patients, this would provide further impetus to treat HCV early and aggressively in this population.

Myocardial injury and vascular complications associated with HIV can be differentiated by the use of cardiac MRI. Cardiac MRI is an established modality for the evaluation of myocardial injury and cardiac function(10, 11). Infarcted regions in the myocardium, having undergone scar formation with collagen deposition, have a much slower washout rate of gadolinium-based contrast than healthy myocardium, leading to significantly increased signal intensity on T1-weighted imaging. Therefore, the presence and size of regional myocardial fibrosis due to ischemic heart disease can be accurately assessed with delayed contrast enhancement MRI (12). Unlike computed tomography, with which Hounsfield units can be used as a reference scale for attenuation, with conventional MRI techniques, signal intensity is expressed on an arbitrary scale that differs from one imaging examination to another and therefore is unsuitable for direct signal quantification. Theoretically, diffusely fibrotic myocardium would accumulate contrast in a similar fashion to regional scarring, but calculation of the T1 time is required for its quantification, and is a technique that we have expertise with at the NIH. Measurement of cardiac function is a well described prognostic tool to evaluate myocardial health, and is also an integral component of a complete cardiac MRI conducted at the NIH. This modality may be effective in distinguishing variable myocardial injury between HIV mono-infected and HIV/HCV co-infected individuals. In

fact, a prior study of 18 patients demonstrated worse cardiac function and morphology in HIV/HCV patients who underwent cardiac MRI and spectroscopy for measures of cardiac function, myocardial fibrosis, and steatosis which compared to HIV mono-infected controls(13). However further studies are necessary to reinforce this finding, and elucidate underlying mechanisms of injury.

The objective of this study is to determine the impact of functional cure of HCV (sustained virologic response [SVR]) on cardiovascular risk and progression of CVD in a population of HCV mono-infected and HIV/HCV-coinfected patients compared to HIV mono-infected controls.

1.2 Institutional Overview

Overview of the DC PFAP Hepatitis Program

In 2008, the National Institutes of Health and the DC Department of Health collaborated to establish the DC Partnership for HIV/AIDS Progress (DC PFAP), a partnership for community-based clinical care and research whose aim is to reduce the incidence and prevalence of HIV/AIDS in the District of Columbia. A plan was developed to create a research program to build a sustainable model for urban areas working to reduce the HIV/AIDS crisis. A needs assessment within the area's medical community demonstrated a significant deficit in hepatitis C virus care and treatment. This led to the development of a Hepatitis branch within DC PFAP, rooted in direct subspecialty medical services and clinical research addressing the limitations of standard of care therapy.

The Hepatitis program is currently based at the Institute of Human Virology and operates out of three campuses: (1) clinical partners within Washington DC, (2) National Institutes of Health, Bethesda, MD and (3) University of Maryland Institute of Human Virology, Baltimore, MD. The overarching goals of the programs are to:

- establish improved access to subspecialty care for underinsured patients with HIV
- develop access to HIV- and hepatitis-related research for residents of DC
- expand integrated care for hepatitis C in the community HIV clinics
- provide national leadership in the development and delivery of effective, safe, convenient therapies, initially focusing on HCV

The clinical aspects of the program are set within partner centers in Washington DC and Baltimore City. In the Unity clinic system in Washington DC, we have established relationships with the providers and access to a cohort of patients with HIV and Hepatitis C. In Baltimore City, the Center for Infectious Disease (CID) provides comprehensive care services for a range of infectious diseases, including HIV and hepatitis C. Patients are managed by state of the art standard of care as well as offered opportunities to participate in clinical research as appropriate. We also have an active clinic at the UMB Drug Treatment Center (DTC) treating patients for HCV. To date, over 1240 HIV and HCV infected patients have been linked to care and over 900 patients cured of hepatitis C through treatment with novel DAA therapy within subspecialty clinics in the Baltimore and DC areas. Through direct linkage to care, effective treatment, and continual outcome

measurement, the Hepatitis program has developed an effective model for management of hepatitis C in an urban setting.

University of Edinburgh:
Nicholas Mills, MD, PhD, University of Edinburgh, Anoop Shah, PhD, University of Edinburgh are laboratory collaborators with Dr. Poonia. They are experts the field of cardiovascular biomarkers and will conduct hsTRP assasy using the samples collected from this study. UMB has a collaborative agreement and MTA between UMB and Univ of Edinbugh to support research protocols done at UMB/IHV and Dr. Poonia's lab.

The National Institutes of Health, Bethesda, MD
The National Institutes of Health, Bethesda, MD campus will provide access to advanced cardiac MRI imaging and other clinical research resources not available at the clinical sites. Henry Masur, MD is the NIH Intramural site Principal Investigator and will oversee the protocol and all the individuals working on it at The NIH Clinical Center. These individuals are listed in the UMD Protocol as Sub-Investigators or Research Assistants may include federal employees, special volunteers, and/or contractors. Dr. Masur will be authorized to obtain informed consent, have access to identifiable data, and participate in data analysis and manuscript preparation/review. Research Assistants (Laura Nussdorf, BA; Christopher Brockus, BA) will provide research support to the protocol by scheduling imaging, escorting participants to radiology appointments the Clinical Center, and data collection as needed. Arlene Sirajuddin, MD and Mark Ahlman, MD are expert radiologists in cardiac MRI and will provide analysis of all imaging for those participants. Mary Hall will provide regulatory support for the NIH site. She will not obtain informed consent but may have access to identifiable data.

Poonam Mathur, Sarak Kattakuzhy, Elana Rosenthal, Rahwa Eyasu and Rachel Silk, are UMB sub investigators who are also special volunteers at NIH and are fully credentialed and able to see research patients at the NIH. They are authorized to obtain informed consent, have access to identifiable data, see patients at NIH and participate in data analysis and manuscript preparation/review.

Data Sharing Among Collaborators
The PI and DC PFAP study team will have access to all data collected from all sites and the NIH will share all the Cardiac MRI data with the DC PFAP.

1.3 Treatment

Until recently, a major limiting factor in expansion of treatment for HCV has been standard of care therapy with pegylated interferon, ribavirin, and for genotype 1 disease, boceprevir and telaprevir. These medications have significant side effect profiles, response-based dosing regimens of over 6 months, and decreased efficacy in key groups including: those with genotype 1 disease, HIV coinfection, and cirrhosis. However, there has been dramatic improvement using all oral direct-acting antiviral (DAA) regimens with sustained virologic response (SVR) rates over 90%, short-duration therapies and well-tolerated,

simple regimens, including for those with HIV coinfection. Several studies using DAA-based therapy have shown comparable rates of sustained virologic response (SVR) in coinfected patients(14-21). In addition, data suggests that HCV eradication with use of antiviral therapy may improve cardiovascular outcomes in mono-infected patients(22). However, there is no data on the benefit of cardiovascular risk after HCV eradication in co-infected patients.

1.4 Rationale

HIV and HCV are diseases of concern in the Baltimore and DC metropolitan areas. New DAA treatments allow for effective treatment of chronic HCV and reduction in risk of extrahepatic comorbidities, including cardiovascular disease. However, no data exists on the role of HCV eradication in mitigating cardiovascular risk in HIV co-infected patients, who at baseline have an increased risk of cardiovascular disease due to the pro-inflammatory state caused by the virus and the use of ART. **This study aims to demonstrate that there is a decreased risk of cardiovascular disease after eradication of HCV in HCV mono-infected and HIV co-infected patients.** The risk factors of these patients will be compared to the risk factors for HIV mono-infected patients and HCV mono-infected patients who achieve functional HCV cure.

2 Study Objectives

2.1 Primary Objective

Determine the change in cardiovascular risk from baseline to after functional cure of hepatitis C among HCV monoinfected and HIV/HCV-coinfected patients, using high-sensitivity C-reactive protein.

2.2 Secondary Objectives

Determine the difference in change (pre vs. post functional cure) in cardiovascular risk among HCV monoinfected and HIV/HCV coinfected patients compared to HIV monoinfected patients, using high-sensitivity C-reactive protein.

Compare the difference in levels of cardiac biomarkers between HCV monoinfected, HIV/HCV coinfected, and HIV monoinfected patients at baseline

Determine the difference in change (pre vs. post functional cure) in cardiac biomarkers among HCV monoinfected and HIV/HCV coinfected patients, compared to HIV moninfected patients.

2.3 Exploratory Objectives

1. Compare the difference in cardiac MRI between HCV monoinfected, HIV/HCV coinfected, and HIV mono-infected subjects at baseline. MRI parameters that will be assessed are the native myocardial T1, myocardial T2, and myocardial extracellular volume fraction (to look for myocardial inflammation and small

vessel disease). Gadolinium enhacement will be used to look at macroscopic fibrosis.

2. Determine the difference in change (pre vs. post functional cure) in cardiac MRI in HCV monoinfected and HIV/HCV coinfected patients, compared to HIV monoinfected patients. MRI parameters that will be assessed are listed in exploratory objective 1.
3. Determine the relationship between immune markers of activation, cardiac biomarkers, and MRI in HIV positive and negative subjects. MRI parameters that will be assessed are listed in exploratory objective 1.
4. Compare the difference in levels of cellular and soluble immune markers of activation between HCV monoinfected, HIV/HCV coinfected, and HIV monoinfected subjects at baseline.
5. Determine the difference in change (pre vs. post functional cure) in cellular and soluble immune markers of activation HCV monoinfected and HIV/HCV coinfected patients, compared to HIV moninfected patients.

3 Study Design

3.1 Description of the Study Design

This is a pilot, intervention, non-randomized, controlled prospective study. We will enroll 90 patients into the following groups. Up to 200 patients will be consented.

Group 1: HCV mono-infected patients (n = 30)

Group 2: HIV/HCV co-infected patients (n = 30)

Group 3: HIV mono-infected patients (n = 30)

Patients with HCV mono-infection (Group 1) or HIV/HCV co-infection (Group 2) will receive therapy with any FDA-approved medication for hepatitis C treatment, per standard of care in the AASLD/IDSA HCV Treatment Guidelines and/or the discretion of the investigator.

3.2 Study drugs

Direct Acting Antivirals (DAAs): For the treatment of chronic HCV, patients will be treated with one of the following FDA-approved fixed-dose combination products : Elbasvir/Grazoprevir (Zepatier), Sofosbuvir/Ledipasvir (Harvoni), Sofosbuvir/Velpatasvir (Epclusa), Glecaprevir/Pibrentasvir (Mavyret), Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi). Some of these medications require administration of concomitant ribavirin. Medication regimens will be administered as standard of care per the AASLD/IDSA HCV Treatment Guidelines. Common side effects (those that occurred in more than 5% of the patients in clinical trials) of these medications are listed below:

Elbasvir/Grazoprevir (Zepatier):

- Fatigue
- Headache

Sofosbuvir/Ledipasvir (Harvoni):

- Fatigue
- Headache
- Nausea
- Diarrhea
- Insomnia

Sofosbuvir/Velpatasvir (Epclusa):

- Headache
- Fatigue
- Nausea
- Insomnia
- Lack of energy

Glecaprevir/Pibrentasvir (Mavyret):

- Headache
- Fatigue
- Nausea
- Diarrhea

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi):

- Headache
- Fatigue
- Diarrhea
- Nausea
- Insomnia
- Lack of energy

Ribavirin - Women of childbearing potential who receive ribavirin **must** commit to abstinence from sexual activity, or use two forms of contraception during treatment and for the 6 months after completion of ribavirin. Men receiving ribavirin who are sexually active with women **must** commit to abstinence from sexual activity, or they and their partner must use two forms of contraception during treatment and for the 6 months after completion of ribavirin. The most common side effects (occurring more than 5% of the time in clinical trials) are:

- Fatigue
- Lack of energy
- Body aches
- Fever
- Headache
- Anemia

- Rash

3.3 Research Strategy

A total of up to 200 people will be consented for the study from existing clinical sites sites and long-term natural history studies. The total N for the study is 90, HIV (n = 30), HIV/HCV (n=30), and HCV (n=30). The investigators have established clinics and networks in DC and Baltimore that have successfully recruited these patient populations for studies since 2010, including the ASCEND trial which accrued 600 patients in 10 months. Study participants will be selected based on inclusion criteria, and will be seen for study visits at clinics embedded at one of 2 sites:

1) Unity Healthcare, Washington, DC
    a. An organization which serves as DC's largest network of community health centers providing comprehensive care services including primary care, HIV care, and Hepatitis B and C treatment.
2) Institute of Human Virology, Clinical Research Unit, Baltimore, MD

All participants HIV/HCV co-infected or HCV mono-infected patients will be treated for chronic HCV with DAAs as per standard of care (see 3.1 and 3.2.).

3.4 Primary Hypothesis

The primary hypothesis is that treatment and functional cure of HCV in HCV-monoinfected and HIV/HCV-coinfected patients should lead to decreased cardiovascular risk, as measured by at least a 2-fold decrease in high-sensitivity C-reactive protein (hsCRP) by 12 months post-functional cure of HCV.

4 Study Population

Participants are adults (age 18-70) patients infected with HIV, HCV and HIV/HCV.

4.1 Rationale for Subject Selection

Subjects of any gender will be considered for inclusion in this study. There will be no racial, ethnic, or gender discrimination. Persons in jail or prison are not eligible for this study (see 4.3.2). Pregnant and breastfeeding women will not be eligible (see section 4.3.1).

4.2 Subject Inclusion Criteria

To be eligible for participation on this protocol, a participant must satisfy all of the following conditions:

1. Age ≥18 years old
2. Able and willing to sign informed consent

3. Chronically infected with HCV (any genotype), defined as any individual with documentation of positive HCV antibody and positive HCV RNA test (HCV RNA of 2,000 IU/mL or greater)
4. If HIV+, suppressed on a stable, protocol-approved, ARV regimen for ≥ 8 weeks prior to enrolling in the study
    a. HIV RNA < 50 copies/mL (or < LLOQ if the local laboratory assay's LLOQ is ≥50 copies/mL) prior to Screening. Subjects with an isolated or unconfirmed HIV RNA > 50 copies/mL (or > LLOQ if the local laboratory assay's LLOQ is ≥50 copies/mL) are not excluded.
    b. CD4 count >100 cells/mm3
5. Willing to have samples stored for future use
6. If tested positive for NS5A resistance-associated polymorphisms or PEG-IFN and ribavirin experienced, able to tolerate ribavirin-containing regimen for 16 weeks. Ribavirin will be administered at the discretion of the PI.
7. Women of childbearing potential who receive ribavirin will have to be willing to commit to abstinence from sexual activity, or use of two forms of contraceptive during treatment and for the 6 months after completion of ribavirin. Men receiving ribavirin who are sexually active with women will also have to be willing to commit to abstinence from sexual activity, or use of two forms of contraceptive during treatment and for the 6 months after completion of ribavirin.

4.3 Subject Exclusion Criteria

A participant will be ineligible to participate in this study if any of the following criteria are met:

1. Decompensated liver disease (Childs Pugh B or C)
2. Unable to comply with research study visits
3. Poor venous access not allowing screening laboratory collection
4. Have any condition that the investigator considers a contraindication to study participation
5. Pregnant or breastfeeding woman
6. Prior HCV treatment with Direct-Acting Antivirals. Note: Patients who are treatment-experienced with PEG-IFN/RBV will not be excluded; their inclusion in the study will be considered by the PI.
7. HIV+ patients with prior HCV treatment who achieved sustained virologic response (SVR)/ functional cure
8. Use of a concomitant medication that is contraindicated with the use of the DAA for HCV treatment (per package insert)
9. Coinfection with HCV and HBV, in partcular HBsAg + patients.
    a. Patients with HBcAb+ will not be excluded, but will have HBV DNA levels checked and will be monitored while on DAA therapy and medically managed as considered appropriate by the PI.
10. Have any condition that the investigator considers a contraindication to study participation or not eligible per standard of care for HCV treatment

11. Patients with the following devices are excluded from participating in the cardiovascular MRI study:
    - Central nervous system aneurysm clip
    - Implanted neural stimulator
    - Implanted cardiac pacemaker or defibrillator
    - Cochlear implant
    - Ocular foreign body (e.g. metal shavings)
    - Implanted insulin pump
    - Metal shrapnel or bullet
12. The following groups of people are also excluded from participating in the cardiovascular MRI study:
    - Patients with stable renal disease (estimated glomerular filtration rate (eGFR)<30ml/min/1.73m2 body surface area. The eGFR must be within two weeks of the the MRI exam.
    - Patients with acute renal disease.
13. Patients who choose to have the cardiac MRI and are over 60 years of age, have a history of renal failure, or have type I or II diabetes mellitus must have laboratory tests the same day as the MRI exam.
14. Positive urine drug screen at screening. Not all patients with positive drug screen will be excluded; decision will be made by the PI.

4.3.1 Justification for Exclusion

Pregnancy: Pregnant women are excluded from this study per FDA guidance, as there are no studies of DAAs in pregnant women, and no DAA is currently FDA approved for use in pregnant women.

Breastfeeding: Breastfeeding women are excluded from this study per FDA guidance as there are no studies of DAAs in lactating women, and no DAA is currently FDA approved for use in lactating women.

Exclusion of Children: Safety and effectiveness of DAAs have not been established in pediatric patients, and as such subjects 18 years of age or younger will be excluded from the study. Because insufficient data regarding dosing or adverse events (AEs) are available in adults to judge the potential risk in children, this study poses greater than minimal risk and does not meet the Department of Health and Human Services guideline 45 Code of Federal Regulations (CFR) 46, subpart D, governing the participation of children in research.

4.3.2 Incarcerated Participants

Participants who become incarcerated during the course of the study may have to be withdrawn; continued collection of data from incarcerated subjects would be on a case-by-case basis after consultation with the IRB.

5 INTERVENTIONS

5.1 Concomitant Medications and Procedures

All concomitant prescription and over the counter medications taken during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

1.2 Prohibited Medications

Contraindicated medications will be determined per the package insert of the DAA, per standard of care.

6 Study Schedule

Study visits, including screening, will occur at the Center for Infectious Diseases (CID) or Drug Treatment Center (DTC) at the University of Maryland, or a Unity Healthcare clinic, based upon scheduling availability to accommodate each treatment group. The research coordinators will also oversee research operations in the clinics. See Appendix B for a detailed Study Schedule.

All phlebotomy related to the study will be done by a phlebotomist working in the clinic or clinic staff. All laboratory studies related to standard of care will be performed as per the standard practice at the site. All blood samples for storage for research will be couriered to the IHV lab.

All Cardiac MRIs will be performed at the National Institues of Health (NIH).

Participants will be given a calendar of scheduled study visits and will be informed that any clinic visits outside of scheduled study visits may be either unscheduled visits or non-study visits. Subjects will receive this information when given the visit calendar.

Participants who are no-show for visits will be contacted as per the standard procedure for missed visits at each clinic site.

6.1 Screening /Enrollment

Screening will occur at the collocated HCV clinics at the Unviersity of Maryland Insistutes of Human Virology, CID or DTC, and the Unity Healthcare Center. Subjects who meet inclusion criteria and who consent to the study will be enrolled. Outside labs performed within the last 6 months may be used to determine eligibility. Women of childbearing potential will have a pregnancy test at screening visit. All screeners will submit a urine drug screen.

6.2 Interim Visit

Up to 36 patients (12 from each group) will have a cardiac MRI performed at the NIH after screening but before Day 0 (the start of HCV treatment). See Appendix C for MRI procedure and specific inclusion and exclusion criteria.

6.3 Standard of care HCV treatment

All participants with HCV will be started on HCV treatment on Day 0 after confirming eligibility. Patients will complete visits and laboratory monitoring as per standard of care guidelines.

6.4 Study procedures – HCV treatment

During HCV treatment and in the follow-up period, patients with HCV will undergo monitoring for treatment adherence and safety per Standard of Care. Laboratory parameters and imaging used as part of the study endpoints are listed below. See Appendix B Study Schedule.

Cholesterol measurements
Patients' total cholesterol and LDL cholesterol will be obtained at screening and week 72 for cardiac risk calculations.

Cardiac biomarker and systemic inflammation assessment
For all participants, labs will be drawn at screening, week 24, and week 72: high sensitivity CRP (hSCRP), high sensitivity TRP (hsTRP), soluble markers of inflammation (IFN-Ɣ, TNF-α, IL-6, CXCL9, CXCL10, CXCL11) and activated and exhausted naïve and memory T cells (percent of CD8+ and CD4+ T-cells which are HLA-DR+, CD38+, Tim-3+, or PD-1+).

Cardiac MRI
A subset of patients will undergo cardiac MRI; up to 12 patients will be recruited from each of the three groups to undergo cardiac MRI at the NIH clinical center at Day -7 (interim visit) and week 72. Patients who are claustrophobic or cannot tolerate the MRI procedure will not be selected for this portion of the study. Cardiac MRI will be utilized to assess changes in myocardial injury, degree of post-contrast enhancement, T1 mapping, and the function of the myocardium. See Appendix C for more details.

6.4.1 Stored sample collection

Blood samples for storage and research will be obtained at screening (total of 11 tsp), and at weeks 24 and 72 (a total of 9 ½ tsp). Samples collected will include:

- Serum storage (10 mL) SST/tiger top (2 teaspoons)
- Plasma storage (6ml) EDTA (1 teaspoon)
- DNA paxgene will be collected (8.5ml) one time at baseline (1 ½ teaspoon)
- RNA paxgene will be collected (2.5ml) (1/2 teaspoon)

- Peripheral blood mononuclear cells (30 ml) Green top/heparin (6 teaspoons)

6.4.2 HIV and HCV monitoring

HCV RNA will be checked per standard of care. HIV VL and CD4 will be checked per standard of care for HIV mono- and co-infected patients. HIV antibody/antigen will be checked at screening for those who are HCV mono-infected.

6.4.3 Viral sequencing

Individuals with new seroconversion to HIV will have sample sent for viral sequencing and phylogenetic analysis. Individuals with detectable HCV RNA after completion of HCV treatment or new infection during the follow up period will have current sample, and baseline stored sample sent for viral sequencing and phylogenetic analysis.

6.4.4 Linkage to care

Any participant who seroconverts to HIV+ will be immediately linked to care, in DC or in Baltimore.

6.5 Early Termination Visit

Participants who discontinue HCV treatment prior to treatment completion for medical or personal reasons will be given the option of being followed as per study schedule for lab monitoring.

7 Potential Risks and Benefits

7.1 Potential Risks

Given this investigation is centered on a standard model of care, the main risks are related to any blood draw outside of standard of care, and loss of confidential data.

Participants who receive treatment for HCV may experience side effects from the medication they receive. They will receive one of the following medication to treat hepatitis C: Elbasvir/Grazoprevir (Zepatier), Sofosbuvir/Ledipasvir (Harvoni), Sofosbuvir/Velpatasvir (Epclusa), Glecaprevir/Pibrentasvir (Mavyret), Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi).

Common side effects (those that occured in more than 5% of the patients in clinical trials) each medication is listed below:

Elbasvir/Grazoprevir (Zepatier):

- Fatigue
  Headache

Sofosbuvir/Ledipasvir (Harvoni):

- Fatigue

- Headache
- Nausea
- Diarrhea
- Insomnia

Sofosbuvir/Velpatasvir (Epclusa):

- Headache
- Fatigue
- Nausea
- Insomnia
- Lack of energy

Glecaprevir/Pibrentasvir (Mavyret):

- Headache
- Fatigue
- Nausea
- Diarrhea

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi):

- Headache
- Fatigue
- Diarrhea
- Nausea
- Insomnia
- Lack of energy

Other potential risks include risks of phlebotomy that include: pain, bruising, fainting and very rarely, infection. These risks will be minimized by having trained staff perform the procedure.

There is potential for loss of confidentiality, which will be minimized by providing privacy during study visits. In addition, all laboratory specimens, and research records will be coded by a number to maintain subject confidentiality. Electronic data will be password protected.

Potential risks from MRI are outlined in Appendix C. Of note, the cardiac MRI is considered to be greater than minimal risk. If you elect to have the cardiac MRI, you will be required to sign a separate consent form which will explain the procedure and risks in more detail.

7.2 Potential Benefits

Subjects may be cured of hepatitis C during the course of this study. Also, they will contribute to the body of scientific research on treatment of hepatitis C and cardiodvascular risk in people with living with HIV and/or HCV. Furthermore, by achieving functional cure of HCV, subjects will no longer be a potential source of HCV transmission in the community. It is possible that subjects will receive no benefit from the study participation.

8 Stored Samples and Future Research

We will study the viral and host immunity to HCV and HIV in all patients. The results will be used to characterize each individual with regards to immune status and chronicity of disease. Studies on research samples may include the following:

A] HCV genome sequencing may be performed on plasma using the protocol as described and compared for variability and relatedness of sequences.

B] We will screen sera from all patients for differential expression of protein using multiplex cytokine arrays, which has the capability of detecting several different cytokines and other biologically relevant proteins.

C] We will perform detailed phenotypic and functional evaluation of immune cell types in the periphery. This will help us in determining the nature of antiviral immune responses in patients who are chronically infected, achieve SVR and acquire new HCV and HIV infections. Determination of specific immune defects in these individuals are important milestones in deciding future therapeutics and protective immunity to reinfection. Exhaustion and activation markers on T, B and NK cells will be quantified. Specific immune responses against pooled HCV peptides will be performed using an ELISPOT assay and/or flow cytometry.

Future use of the specimens will be based on the scientific merit of the investigation and would be decided by the Principal Investigator. They would be related to the study of HCV and/or HIV. Other investigators may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval. If approved, and once a Material Transfer Agreement (MTA) has been established, the study team may send de-identified samples to the collaborators. Investigators will use stored samples only for research.

8.1 Intended Use:

Some blood samples may be stored for future analysis in this research study. These samples will be stored by the IHV researchers and may be used in future research to learn more about HCV and HIV, the immune system and/or other related medical conditions. The blood will be used over time to gain a better understanding of the pathogenesis of HCV and HIV. Genetic testing will be performed. Different analytical

and laboratory methods will be employed including but not limited to: PCR, ELISA, ELISPOT and immunohistochemistry; RNA/DNA, cytokine and antibody quantitation; viral particle detection and identification of genetic markers. The consent will include language for specimen storage.

8.2 Storage:

Samples will be kept in secure facilities with limited access. Samples and data will be stored using a unique identifier. Only investigators and study staff will have access to the samples and data.

8.3 Tracking:

Extra blood samples will be stored using a unique identifier that only the study team can trace back to the participants. These stored samples as well as a linkage file will be maintained in a database that will be managed by the Investigators and/or Study Coordinators and will be maintained on the IHV server. This database will also be stored on the password-protected computer of the Lead-Investigator/Study Coordinator in an encrypted and/or password-coded file.

8.4 Disposition at the Completion of the Protocol:

At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol. Final disposition of any samples cannot be done without written permission from the PI.

8.5 Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:

- Any loss or unanticipated destruction of samples or data resulting in a violation that compromises the scientific integrity of the data collected for the study will be reported to the IRB.
- Participants may request at any point not to have their samples stored. In this case, the Principal Investigator will destroy all known remaining samples and report what was done with the samples to both the participant and to the IRB. This decision will not affect the subject's participation in any other protocols.

Generally, the results from the research stored samples will not be given to the participant's primary care provider or appear in the medical record. This is because the test results, unlike routine medical testing, may be experimental or preliminary. The relevance of these tests to direct patient care may be unknown. At the participant's request, the results of any research tests will be discussed with the primary care physician by the Investigators.

9 Assessment of Safety

As this is a pilot, non-randomized, controlled perspective study involving standard of card treatment, with interventions limited to non-standard of care blooddraws and cardiac imaging, safety issues are not expected. Only those reportable Adverse Events (AEs) related to the research procedures will be reported or those not expected from cardic MRI (expected MRI AEs are Mild allergic reaction to contrast agents; Acute renal insufficiency related to iodine-based contrast agent; Subcutaneous injection of contrast agents). The PI will review the safety data and report any unexpected events to the IRB along with the annual continuing review.

9.1 Recording/Documentation

At each contact with the patient, information regarding adverse or unexpected events related to research procedures will be elicited by appropriate questioning and examinations and will be immediately recorded in electronic progress notes. Source documents will include an electronic health record and laboratory reports. Source documents will be reviewed in a timely manner by the research team.

9.2 Definitions

Adverse Event: Any untoward medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

Protocol Deviation: Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

- Those that occur because a member of the research team deviates from the protocol.
- Those that are identified before they occur, but cannot be prevented.
- Those that are discovered after they occur.

9.3 Reporting Protocol deviations, AEs and Deaths

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected adverse events will not be reported to the IRB unless they occur at a rate greater than that known to occur in those having phlebotomy procedures normally. If the rate of these events exceeds the rate expected by the study team, the events will be classified and reported. Deaths related to the natural history of hepatitis will be reported at the time of continuing review (see annual reporting to the IRB). If a death occurrs while the participant is at the NIH it would be reported to the Clinical Director of the Clinical Center, the Clinical Director of NHLBI, and the UMB PI in real time as reported as required by UMB IRB.

9.3.1 Expedited Reporting to the IRB

Any reportable new information (RNI) will be reported to the IRB within 5 business days. This includes:

1) Information that indicates a new or increased risk, or a safety issue.
2) Any harm experienced by a subject or other individual, which in the opinion of the investigator are unexpected and probably related to the research procedures.
3) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
4) Failure to follow the procedure due to the action or inaction of the investigator or research staff.
5) Breach of confidentiality.
6) Change to the protocol taken without prior IRB review to eliminate an apparently immediate hazard to a subject.
7) Complaint of a subject that cannot be resolved by the research team.
8) Premature suspension or termination of the research by the sponsor or the investigator.
9) Audit, inspection, or inquiry by a federal agency.
10) Written reports of study monitors.

The NIH site PI and/or study team will report any RNI to the UMB PI so that they are reported within the above timeframe to the UMB IRB.

9.3.2 Waiver of Reporting Anticipated Protocol Deviations, Expected non-UP AEs and Deaths

Deviations in the protocol that do not rise to the level of serious or continuing non-compliance, and unanticipated or adverse events that are NOT serious, unexpected AND related to research protocols need not be reported in an expedited manner to the IRB. Rather, such RNI should be reported as a group at the time of annual renewal (see below)

9.4 Annual Reporting to the IRB

The following items will be reported to the University of Maryland IRB in summary at the time of Continuing Review:

- Serious adverse events or deaths that are not related to the research
- All adverse events associated with research including expected AEs Protocol deviations. This includes AEs related to phlebotomy within 48 hours of procedure.
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported

9.4.1 Type and Duration of the Follow-up of Subject after Adverse Events

All SAEs and non-serious AEs identified in this study will be followed until resolution or until the PI judges the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that the follow-up may be required for some events after the participant discontinues participation from the study. These events will be reported to the IRB annually.

10 Withdrawal of a Subject

A participant may withdraw from the study at any time. As part of their duties to ensure that research participants are protected, the IRB, IHV, or other government agencies may discontinue the study at any time. Voluntary withdrawal from the protocol may occur at any time at the request of either the participant or the PI. If a request is made to withdraw from the protocol, all further planned study procedures will be immediately cancelled and further follow-up will be terminated. Samples and data already collected may continue to be used. If a patient becomes pregnant during the course of the study, the patient will be discontinued from the study.

Of note, women who become pregnant during the study will be withdrawn and hepatitis C treatment will be stopped. She will be instructed to see an obstetrician and inform the doctor of her specific hepatitis C regimen at the time of conception. If the partner of a man on hepatitis C treatment gets pregnant, he will not be withdrawn from the study, but told to use condoms during intercourse and instruct his partner to let her obstetrician know of his hepatitis C treatment regimen at the time of conception.

10.1 Return of Withdrawn/Removed Subjects

A participant who has withdrawn may not return to the study.

11 Remuneration Plan for Subjects

Participants will not be renumerated for receiving HCV treatment.

Participants will receive $25 remuneration as gift cards at those visits where stored sample blood draws are completed. Those visits are Screening, week 24, and week 72. If additional visits are needed to obtain bloodwork or imaging, this additional visit would also warrant a $25 remuneration. We will not exceed a maximum of 3 additional visits and will encourage combined visits.

Participants will receive $100 remuneration as gift cards provided by UMB study staff whilst working as special volunteers at the NIH site when participants have an MRI. These visits are at the time of day -7 (interim visit) and week 72. Poonam Mathur, Sarak Kattakuzhy, Elana Rosenthal, and Rachel Silk, are UMB sub investigators who are also special volunteers at NIH and are fully credentialed and able to see research patients at the NIH. They are also authorized to obtain informed consent, provide remuneration to subjects visiting the NIH site, have access to identifiable data, see patients at NIH and participate in manuscript preparation/review.

12 Monitoring

As this is an observational study with intervention limited to laboratory and radiologic data collection, safety issues are not expected. The PI and the study team will conduct regular monitoring of safety and report to the IRB as specified in section 9.

13 Statistical Considerations

13.1 Sample Size Justification and Power

The proposal primary outcome for cardiovascular risk is change in hsCRP. The primary hypothesis is that HCV eradication will result in at least a two-fold decrease from the baseline elevated hsCRP to 12 months post-functional cure in HCV-monoinfected and HIV/HCV-coinfected patients, respectively. Based on a previous study, mean hsCRP before starting IFN-therapy in HCV-monoinfected patients was 0.97±0.11 mg/L compared to 0.07± 0.07 mg/L in healthy controls(23). Among SVR patients the median hsCRP at baseline was 0.64 mg/L and decreased to 0.25 mg/L after treatment. With a sample size of 30 patients in each group, we assume than 95% will achieve SVR with Zepatier (elbasvir/grazoprevir), resulting in a sample size of 28 patients in each group. In a paired t-test analysis (from baseline to 12-month post-treatment), with α=0.05, power of 90% (1-β), and standard deviation (σ) = 0.15, we will be able to detect a true difference in the mean hsCRP response of matched pairs of 0.1 mg/L in each group or 0.8 mg/L with 80% power.

13.2 Statistical Analysis

We will perform univariate analysis to describe the demographic and clinical characteristics of the study population. Count with percentages will be calculated for categorical variables and mean + standard deviation or median (interquartile range) for continuous variables. The independent variable is the three groups of participants with HCV, HIV/HCV, and HIV. Separate analysis will be done for each study group for the change in the primary outcome of HsCRP, from baseline to 18 months after baseline, in a paired t-test analysis, as well as for the secondary outcomes of cardiac biomarkers, MRI, and cellular and soluble immune markers of activation. Baseline comparison of hsCRP, cardio biomarkers, MRI, and cellular and soluble immune markers of activation between the three groups of participants will be performed using one-way or Kruskal-Wallis analysis of variance (ANOVA) for continuous variables and chi-square test of independence or Fisher's exact test for categorical variables. A linear regression model will be used in adjusted analysis for continuous dependent variables, while logistic regression model will be used in adjusted analysis for binary dependent variables. All analysis will be conducted in SAS, version 9.4 (SAS Institute, Inc., Cary, NC) with a P-value of less than 0.05 indicating statistical significance.

14 Ethics/Protection of Human Subjects

14.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will personally sign and date the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. Consenting process will be documented in the record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Per NIH policy, subjects participating in the MRI portion of the study will be consented with a NIH consent for the cardiac MRI that takes into account that the NIH is subject to the Privacy Act and is therefore not a HIPAA covered institution.

14.2 Illiteracy and Consenting

As the majority of the patient populations from which the study participants are drawn are literate, written consent will be obtained. Per UMB IRB policy, for participants unable to read, the written informed consent and any other written information will be read and explained to the participant by the person obtaining consent. An impartial third party will be present for the entire consent process. Once the subject has orally consented, the participant and witness will sign the consent form.

14.3 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, FDA, the Joint Commission or the HHRP.

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APPENDIX B: Study Procedures Table

					M6	M18
HCV Treatment	**Screening**	**Interim visit (Day -7)**	**Day 0**	**End of Treat-ment**	**Week 24**	**Week 72**
Provider Visit	X^		X	X	X	
HCV SOC Labwork	X			X	X	
HCV RNA	X			X	X	X
HCV Ab	X^					^
HIV 4th gen Ag/Ab	X					
HIV SOC Labwork	^					
HBV DNA (for HBcAb positive)	X^					
Total Cholesterol and HDL Cholesterol	X^					X^
Fibroscan or Fibrosure	X^				X^	
hsCRP, hsTRP	X^				X^	X^
Markers of inflammation	X^				X^	X^
Memory T cells	X^				X^	X^
Cardiac MRI		X^				X^
Urine Drug Screen	X^					

X= HCV mono- and HIV/HCV co-infected
^= HIV mono-infected

APPENDIX C: Cardiac MRI

Introduction and MRI Procedure

Cardiovascular magnetic resonance imaging (MRI) is an excellent imaging modality capable of assessing cardiac anatomy, myocardial function, myocardial infarction/fibrosis, as well as many other types of myocardial diseases. Patients infected with the hepatitis C virus are at increased risk of cardiovascular disease. Cardiac MRI can be used to assess for epicardial coronary artery plaque, sequela of epicardial coronary artery disease, such as myocardial infarction, as well as microvascular disease.

Each patient participating in the MRI scan will receive an oral and written explanation of the purposes, procedures, and risks of this study in language appropriate for the individual's level of understanding.

All cardiac MRI scans for this study will be performed on an FDA approved 3.0T or 1.5T scanner (Aera - Siemens Healthcare, Erlangen, Germany). The radiofrequency power levels (SAR limits) will be kept within the FDA established limits. A body coil will be used during the exam. A body coil is a noninvasive device external to the body that acts as antennae to receive radiofrequency signals out of the body. The body coil used during the MRI exam will follow FDA parameters.

For the cardiovascular MRI exam, patients will receive an intravenous injection of gadolinium chelate (Gadavist, 0.15 mmol/kg) via an MRI compatible power injector.

Inclusion Criteria for the Cardiovascular MRI

18 years of age or older
Written informed consent

Exclusion Criteria for the Cardiovascular MRI

Patients with the following devices are excluded from participating in the cardiovascular MRI study:

- Central nervous system aneurysm clip
- Implanted neural stimulator
- Implanted cardiac pacemaker or defibrillator
- Cochlear implant
- Ocular foreign body (e.g. metal shavings)
- Implanted insulin pump
- Metal shrapnel or bullet

The following groups of people are excluded:

- Pregnant women
- Lactating women unless they are willing to discard breast milk for 24 hours after receiving gadolinium
- Patients with stable renal disease (estimated glomerular filtration rate (eGFR) < 30ml/min/1.73 m^2 body surface area). The eGFR must be within 2 weeks of the MRI exam. Patients who are over 60 years of age, have a history of renal failure, or have type I or II diabetes mellitus must have laboratories the same day as the MRI exam.

- Patients with acute renal disease.

Monitoring Patients during the Cardiovascular MRI scan

The cardiovascular MRI exam is expected to last 60 to 90 minutes in duration. The MRI technologist will monitor the exam. Monitoring includes continuous ECG-gating. Blood pressure and pulse oximetry will be measured if clinically indicated. Patients may elect to withdraw from the MRI scan at any point.

Benefits/Risks of the Cardiovascular MRI

The cardiovascular MRI exam with gadolinium contrast involves greater than minimal risk, however may be of direct benefit to the individual patients [45 CFR 46.102(i)]. A clinical report of the exam will be available for the patients' physician.

MRI does not use ionizing radiation, and is extremely safe on a properly screened population. There is potential risk related to the magnetic field strength in patients with implanted metal devices (cochlear implants, etc), resulting in movement of these objects and subsequent harm to the patients. Patients will be screened for these objects (see exclusion criteria above) and excluded if they meet any of the exclusion criteria.

Peripheral nerve stimulation is unlikely to occur with our imaging parameters. It occurs when the magnetic field gradient switch occurs so fast that it results in peripheral nerve depolarization. The patient may feel a twitch or possibly some pain. Patient education as well as audio feedback from the patient during the exam will be used for the issue of possible peripheral nerve stimulation.

The scanner is operated within FDA guidelines for radiofrequency power levels. However, there is a small chance that a damaged or dysfunctional coil could cause some local warming in the body. Thus, for safety purposes, we ask all patients to report this sensation so we can modify scans and also verify the integrity of the hardware.

Gadolinium Administration for the Cardiovascular MRI exam

Patients must have an IV placed for gadolinium administration. Potential risks of IV placement include discomfort, bruising/bleeding, and vasovagal reactions.
The gadolinium agent used for the cardiovascular MRI exam, Gadavist, is commercially available and routinely used in hospital radiology practices. Studies in large patient populations have shown that gadolinium is safe without side effects in the majority of patients. If side effects occur, they are often mild and include headache and nausea. Severe reaction such as shortness of breath, wheezing, and hypotension are rare.
The US Food and Drug Administration has issued a warning that the administration of gadolinium (updated September 9, 2010) has been associated with development of a disease call nephrogenic systemic fibrosis (NSF). All cases to date have occurred in patients with severe renal disease, including patients on dialysis. NSF has been nearly eradicated by avoiding gadolinium contrast use in patients with creatinine clearance <30cc/min.[4-7]

On July 27, 2015, the US Food and Drug Administration issued a safety announcement stating that they are investigating the risk of brain deposits of gadolinium contrast agents. Several studies have shown a correlation between high signal intensity

in the dentate nucleus and globus pallidus of the brain on unenhanced T1-weighted images and the number of previous administrations of gadolinum contrast agents in both adult and pediatric patients with normal renal function, suggesting deposition of the gadolinium contrast agent into the brain.

More recently, autopsy studies have confirmed that gadolinium deposits in the brains of patients with normal renal function as well as in other organs including the bones and the skin. Murata et al showed that macrocyclic gadolinium contrast agents deposit in the body to a significantly lesser degree than the linear open chain gadolinium contrast agents. The effects (adverse or otherwise) of gadolinium deposition in patients with normal renal function remains unclear and the FDA investigation is ongoing.

The gadolinium agent used for our cardiovascular MRI exams is Gadavist, which is a macrocyclic type of gadolinium contrast based agent. Macrocyclic agents are currently considered the safest type of gadolinum based contrast agent available.

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