**AOSC Project Proposal DUE FEBRUARY 1, 2013 (Sample)**

**(Please submit as a typed Word file)**

**Student Name:** Sample

**Mentor Name:** Sample

**Mentor Department and Division:** Sample, Northwestern University

**Mentor Email:** Sample

**Date**: 1/20/2013

**Project Title:**  Cryptogenic liver disease in HIV-seropositive men

**Background:**

Liver disease is now the leading cause of morbidity and mortality in HIV-seropositive patients. Although it is known that co-infection with HIV and hepatitis B and/or hepatitis C virus leads to more rapidly progressive liver disease, recent reports indicate that some HIV-positive patients develop severe cryptogenic liver disease (progressive liver disease in the absence of other known causes of hepatic disease). This may be due to a rare form of liver disease called Nodular Regenerative Hyperplasia (NRH). In the general population, most cryptogenic liver disease is likely due to obesity and the metabolic syndrome causing fatty liver. It has not been previously studied whether cryptogenic cirrhosis or liver failure in HIV-seropositive patients occurs in a similar manner. Therefore, we will perform a retrospective cohort study of HIV-infected and noninfected patients with cryptogenic liver disease undergoing liver transplantation evaluation to determine the etiology and associated risk factors for the development of end-stage liver disease (1).

**Hypothesis or Research Question:** Advanced cryptogenic liver disease in HIV-infected patients is caused by nodular regenerative hyperplasia (NRH), rather than cirrhosis.

**Significance:** Liver disease is now the leading cause of mortality in HIV-seropositive patients. The pathogenesis of cryptogenic liver disease in HIV-positive patients is poorly understood.

**Study Design (1 page maximum):**

* A single-centre retrospective cohort study of patients with advanced liver disease receiving medical care at the out-patient liver transplant evaluation clinic and HIV center at Northwestern Memorial Hospital (Chicago, IL, USA) between 1986 and 2007.
* Patient charts or Electronic Data Warehouse (EDW) data from approximately 725 patients followed in the liver transplant clinic and 115 patients with HIV and end-stage liver disease will be screened
* Subjects are included if they have clinical evidence of: decompensated liver disease, or portal hypertension as defined by gastroesophageal varices, ascites or hepatic encephalopathy.
* All subjects must have been evaluated by a hepatologist and an infectious diseases specialist.
* Patients are excluded if they had evidence of acute or chronic viral hepatitis infection, autoimmune hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease, excessive alcohol use as defined by the National Institutes of Alcohol Abuse and Alcoholism (more than 4 drinks daily for men or more than 3 drinks for women) or any other known cause of hepatic disease
* All clinical data will be abstracted retrospectively by a review of out-patient electronic or paper medical records or from the Electronic Data Warehouse (EDW), and data will include the following factors:
	+ Demographic information (age, gender, ethnicity, education, marriage or equivalent status)
	+ Family history of liver disease
	+ Alcohol consumption
	+ Medication history
	+ Body mass index (BMI) at time of transplantation evaluation
	+ Complications of liver disease (encephalopathy, ascites, SBP, variceal bleeding)
	+ Clinical outcomes will specifically include death while on the transplant list and time from listing until liver transplantation.
	+ Laboratory data collected will include: complete blood count, serum chemistries, prothrombin time, viral hepatitis serologies, serum ferritin, alpha-fetoprotein, Hg A1C and lipid panels.
	+ Clinical and laboratory data collection specific to HIV-infected patients will include length of HIV diagnosis, AIDS-defining illnesses, CD4 cell count measurements, HIV viral load (VL) determinations, prior use of DDI of D4T and clinical evidence of lipodystrophy.
	+ Two severity of illness scores will be utilized in this study: the Child–Pugh–Turcotte (CPT) score and Model of End-stage Liver Disease (MELD) score. The highest recorded scores for each patient will be included for analysis.
* A radiologist blinded to clinical data will re-confirm all abdominal imaging findings
* Radiographic findings determined to be consistent with cirrhosis will include: enlarged left/caudate hepatic lobe and atrophied right lobe; signs of portal hypertension; transverse gallbladder; deep notch sign; prominent fat in gallbladder fossa; and nodular liver
* Liver biopsies and liver explants will be re-analysed by two blinded pathologist using a five-stage fibrosis scoring system (F0–F4). Reticulin silver-impregnated stains will be evaluated for evidence of FNH

**Subjects (if applicable)**

**Entry Criteria:** Retrospective chart review

**Recruitment:** Not applicable

**Justification of project feasibility:** There area large numbers of patient charts that are readily available and that can be retrospectively reviewed in both cohorts. Power calculations will be performed with the assistance of a statistical consultant. If required, the sample size can be extended to include patients from 2008 to the present.

**Statistical Analysis (statistical consultation can be provided):** Statistical analysis will be conducted using ANOVA or Chi-squared analysis. When continuous variables are compared between two groups, unpaired t-tests will be used for normal distributions and Mann–Whitney rank sum tests for non-normal distributions. A p-value of <0.05 is considered statistically significant. Of note, this statistical analysis will be further discussed with a consulting statistician. Power Size Calculation: <http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx>

**Does the study require IRB approval:** Yes

**If so, what is the IRB status of the study:** Submitted 1/14/2013

**Appropriate references (approximately 5-20) should be provided.**

The above sample protocol was based on :
1. [Dinh MH](http://www.ncbi.nlm.nih.gov/pubmed?term=Dinh%20MH%5BAuthor%5D&cauthor=true&cauthor_uid=19459992), [Stosor V](http://www.ncbi.nlm.nih.gov/pubmed?term=Stosor%20V%5BAuthor%5D&cauthor=true&cauthor_uid=19459992), [Rao SM](http://www.ncbi.nlm.nih.gov/pubmed?term=Rao%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=19459992), [Miller FH](http://www.ncbi.nlm.nih.gov/pubmed?term=Miller%20FH%5BAuthor%5D&cauthor=true&cauthor_uid=19459992), [Green RM](http://www.ncbi.nlm.nih.gov/pubmed?term=Green%20RM%5BAuthor%5D&cauthor=true&cauthor_uid=19459992). Cryptogenic liver disease in HIV-seropositive men. [HIV Med.](http://www.ncbi.nlm.nih.gov/pubmed?term=green%20rm%20stosor) 2009 Aug;10(7):447-53.