CHRONIC HEPATITIS B AND C COHORT STUDY (CHECS)
BACKGROUND AND NEED

Chronic hepatitis B and C represent a major health problem for the United States. The Centers for Disease Control and Prevention (CDC) estimates that approximately 3.2 million Americans are chronically infected with hepatitis C virus, with an estimated 8,000-10,000 hepatitis C virus-related deaths annually. The incidence of acute hepatitis C declined during the 1990’s but has plateaued in recent years. While the incidence of acute hepatitis B has declined markedly since 1990, an estimated 1.25 million Americans remain chronically infected, with an estimated 3,000-5,000 chronic hepatitis B virus-related deaths per year. In the United States, African-Americans are disproportionately affected by chronic hepatitis C virus infection, representing 12% of the U.S. population but approximately 22% of those with the disease. A similar disparity by race exists for Asian/Pacific Islanders, who represent only 4% of the U.S. population but over half of those with chronic hepatitis B infection.

Data from longitudinal cohorts of patients with chronic hepatitis B and C virus infection are needed to understand the spectrum of disease, the natural history, and the public health impact of chronic viral hepatitis. Moreover, current surveillance activities in CDC’s Division of Viral Hepatitis do not follow cases of chronic viral hepatitis longitudinally to monitor treatment and clinical outcomes. Typically, clinical trials of anti-hepatitis drugs (for B or C) are conducted for 24-96 weeks, and patients in these small trials are not usually followed beyond demonstration of therapeutic effectiveness. In addition, much of what we know about the course and manifestations of chronic hepatitis B and C virus infection and associated chronic liver disease comes from much smaller cohort studies that were done before the modern therapeutic era and often included patients coinfected with HIV. With the advent of new therapies for chronic viral hepatitis, the need for a longitudinal observational cohort of persons chronically infected with hepatitis B or C virus has increased.
PROJECT PROPOSAL

To improve the understanding of chronic viral hepatitis and the impact of screening, care, and treatment recommendations, the Chronic hepatitis B and C cohort study (CHeCS) will establish the first comprehensive U.S. longitudinal observational cohort of 15,000 or more patients with chronic viral hepatitis B and C (approximately 3,000 with HBV and 12,000 with HCV). Cohort studies of HIV/AIDS, on which the CHeCS is based, have substantially informed the care and secondary prevention of HIV. For example, data from CDC’s HIV Outpatient Study (HOPS) have informed decisions about the effectiveness of and when to initiate antiretroviral therapy, assessed host factors associated with lipodystrophy, studied preventive therapy for cryptosporidiosis, examined cancer rates, observed the increased incidence of myocardial infarction in protease-inhibitor-drug takers, and many other clinical issues. To ensure rapid implementation of the project, CHeCS will be managed by the CDC Foundation under the scientific direction of CDC. The Foundation expects that, with funding secured, subcontractors would be ready to begin work in January 2009.

Study Objectives

The main objectives of this cohort research are: to determine the extent of the health burden and mortality from chronic hepatitis, to learn where, when and why people who access care are tested, to understand the spectrum and natural history of disease associated with chronic viral hepatitis, as therapies evolve; to monitor the implementation and effectiveness of recommended chronic viral hepatitis care practices, and identify any barriers to this implementation; to monitor the evolution of risk behaviors; to understand the potential costs of care; to understand access and linkage to care (who is in care and who is receiving therapy); and to understand the types of therapy in use, the benefits and risks associated with therapy, and factors influencing outcome of therapy that can be used for guiding treatment services and for planning secondary prevention efforts and care.

Specific studies of benefits and risks associated with therapy can include analyses of the long term safety and efficacy of therapy and specific classes of therapy, the short- and long-term consequences of therapeutic resistance, and the long term consequences of success or failure of various classes or types of therapy.

Suggested initial analyses, presentations and publications include:

1) Basic description of the cohort/methodology. An abstract describing CHeCS has been submitted for the upcoming American Association for the Study of Liver Disease (AASLD) meeting in
November 2009. A “methods” paper will be written early to provide a reference for subsequent study-papers.

2) Where, when and why people got tested for viral hepatitis. This information will mainly come from intake interview and corroborated by medical and lab records. This will include an assessment of how many people were tested for HBV and HCV within the health care systems and where and why they were tested. This information will inform better public health efforts at targeting and screening populations likely to be infected (e.g., ER visitors; patients with other clinical problems with suddenly elevated liver function tests, etc). A larger study, assessing rates of testing and infection with HBV and HCV in the total CHeCS patient population (six integrated medical systems), will be performed when a sufficient number of patients are in the CHeCS database (see below for sources of information).

3) Adherence to drug therapy/Factors associated with successful therapy. This is asked in the intake questionnaire, that will also query many factors that may affect adherence in the general clinical population (outside of controlled clinical trials)--e.g., alcohol/substance abuse, tolerability and side effects of drugs taken over many weeks, months, or years, etc. In addition to patient factors, clinic and treating physician factors can also be examined. Once CHeCS is fully operational, a more focused sub-study can be done, comparing chart notes on prescriptions, pharmacy prescription fill rates and involving more in-depth interview of a large subset of patients.

4) Spectrum of disease/causes of death. Therapy and timing of therapy, and current medical screening and care, for both HBV and HCV are focused on liver pathology and other hepatic and viral lab parameters. However, other organ systems--renal, cardiac, others--may be affected by these chronic viral infections. We think some early analyses should analyze the available health care electronic records (clinics, hepatology and other, hospital data, emergency room visits, etc) and look at rates of diseases and deaths in the CHeCS. Because we will have data that can control for confounding variables not normally collected, such as smoking and drinking, analyses can be controlled for these important factors.

Inclusion of patient behavioral data on factors that may impact health outcomes in hepatitis, such as alcohol or drug use, access to care, quality of life, and adherence to prescribed therapies, is essential in order to be able to correctly interpret clinical outcomes. Such behavioral data, while part of recommended clinical practice, are not consistently available through clinical chart review and will require survey of a substantial proportion of participating patients.

Data will be collected over a five-year period in real-time and include clinical and laboratory information collected during physician-patient interactions and information offered by patients in an automated computer-assisted self interview (ACASI), a confidential self-administered
patient interview conducted at least yearly for the duration of the project. Of particular additional value will be the incorporation into this data set of clinical data collected before patients begin follow-up in CHeCS, the intention being to maximize the period of observation after a diagnosis of chronic viral hepatitis.

Data Sources for CHeCS Patients

The CHeCS database will include the following information from the sites on all chronic hepatitis B and C patients in the cohort:

- Electronic medical records (EMR) from all the CHeCS hepatology clinics/clinicians;
- EMR from all other clinics, hospitals, emergency rooms/departments allied with those hepatology clinics (per integrated medical systems);
- Data from intake interview, such as country of origin, cig/alcohol/substance use, where/when tested, psychosocial measures, etc.;
- Data as entered at each site through CHeCS data entry screens, especially liver biopsy results and drug resistance testing results;
- Billing information (used to monitor completeness of CHeCS data—eg, does CHeCS have data from lab tests that were billed); and
- Ancillary data from other data systems, e.g. death registries, HIV/AIDS reporting system, etc.

Data on non-CHeCS Patients

In addition, because the sites represent integrated medical records systems, access to information on non-CHeCS (non-HBV/HCV) patients will be available for analyses that require comparisons of CHeCS with non-CHeCS patients, such as rates of hepatitis-test positivity in all those tested within the medical systems.

Study Sites

CDC Foundation has received a formal proposal for participation in CHeCS from clinical sites located in urban centers in six states: Alaska, Hawaii, Michigan, New Mexico, Oregon, and Pennsylvania, all of which participate in the HMO Research Network. The table below lists the group of five HMO Research Network institutions, which are collaborating under the direction of the Principal Investigator, Stuart Gordon, MD, at Henry Ford Health System. Four different integrated health care systems, all of which have health maintenance organization (HMO)
components, are represented among the five study sites. The first three sites listed collect data from on average about 30 to 70% non-HMO clinic patients.

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<thead>
<tr>
<th>HMORN Site</th>
<th>Principal Investigator</th>
<th>Hep B Patients</th>
<th>Hep C Patients</th>
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<tr>
<td>Henry Ford Health System (Detroit)</td>
<td>Stuart Gordon, M.D.</td>
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<td>Geisinger Health System (Danville, PA)</td>
<td>Joseph Boscarino, Ph.D., MPH</td>
<td>181</td>
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<td>Lovelace Clinic Foundation (Albuquerque)</td>
<td>Margaret J. Gunter, Ph.D.</td>
<td>73</td>
<td>1674</td>
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<td>Kaiser- Hawaii (Honolulu)</td>
<td>Cynthia Nakasato, M.D.</td>
<td>575</td>
<td>789</td>
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<tr>
<td>Kaiser- Northwest (Portland, OR)</td>
<td>Allison Naleway, Ph.D.</td>
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One additional independent site in Alaska under senior investigator Brian McMahon, MD will participate as a separate cohort site, the Alaska Native Tribal Health Consortium (ANTHC) Hepatitis B and ANTHC Hepatitis C Registries. About 1,500 Alaskan Native and American Indian (AN/AI) patients with chronic HBV infection and about 1,000 patients with HCV infection have been followed by the CDC’s Arctic Investigations unit for up to 20 years. Both retrospective and prospective Alaska registry data will be included in CHeCS.

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<tr>
<th>Alaska Native Tribal Health Consortium (ANTHC)</th>
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<th>Hepatitis C</th>
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**TOTAL PROPOSED COHORT**

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**Note:** The total number of patients shown above includes those for whom current and retrospective data are available (i.e., not limited to 2008, as in the POC/Feasibility Study discussed below).
Proof of Concept/Feasibility Study

To assess the feasibility of enrolling large numbers of chronic HBV and HCV patients in the Chronic Hepatitis Cohort Study (CHeCS) and to determine the types of clinical data readily available from electronic medical records, CHeCS investigators performed a pilot study of chronic hepatitis patients seen during the year 2008 only at the participating health systems. This effort was generously funded by seed money from Vertex Pharmaceuticals. Data were relatively easily obtained for over 11,000 (Please refer to “Note” above) chronic hepatitis B and C patients in six metropolitan areas.

The 2,121 chronic HBV patients were: usually (68%) 30-60 years-old; 53% male; 20% covered by public insurance (Medicare/Medicaid); 31% were Asian or Pacific Islanders, 18% Black; 15% of whom received drug therapy in 2008--usually entecavir, lamivudine, adefovir, tenofovir, or combinations of those drugs; had been followed in the health care system over two years (mean, 25.0 mos); 6% of whom had a liver biopsy in 2008; 54% of whom had HBV DNA levels that were “undetectable”; and 3% of whom had died in 2008.

The 9,163 chronic HCV patients were: usually (71%) 40-60 years-old; 55% male; 29% covered by public insurance; 15% Black, 6% Hispanic; 8% of whom received drug therapy in 2008--usually, pegylated interferon and ribavirin; had been followed in the health care system over three years (mean, 37.1 mos); 7% of whom had a liver biopsy in 2008; 22% of whom had HCV RNA levels over 1 million copies/μl; and 3% of whom had died in 2008.

Despite focusing only on the year 2008—not the 2004-present time frame for patients to be enrolled in the full study—this pilot study indicates the breadth and depth of information available to CHeCS researchers. As well, it provides unique preliminary data on a broad sample of chronic hepatitis B and C patients nationwide.