



California Pacific  
Medical Center

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# LiverReview

CALIFORNIA PACIFIC

LIVER DISEASE MANAGEMENT AND TRANSPLANTATION SERVICES

SPOTLIGHT ON LIVER AND GASTROENTEROLOGY  
ISSUES FACING MINORITY POPULATIONS

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## Hepatitis C and HIV Co-Infection on the Rise

Approximately one-third of U.S. patients infected with human immunodeficiency virus (HIV) are co-infected with hepatitis C virus (HCV). Research is underway to better understand the simultaneous management of these infections and resulting liver disease progression.

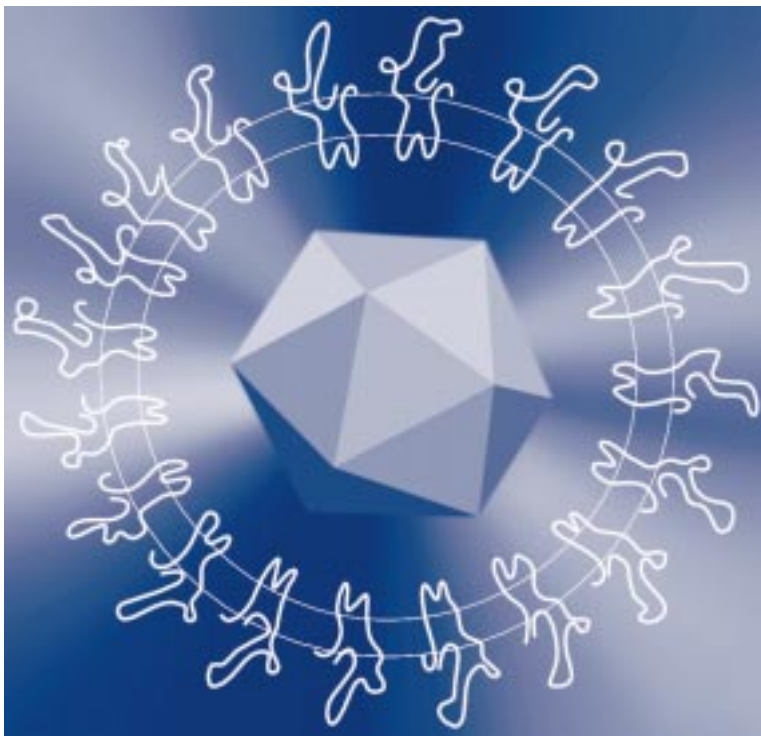
“There are many similarities between HIV and HCV,” says Natalie Bzowej, MD, PhD, of California Pacific Medical Center’s Liver Disease Management and Transplant Program. “Both are single-stranded RNA viruses that share a similar genome structure. However, the protease inhibitors used in the successful treatment of HIV have no beneficial effect on HCV.”

HCV is the only member of the genus Hepacivirus in the Flaviviridae family (see diagram). The HCV genome has a single large open reading frame that encodes a 3,000 amino acid polyprotein that is cleaved into 10 structural or nonstructural proteins by proteases.

### Impact of HIV on HCV Disease

Nationally, 300,000 patients are estimated to have HIV and HCV co-infection. This high number is likely attributed to shared risk factors for disease transmission, most importantly intravenous drug use. Nonparenteral risk factors (vertical or sexual) are much more important for HIV than HCV.

HIV likely worsens HCV liver disease and co-infection is associated with higher HCV viral loads. Evidence suggests an increased rate of fibrosis and cirrhosis progression, as well as liver-related mortality among co-infected patients. The effects of HCV on HIV are more controversial. While one study shows no adverse effects, another shows an increased risk of progression to AIDS and death.



Schematic representation of HCV

“With the development of highly active antiretroviral therapy (HAART), HIV-infected patients are living longer and experiencing increasing morbidity and mortality from other underlying diseases such as HCV infection,” explains Bzowej. In 1991, end-stage liver disease was the leading cause of death in 11% of HIV patients whereas in 1998, 50% of co-infected patients died due to liver disease.

### Management of HIV and HCV in Co-infected Patients

In the majority of co-infected patients, HIV management is the same as in patients with only HIV infection. The Liver Team advocates treatment of both viruses where possible, but in staggered phases. Generally, HIV treatment is recommended first with careful monitoring for hepatotoxicity associated with some of the antiretroviral drugs. Initiation of HAART may increase the alanine aminotransferase (ALT) and viral load for the first three to four months. While concerns have arisen regarding the potential hepatotoxicity of these drugs, elevated liver tests generally return to baseline within twelve months and rarely does therapy have to be interrupted or discontinued. Patients should be counseled against consuming alcohol.

continued on p.2

#### PAGE ONE

Hepatitis C and HIV  
Co-Infection on the Rise

#### PAGE TWO

Uncovering the History and  
Optimal Treatment for  
Hepatitis B Infection in  
Asian Populations

#### PAGE THREE

Uncovering the Natural  
History of Hepatitis C in  
African Americans

Women Suffer  
Disproportionately from  
Irritable Bowel Syndrome

#### PAGE FOUR

Oakland-based Clinic Offers  
Transplant Evaluation and  
Research Trials

HCV vs. HIV Infection		
	HCV	HIV
<b>U.S. Infections</b>	4 million	<1 million
<b>Worldwide</b>	170 million	40 million
<b>Daily Production of Virus</b>	10 <sup>12-13</sup>	10 <sup>10</sup>
<b>Curable?</b>	Yes	No

### Increasing Relevance of HCV in HIV-Infected Patients

Potent combination therapy for HIV has resulted in successful suppression of HIV virus replication, prevention of drug resistance and thus, a decrease in the death rate from HIV.

Patients with HIV who are diagnosed with HCV should receive a liver evaluation and possibly treatment for their HCV disease. A liver biopsy will stage the extent of liver disease and need for

treatment. Because the natural history of these infections is not well understood, HIV/HCV co-infected patients should be enrolled in clinical trials whenever possible.

**5 STEPS FOR MONITORING LIVER DISEASE IN HIV-POSITIVE PATIENTS**

1. Screen HIV-infected persons for HCV
2. Advise HIV- and/or HCV-infected patients of the deleterious effects of alcohol
3. Screen patients for the hepatitis A and B viruses. If negative, patients should be vaccinated
4. Have HIV/HCV co-infected patients examined to determine the extent of liver disease and possible need for treatment
5. Monitor liver enzymes after co-infected patients initiate HAART therapy. Hepatitis flares do not necessarily prohibit HAART use in co-infected patients

## Uncovering the History and Optimal Treatment for Hepatitis B Infection in Asian Populations

### High Infection Incidence Prompts Closer Examination and Research of Virus

Understanding the natural history of hepatitis infection will one day result in tailor-made treatments for a patient’s virological, histological and clinical profile. Yet while such treatments are still years from development, current research of ethnic and gender response to hepatitis is helping physicians better understand the natural history and treatment differences in various populations.



Hepatitis B virus (HBV) infection, one of the most common viral infections in humans, is of particular interest to researchers because of its high incidence among Asian populations. In Asia-Pacific areas such as Southern China, Korea, Philippines, Melanesia, Micronesia and

Polynesia, more than 10% of the population have chronic hepatitis B, of which about 25 – 40% will eventually die of liver disease.

### Natural History of HBV In Chinese

Locally, HBV and its natural history are of particular interest because of California’s large Asian population. Because HBV can hide inside the body, people often do not know they have the infection until being specifically tested.

In Chinese populations, HBV infection is usually acquired perinatally, so its natural history is very different than in Caucasian populations where it is

typically acquired in adulthood. For Caucasians with chronic HBV infection, there are two phases:

- Hepatitis B e antigen (HBeAg) positive phase— This early stage consists of active HBV replication and variable degrees of inflammatory activity in the liver.
- Seroconversion from HBeAg to anti-Hbe—In this phase, there is typically a decrease in viral replication and remission of disease activity with integration of HBV DNA into the liver cell DNA with the increased subsequent risk of liver cancer.

Conversely, Chinese patients with HBV have an additional immune-tolerant period at the first phase of infection. Although they are HBeAg positive and have high serum HBV DNA levels, Chinese patients are asymptomatic with normal serum alanine aminotransferase (ALT) levels and minimal liver damage. This period can last for more than 20 to 30 years. The immune tolerance among Chinese may be related to the transplacental transfer of maternal HBeAg. Once seroconversion from HbeAg to anti-Hbe occurs, the ultimate outcome of chronic HBV infection appears to depend on the duration and severity of liver damage during the immune clearance phase.

### Treatment Options

Until recently, the only approved agent for treatment of chronic HBV infection in many countries has been interferon-a (IFN-a). Now, thymosin-a1 and lamivudine monotherapy have also been approved in China and in the U.S., lamivudine has received approval. In Asian populations with chronic HBV, IFN-a has shown to be effective in terminating viral replication of HBV and lamivudine has proven to be effective in suppressing HBV DNA. While these results are promising, the long-term benefit of both therapies remains to be determined and research into treatment response continues.

# Discovering the Course of Hepatitis C in African Americans

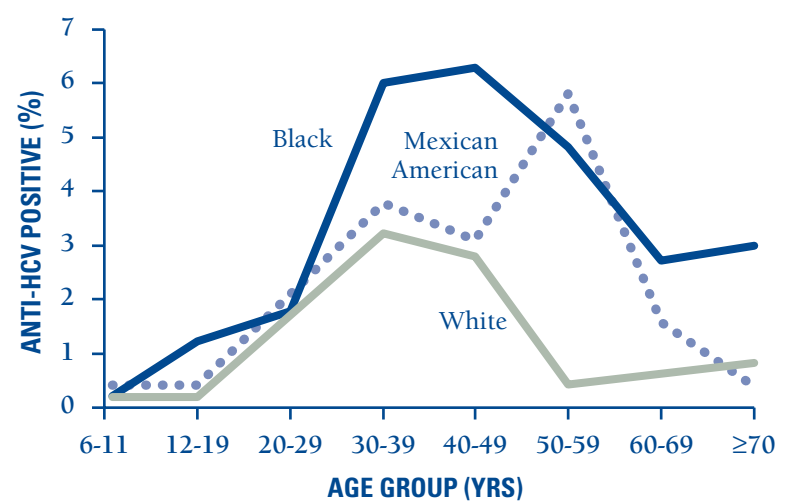
Hepatitis C virus (HCV) is one of the most important causes of liver disease in the United States, affecting approximately 4 million or 1.8% of the population, of which 2.7 million are chronically infected. African Americans and young people aged 30-39 have the highest prevalence of hepatitis C.

Since 1989, the annual incidence of new HCV infections has declined by more than 80% to approximately 36,000 new infections per year. Current cases being identified largely represent infections that have been acquired much earlier. For this reason, the impact of hepatitis C infection is expected to grow for many years to come.

## Natural History and Treatment of Hepatitis C in African Americans

Limited data on the natural history of HCV suggests a slower rate of fibrosis progression in African Americans than Caucasians. Among African Americans, the response rate to interferon monotherapy for HCV is lower than in Caucasian populations. This contrasts with the higher response rates to interferon for hepatitis B among African Americans. An inherent difference in the immune response is thought to be responsible for these differences and is the subject of ongoing research studies at California Pacific's Liver Clinics.

## PREVALENCE OF HEPATITIS C VIRUS (HCV) INFECTION BY AGE AND RACE/ETHNICITY - USA, 1988-1994



Source: Third National Health and Nutrition Examination Survey, CDC.

# Women Suffer Disproportionately from Irritable Bowel Syndrome

As the most common of the 20 functional gastrointestinal (GI) disorders, irritable bowel syndrome (IBS) affects 15-20% of U.S. adults, of which 70% are women. IBS is a 'diagnosis of exclusion,' meaning it is based on symptoms and tests are required to rule out other symptom causes. If these tests prove negative, an IBS diagnosis can be made. Symptoms of IBS include lower abdominal pain/discomfort, altered bowel function with features of disordered defecation (urgency, altered stool consistency and frequency, incomplete evacuation) and bloating.

Nearly 1 in 20 women with IBS report being hospitalized in the previous year and another 25% have reported being hospitalized for IBS in the past. Overall, data shows that women with IBS have 71% more abdominal or intestinal surgeries and at least twice as many gallbladder operations, hysterectomies and appendectomies than women without IBS.

Unfortunately, the pathophysiology of IBS is not well understood. According to Natalie Bzowej, MD, PhD, gastroenterologist with California Pacific's Liver Disease Management and Transplant Program, "The treatment of IBS is aimed at controlling specific symptoms rather than treating the underlying cause and there is no one drug that will control all the symptoms." "Successful treatment often depends on implementing a multidisciplinary approach and includes diet modification, fiber supplements, an exercise regimen, drugs and psychological and behavioral treatments," says Bzowej.

## Development of New Drugs Offers Hope for Treatment

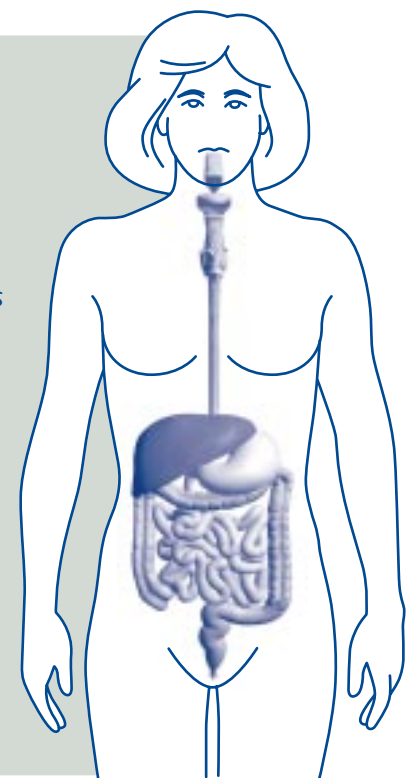
"There is much hope for serotonergically active drugs in treating IBS," says Bzowej. "Most patients will have heard about a drug called Lotronex® (alosetron hydrochloride) which recently had good success rates for treating multiple symptoms of IBS, including pain in the diarrhea-predominant IBS patient.

Unfortunately, the FDA recently withdrew Lotronex from the market because of side effects."

Last year, the FDA approved Zelmac® (tegaserod), which should be available this year for treatment of IBS in women who have constipation as their predominant symptom. Other IBS drugs in development include Cilansetron, a medication that treats diarrhea-predominant IBS that is currently being evaluated in large-scale clinical trials and a "substance P antagonist," a new class of IBS drug.

## THE FUNCTIONAL GI DISORDERS INCLUDE:

- Irritable Bowel Syndrome (IBS)
- Esophageal Disorders and GERD
- Constipation
- Gastroduodenal Disorders
- Diarrhea
- Pelvic Floor Pain
- Abdominal Bloating or Pain
- Incontinence
- Biliary Disorders



# Oakland-based Clinic Offers Transplant Evaluation and Research Trials



East Bay Clinic Staff Barbara Cahoon-Young and Grant Young

To better serve liver disease patients throughout Northern California and Nevada, California Pacific's Liver Program offers more than 20 outreach clinics that make hepatology consultations, liver transplant evaluations and participation in clinical research studies more convenient for patients.

The East Bay Liver Clinic, located in Oakland, is one such outreach site in which California Pacific's specialists visit the local community to provide expertise in all aspects of liver disease management and

access to clinical research studies. "Unlike many gastroenterology practices in the East Bay area, we offer research trials that draw patients from as far as Santa Cruz and the Sierra Foothills," says Grant Young,

clinic manager who has directed the East Bay Liver Clinic since its 1999 opening. This year, the clinic also added complex management of end stage liver disease (cirrhosis) and liver transplantation services.

Each month, about 50 liver disease patients visit the East Bay Clinic for hepatology or research trial appointments, the majority of whom suffer from hepatitis C. According to Hepatologist Adil Wakil, MD, who oversees the research trials, "While our current research at the clinic centers around hepatitis C—including a focus on minority populations—we are beginning clinical trials for hepatitis B patients and those co-infected with HIV and hepatitis C."

To refer patients to one of California Pacific Medical Center's outreach programs, call (415) 600-1000. To learn about outreach sites and current research trials, visit the Liver Web site at [www.cpmc.org/liver](http://www.cpmc.org/liver).

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