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VIRAL HEPATITIS IN HAWAI'I – DIFFERING PERSPECTIVES

Alan D. Tice MD; Michael Bannan; Kay Bauman MD; Tarquin Collis MD; Alba Hall; William Haning MD; Shoshana Hannemann; C. Bradley Hare MD; Joseph Humphry MD; Robert Jao MD; Carroll Leevy MD; Heather Lusk; Edward Ochoa; Neal Palafox MD; Nancy Withers MD, MPH; and Kenneth Akinaka

The Hawaii State Legislature

hereby presents this certificate to

HEPATITIS SUPPORT NETWORK OF HAWAII 2008

WHEREAS, the Hawaii State Legislature is honored to recognize those special individuals and organizations for their commitment to the health arena and for selflessly working to help those in need; and

WHEREAS, the HEPATITIS SUPPORT NETWORK OF HAWAII will host a public health campaign to educate Hawaii's homeless regarding the dangers of spreading infectious and blood-borne diseases; and

WHEREAS, the HEPATITIS SUPPORT NETWORK OF HAWAII was awarded a $10,000 grant from the Public Health Fund Committee of the Chamber of Commerce of Hawaii, and will use the funds to purchase "save-a-life safety kits" which contain soap, bandages, razors, toothbrushes, and nail clippers together with basic infectious disease information; and

WHEREAS, August 18, 2008, marks the start of a fundraising and educational awareness campaign to purchase and distribute more "save-a-life safety kits" and provide greater awareness of infectious diseases; and

WHEREAS, due to the outstanding commitment to providing life saving kits and education on infectious diseases to the people of the State of Hawaii, the HEPATITIS SUPPORT NETWORK OF HAWAII is recognized as an outstanding advocate for humanity by the Hawaii State Legislature; now, therefore,

The Twenty-fourth Legislature of the State of Hawaii hereby commends and applauds the HEPATITIS SUPPORT NETWORK OF HAWAII for their steadfast commitment to the field of healthcare and infectious disease prevention, and extends to them its warmest aloha and best wishes for continued success in all future endeavors.

Representative John Mizuno

Calvin K.Y. Say, Speaker of the House

Patricia Mau-Shimizu, House Chief Clerk

Senator Suzanne Chun Oakland

Colleen Hanabusa, President of the Senate

Carol Taniguchi, Senate Chief Clerk

Viral Hepatitis in Hawai'i – Differing Perspectives

Alan D. Tice MD; Michael Bannan; Kay Bauman MD; Tarquin Collis MD; Alba Hall; William Haning MD; Shoshana Hannemann; C. Bradley Hare MD; Joseph Humphry MD; Robert Jao MD; Carroll Leevy MD; Heather Lusk; Edward Ochoa; Neal Palafox MD; Nancy Withers MD, MPH; and Kenneth Akinaka

Abstract

This publication contains information from a conference titled "Individual Perspectives on the Silent Epidemic of Viral Hepatitis in Hawai'i" held in October of 2007 with updates and additional contributions from annual conferences in 2008 and 2009. These conferences were sponsored by the Hepatitis Support Network of Hawai'i and held in Honolulu, Hawai'i at the Queen's Conference Center.

The primary objectives of the conferences have been to heighten awareness of viral hepatitis in Hawai'i and to bring together health care professionals to learn about these infections and to help them respond to the challenges they bring to the people of Hawai'i. The initial conference was oriented to present the unique and individual perspectives of patients, physicians, and other healthcare providers specific to the complex issues of hepatitis in an effort to help them understand their role in the context of others and to develop a team approach in responding to this epidemic.

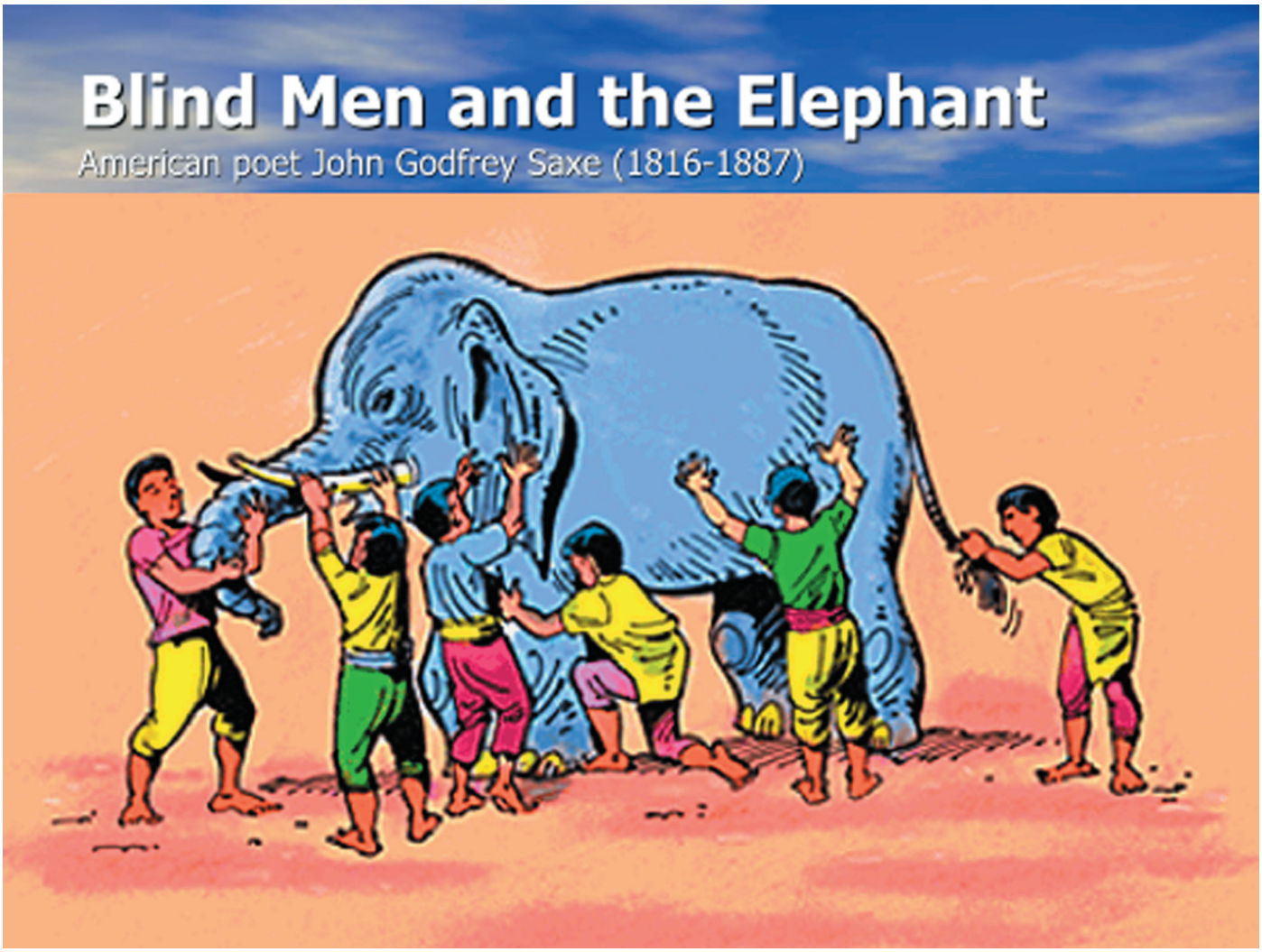

Figure 1.— Parable of the blind man examining the elephant; each presents a different perspective that can be brought together to better understand the animal.

I. Introduction

Alan Tice MD

Viral hepatitis infections, particularly hepatitis A (HAV), hepatitis B (HBV), and hepatitis C (HCV) are a significant problem worldwide. HAV has been nearly eliminated in Hawai'i due to immunizations, food safety, and the fact that it has no chronic form. HBV and HCV, however, are transmitted primarily through activities that involve percutaneous or mucosal contact with infectious blood or body fluids. They are similar and unique because of their capacity to cause persistent and often life-long infections. Over long periods of time, chronic liver inflammation and damage can contribute to the development of cirrhosis with organ failure and hepatocellular carcinoma, which is usually fatal. In 2006, chronic liver disease and cirrhosis comprised the 12th most common cause of death for adults in the United States between the ages of 25 and 64.[1] Hawai'i has the highest rate of liver cancer per capita in the United States, largely due to the incidence of HBV and HCV and delayed diagnosis.[2] Globally, chronic HBV affects approximately 350 million people, with an estimated 1.4 million cases occurring in the United States, although the rate of new cases has declined since routine vaccination of children was recommended in 1991.[3] The situation in Hawai'i is unusual because of its high immigrant population, with data that indicates that 5% to 10% of Asian/Pacific Islander Americans are chronically infected with HBV, compared with 0.2% to 0.5% of the overall US population.[4]

HCV is the most common bloodborne infection in the United States, representing approximately 4 million chronically infected persons. HCV lives in approximately one in 50 Americans, or about 2% of the total population.[3] Hepatitis C becomes a chronic disease in 85% of patients, and surfaces with cirrhosis and/or liver cancer decades after infection. HCV differs from HBV in that it can be eradicated, but there is no effective vaccine to prevent it.

High risk factors for which hepatitis screening is recommended include: injection drug use, nasal inhalation of cocaine, chronic renal failure on dialysis, incarceration, multiple sexual partners, transplantation or transfusion of blood products, occupational exposure to blood products, body piercings, tattoos, and birth to mothers with the virus.[3] Therapy is available to suppress HBV in most people and to eliminate HCV in more than half of people infected.

These viruses, which are fatal to a growing number of individuals, pose a challenge to healthcare systems, healthcare providers, and the communities in which the virus is prevalent. Termed a 'Silent Epidemic', many patients are asymptomatic for decades before developing end stage liver disease or cancer. New and effective medications have been developed to help slow this epidemic and treat those who are already infected. For end stage liver failure, the best option for most individuals is a liver transplant, but it is increasingly difficult to obtain due to lack of qualified donors. Recent numbers show that there are about 15,000 patients currently registered on the liver transplant waiting list of the United Network for Organ Sharing, while only 4,500 cadaver donor livers become available for transplantation each year.[5] Cadaver donor organ availability seems to have reached a plateau despite initiatives to increase donation. The waiting time for liver transplantation has increased steadily each year, rising from approximately one month in 1988 to more than a year in 1999. Currently, more than one-third of patients in the United States wait longer than two years for a liver transplant, and more patients die each year while awaiting transplantation. There is a critical shortage of donor organs, and this problem will continue to worsen in the foreseeable future. With the increase in the incidence of diagnosed nonalcoholic fatty liver disease and the epidemics of viral hepatitis infections, the number of deaths due to liver disease is expected to escalate in the next decade. Alcoholic liver disease is a frequent co-morbid condition which contributes to a more rapid progression of liver disease with both HBV and HCV. Education and early clinical intervention can be extraordinarily effective in preventing or at least slowing the insidious progression of individuals who have chronic hepatitis.

The objectives of recent annual symposia sponsored by the Hepatitis Support Network of Hawai'i were to educate healthcare providers and community members, provide differing yet complementary perspectives regarding hepatitis issues, and make plans for the future to address the hepatitis needs in Hawai'i. We believe that the parable of the blind men and the elephant is applicable, wherein six learned men went to examine an elephant despite the fact that they could not see (Figure 1). They were asked to describe what the elephant looked like based on a sensory examination, and arguing, each man gave a very different response. A wise leader awakened by the commotion called out, "The elephant is a big animal. Each man touched only one part. You must put all the parts together to find out what an elephant is like." The 'elephant' before us is hepatitis, and requires the attention and collective perspectives of the healthcare community to provide an appropriate response.

This supplement outlines the perspectives of selected patients, physicians, administrators, and healthcare providers in a collaborative effort to present the problems and impacts caused by the 'silent' hepatitis epidemic and to learn solutions to problems encountered in managing viral hepatitis in our community.

II. Perspectives of Patients

Michael Bannan, Alba Hall, Shoshana Hannemann, and Edward Ochoa

A panel of four patients outlined their perspectives regarding the challenges and issues related to viral hepatitis in the following general areas: awareness of the disease prior to diagnosis, stigma associated with hepatitis, significant life transitions, access to care and therapy, and the availability of resources. Patient 1, a 56-year-old man, had a long history of hepatitis B and received a liver transplant following a hepatoma. Patient 2, a 62-year-old man, had hepatitis C and has been apparently cured through therapy. Patient 3, a 52-year-old woman, is co-infected with hepatitis C and human immunodeficiency virus (HIV), and patient 4, a 52-year-old man, had a liver transplant due to hepatitis C infection. A summary of their experiences and observations are outlined in the following section.

Awareness

All four patients described a delay in the diagnosis of viral hepatitis from the time of their initial exposure, and also commented that at the time of their diagnosis they were not made aware of the seriousness of the disease or the resources available as to what should be done about it. Patient 1 was diagnosed with hepatitis B by chance as an adult after the blood bank rejected his donation, although he likely acquired the virus at birth. At the time of his initial diagnosis, he reported that his primary care physician said that the virus was dormant and did not seem concerned. As a result, the patient waited twenty-three years before seeking treatment. Patient 3 was told that she had non-A non-B hepatitis in 1975, but had no follow up and was not aware of the disease progression, or the significance of the diagnosis. She eventually learned more about hepatitis when she was evaluated for HIV after her 22 month old son was diagnosed with an AIDS-related cancer. It was not until she became involved with the Hepatitis Support Network of Hawai'i that the full ramifications of the disease were brought to her attention.

There was a general sense among the patients that if a person felt healthy, they likely did not have an underlying active liver infection. The diagnoses and considerations for treatment generally came in fortuitous ways or through targeted education programs such as in prison or other community screenings.

Stigma

Several patients described the negative stigma associated with having hepatitis C infection, which contributed to their reluctance to deal with the infection personally, or to disclose their histories to health care practitioners. Patient 2 was named a hepatitis C 'vector' while serving a sentence in the Federal Detention Center in Honolulu and was subsequently quarantined in a single cell for three months to allay the fears of other inmates. Patient 3 has been infected for so long that she no longer pays attention to any stigma associated with either hepatitis or HIV and has actually not noticed a stigma associated with HCV; however as a person with AIDS and the mother of two children born with the HIV virus, she is well acquainted with the stigma associated with HIV despite education campaigns funded through government programs such as the Ryan White Act and community foundations. In reference to the perceived stigma on people with either or both viruses, Patient 3 emphasized that it does not matter how someone contracted the virus(es), and that it is counterproductive to talk about what we could have, would have, or should have done to prevent infection. She said that "knowing why does not change the fact that it is," and has been proactive about moving beyond other people's perceptions and, most importantly, "the limitations we place upon ourselves." Stigmata can often be used as an excuse for inaction although it is not a useful one in dealing with the problems faced when managing these evolving epidemics.

Life Transitions

Several patients noted that they successfully transitioned from injection drug use and criminal behavior in their teens to become productive adults with close relationships with families and friends. For many, learning about hepatitis and going through the treatment programs were important in transitioning their life through recognition of the importance of altering behavior, the seriousness of the problems, and the people who came together to support them. They were often proud of their efforts and successes, which they were willing and anxious to share with others. They are all now involved in community outreach programs helping others with hepatitis and related support systems.

Access to Care and Treatment

Most patients were not aware of the recent advances in treatment for hepatitis B and C when they were diagnosed. They often found out about treatment options through educational outreach programs and the media. Once they were tested or screened and found to have hepatitis, it was not always possible to find a physician with knowledge and willingness to treat them. According to the patients, some of the primary care doctors they saw seemed to know little about current treatments with interferons and other potentially toxic medications and their side effects. Referral to a specialist or specialty clinic was often difficult due to long wait lists. Insurance coverage was deemed a significant issue in that many patients didn't qualify for disability as they seemed relatively healthy, or co-payments were prohibitive and discouraged medical evaluation and therapy. Even vaccines to prevent HAV or HBV were at times denied by insurance companies.

Patients noted the mental and personal challenges they faced in making decisions about their care. Although most patients trusted their physicians and followed their advice, not all of the patients did; patient 3 is well aware of the pros and cons regarding HCV treatment, but feels that in her case the benefits do not outweigh the risks, as she perceives the treatment to be extremely debilitating. Her physician agrees with her decision. The personal decisions to obtain treatment or apply for a transplant are critical and should be supported by healthcare providers through education regarding options available to patients.

Undergoing Therapy

The panel of four patients discussed the problems they had with different treatments, including anemia, leucopenia, thrombocytopenia, depression, and fatigue, with symptoms varying among panel participants. Patient 2 noted minimal physical side effects during interferon treatment, but reported short term memory loss that affected his ability to participate in local theater and stage produc-

tions temporarily, although the memory loss resolved completely after the treatment ended successfully and his virus was eventually deemed 'un-detectable.'

Patients 1 and 4 have had successful liver transplants, and recounted the challenges they had in getting livers. Patient 1 had a liver transplant over six years ago following unsuccessful eradication of a hepatoma, and is doing well, although must be careful with side effects and problems associated with an immunosuppressive treatment regimen. Patient 4 was initially rejected for a liver transplant, in part due to his history of injection drug use and incarceration. He felt at the time that he had received a death sentence and had little hope of surviving more than a few months due to vascular changes in his lungs which confined him to a wheelchair and constant oxygen therapy. Through the personal efforts of his physician in Hawai'i he was able to receive a liver more than two years ago, although he has had complications due to an infected stent, chronic pain, and emotional duress due to prior history of sociopathic behaviors. He has nevertheless been a strong advocate for the hepatitis in the community, has spent valuable time with his family and children, and has even been able to run local 10K races.

Available Resources

The Hepatitis Support Network of Hawai'i (HSNH) has helped to provide resources that assist patients in responding to the challenges they face as a result of hepatitis. Community foundations and advocates such as HSNH are vital to providing outreach and education programs to schools, prisons, faith-based organizations, immigrant populations, methadone and drug rehabilitation programs, homeless populations, clinicians, and patients. Increased media attention in the form of articles in newspapers and magazines highlighting the 'Silent Epidemic' and identifying the risk factors and need for testing as well as educational campaigns with posters, brochures, and knowledgeable sales forces sponsored by pharmaceutical companies have also been useful in disseminating information and supporting advocacy services.

Patient 1 is grateful that he is able to turn his experiences with hepatitis B into something positive by serving as a 'buddy,' or mentor, in the American Liver Foundation's Liver Buddies Program, which is designed to help those who have been diagnosed with liver disease by putting them in contact with others to provide moral support and encouragement. Patient 3 said that educating the public about HBV and HCV should be important goals for healthcare practitioners, as well as education about the viruses and available treatments. She believes that it is imperative that patients become proactive in their own treatment plans and that consumers must not be intimidated by health care providers. She thinks that patients are entitled to ask questions and receive qualified answers, as ultimately it is the patient who makes the final decision regarding his or her treatment. The ability to make better, more informed choices with respect to health care engenders a sense of empowerment which contributes to an overall sense of well being.

One concern brought to light is the way in which these viruses affect the families of those infected, especially in the case of patient 3 who was not only co-infected, but also the primary caregiver for two children born with HIV. She made the comment that a parent's mortality is far more frightening to a child than their own. While focusing on a cure is important, patient 3 suggested that emphasis should also be placed on living successfully with the viruses and helping families to cope with the realities of HCV. Patient 3 also mentioned that while the existing social services programs and resources are valuable assets, the system is set up in such a way that it can leave one feeling trapped. Once in the system, especially while trying to ease out of it, life, more than ever, must be organized by priority, with creative financing at the top of the list. Frustrations in transitioning back into the workforce with little or no direction following illness and treatment were discussed. The transition from incarceration to society is often difficult as well, especially with an ongoing viral infection.

The general consensus from the panel of patients was that efforts to educate the public about hepatitis B and C are improving but that outreach efforts and lowering thresholds to accessing care and testing are important for the future.

III. Perspectives of Physicians

A. General Hepatitis Management

Robert Jao MD and Alan Tice MD

From a physician's perspective, there are several major challenges for general hepatitis management in Hawai'i, such as patient access to care, obtaining authorization for affordable treatment, and managing clinical treatment complications.

Access to Care and Treatment

In Hawai'i, the majority of chronic HBV cases are minorities, with ethnicities including: Chinese, Korean, Vietnamese, Filipino, Thai, Laotian, Cambodian, Burmese, Indonesian, Malaysian, Pacific Islander, and Polynesian origins. Many of these people have limited knowledge of medicines and medical care and often do not know the difference between viral hepatitis, HIV, tuberculosis, or leprosy. Hansen's disease (leprosy) may serve as the model of infectious diseases they are most familiar with. As a result, they might be afraid to tell even their families about any type of chronic infection lest they be isolated and rejected. This is a serious problem particularly when there are household members who could benefit from immunizations for HBV. Minorities, who often see physicians as authority figures, may refrain from seeking health care due to lack of confidence in their communication skills, or because of fear or lack of medical knowledge about diseases. Because individuals with HBV or HCV are usually asymptomatic, it is a challenge to convince an otherwise 'healthy' person who may already be apprehensive to expend financial and other resources to seek out testing and eventual treatment.

In Hawai'i there are estimated to be 10,000 to 20,000 people infected with HBV and 30,000 people with HCV who may be considered for therapy. With interferon and ribavirin therapies costing about $50,000 or more per person for a 48-week course of HCV therapy, and $5,000 per person per year for HBV treatment, the total healthcare costs to treat all those who might benefit from treatment is astronomical. The alternative to consider is the cost of end stage liver disease with its complications, and the costs of liver transplants, which are estimated to be approximately $300,000 per transplant, with about 20 performed per year in Hawai'i. Affording proper long term therapy is difficult as patients may not be citizens or have insurance. Patients who are insured or who have subsidized insurance such as Medicaid or QUEST still encounter difficulties in being properly treated for viral hepatitis. Insurance companies often have old, inflexible guidelines and administrative problems and copayments for medications that can be prohibitive. Administrative and paperwork barriers often compromise access, particularly for those who are not proficient in English and are not familiar with the US healthcare system and policies. From a more global perspective, while minority patients may be living in Hawai'i, many of their family members who should also be screened often reside in another country where experience indicates that it is unlikely for them to be able to be tested.

Educational materials and internet content that is translated into native languages for distribution and the use of interpreters are vital for outreach to the minority populations.Encouraging grassroots efforts in the form of advocacy groups and physicians who are willing to go out in the community and seek out individuals who are infected, a "reverse access" concept, are key components to improving access to care within these at-risk populations.

Eligibility for Treatment

Establishing a working physician-patient relationship is important when evaluating treatment options for individuals with hepatitis. The duration of hepatitis treatment ranges from 24 to 48 weeks, and there are often adverse side effects. It is essential to evaluate the patient's individual situation prior to deciding on the appropriate course of treatment. General criteria for initiating therapy include patients' interest and commitment to following through on treatment programs, ability to eliminate drug and alcohol abuse, family and other support groups, a safe living environment, access to insurance, and ability to pay for treatment. Safe treatment programs should begin with a thorough history and physical, basic laboratory tests with screening for co-infections, as well as ensuring emotional and financial support from family or friends, and physician availability and involvement.

Treatment Complications

The duration of therapy for HBV is generally at least six months after suppression of the viral load to undetectable. Indefinite treatment may be recommended depending on the HBV e-antigen and e-antibody. Duration of treatment decisions may be difficult for general practitioners to determine, and expert opinions continue to change depending on the new drugs and information available. Although some of the newest agents are very well tolerated, they are expensive. Resistance to monotherapy over time is an increasing problem. This is especially true with lamivudine (Epivir or 3TC), which is now generic. Resistance has also been detected with telbivudine (Tyzeka) although less with entecavir (Baraclude) and tenofovir (Viread), which has replaced adefovir (Hepsera). There is concern that combination therapy will soon be needed to prevent resistance, as has been the case with HIV. However, combination therapy for naïve patients is not widely covered by insurance companies unless there is proof of prior confirmed resistance to monotherapy.

Managing adverse effects of interferon and ribavirin for HCV is an even greater challenge with complications varying from thrombocytopenia, anemia, or leucopenia and debilitating fatigue and serious depression, sometimes to the point of suicide, if the patient is not followed closely. Psychiatric problems pose additional challenges for practitioners monitoring hepatitis patients. Continued alcohol use and compliance with medication remain significant problems as well. Pharmaceutical companies are often able to help with compassionate use or voucher systems to help with payments and often provide informational brochures. These companies also support education programs in the form of conferences, meetings, and internet programs. Their representatives are generally available to work with primary care providers and specialists to keep them informed of new medications and evolving improvements in the use of therapies.

Initiating a treatment program requires the input of the physician and the patient as well as the payer. The prolonged course of therapy and secondary complications that arise create additional expenses. The side effects of treatment often require frequent support and physician involvement. Differing approaches include the

development of guidelines from evidence-based medicine, which is the usual for many third party payers. Allowing more freedom to responsible physicians to provide individually tailored regimens for patients is also an option. Mid-level practitioners such as physician assistants, nurse practitioners, and nurses can supplement the care necessary for patients to assure safety and regular follow up with screening for hepatocellular carcinomas and liver failure even after treatment is completed.

The Liver Center at Hawai'i Medical Center East in Honolulu, Kaiser Permanente, the Veterans Administration Medical Center, Infections Limited Hawai'i, and multiple private gastroenterology and infectious disease specialists are important sources of specialty care for patients with hepatitis in Hawai'i. These centers serve as sources of information and many have developed programs for analysis of patient databases which can assist in assessing the impact and extent of the disease.

Many people with hepatitis in Hawai'i live outside a geographic area with ready access to specialty care, particularly in the outer islands in Hawai'i where there may not be gastroenterologists or infectious disease specialists within practical access. With the help of the Hawai'i Medical Service Association (HMSA) Foundation and Native Hawaiian Health Department at the University of Hawai'i John A. Burns School of Medicine, sophisticated telemedicine programs are being developed so that experts can be involved with local care of patients in communities with limited medical resources. The specialty centers may also be able to provide advice and consultation to primary care practitioners to help manage the problems encountered and the decisions that need to be made.

B. Managing Hepatitis in Patients with Psychiatric and Substance Abuse Disorders

William Haning MD and Nancy Withers MD, MPH

Hepatitis C has been termed a 'psychiatric epidemic' in that it is estimated that 20% of severely mentally ill patients have HCV, which is about ten times the prevalence in the general US population.[6] Individuals with psychiatric and substance abuse disorders have a much greater risk of developing chronic liver disease including chronic HCV and fatty liver disease than the general population. Many psychiatric patients often develop metabolic syndromes in adulthood due to factors such as diet, lifestyle, and medications, which can lead to nonalcoholic fatty liver disease. The aggressive pharmacotherapy required for management of hepatitis C has emphasized that these medications carry some psychiatric risk, e.g. mood disorders and aggravation of substance abuse. As a result, primary, secondary, and tertiary prevention strategies are the shared responsibilities of the general psychiatrist, addictionist, and general practitioner. These include: 1) reduction of risk for other causes of hepatitis; 2) management of transmissibility of hepatitis; 3) pharmacological suppression of hepatic injury; and 4) management of psychiatric co-morbidity, primarily mood disorders, from the combination of hepatitis and hepatitis therapy.

Common psychiatric and substance abuse disorder co-morbidities accompanying hepatitis C treatment are mood disorders such as depression and hypomania, cognitive disorders such as paranoia and psychosis, delirium which can progress from disorientation to confusion to a comatose state, anxiety, sleep disorders, exacerbation of existing personality disorders, and pathological bereavement. Huckans et al.[7] demonstrated that individuals with and without a history of substance abuse disorders cleared the HCV virus at similar rates, and indicated that patients with co-morbid substance abuse disorders and HCV are capable of successfully completing a course of antiviral therapy. Currently, there are no reliable predictors to determine which individuals might suffer from severe psychiatric side effects, although pre-treatment screenings including Alcohol Use Disorders Identification Test (AUDIT-C), the Beck Depression Inventory, Beck Anxiety Inventory, and the Aggression Questionnaire can stabilize and guide the course of treatment and monitoring.

Just as HIV disease was originally dismissed as an illness of gays, prostitutes, and drug addicts, hepatitis C has also taken on the association with drug addiction. That population, frequently not seen as deserving of any particular attention, and certainly not any priority in epidemiological management, has difficulty speaking for itself, or more correctly, in being heard. Unique challenges in treating individuals with substance abuse and psychiatric disorders and HCV include increased risk for liver disease, identification of safe pharmacotherapy, and availability of adequate treatment facilities.

Increased Risk for Liver Disease

Individuals with substance abuse disorders are at a 40% higher risk for chronic HCV from intravenous or intranasal drug abuse than the general population, and often have co-morbid alcoholic and/or nonalcoholic fatty liver disease. According to Swartz et al.[6] only 54% of those with severe mental illness and HCV infection have a regular source of medical care. General hepatitis C education explaining the 'silent epidemic' is an important aspect in reducing the risk of infection for this subgroup of patients. Specifically, it is important to educate patients about 1) the impact of alcohol use and importance of sobriety, 2) drug abuse and dependence as a means of re-infection, 3) effects of other medications such as acetaminophen and ibuprofen on liver function, 4) transmission of the disease, 5) discussion of health behaviors including the importance of exercise and nutrition as they relate to the risk of fatty liver disease, and 6) making sure patients are aware of vaccinations for hepatitis A and B if they are not protected. In addition, psychiatrist and primary care provider integration to monitor lab results, weight, risk of metabolic syndrome and hyperlipidemia, and treatment and monitoring of interferon and ribavirin for those with chronic HCV are important tools in managing patient care.

Identification of Safe Pharmacotherapy

In the mid-1990s, gastroenterologists were often reluctant to initiate interferon and ribavirin therapy for psychiatric patients with chronic hepatitis C because of their concern about noncompliance, symptom instability, and even risk of suicide. At that time, it was known that interferon could induce serious neuropsychiatric symptoms and worsen pre-existing conditions. Current treatment of chronic hepatitis C involves the use of interferon and ribavirin for 24 to 48 weeks, depending on the viral genotype, and still has the potential to worsen pre-existing psychiatric symptoms and even cause new symptoms and unpleasant side effects to occur. This treatment, which may be effective in curing hepatitis C in a percentage of patients when administered consistently, might also place the in-

dividual at risk for relapse to prior substance dependence, and has the potential to induce symptoms such as depression, aggression or agitation, and anxiety. In addition, insomnia, fatigue, cognitive impairment ("mind fog"), and pain exacerbation have been reported.

Interferon-alfa induced depression is a major limitation for the treatment of chronic hepatitis C, especially for patients with psychiatric disorders. Prophylactic treatment to prevent depression during HCV therapy using citalopram (Celexa) and paroxetine (Paxil) have been shown to significantly reduce the incidence of major depression during the first 6 months of antiviral treatment compared to control groups.[8] Mirtazapine (Remeron) is also a recommended first line antidepressant to consider in treatment. Institutional screening and regular monthly monitoring of affective and cognitive status using standardized instruments such as the Hamilton Depression Index and Brief Psychiatric Rating Scale are recommended to monitor the effects of treatment. The principal pharmacokinetic considerations in setting an antidepressant's dose are inhibiting the metabolism of medications that use the cytochrome P450 CYP 2D6 system, thus raising serum concentrations. Particularly affected are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, as well as the tetracyclic antidepressant mirtazapine.

In addition to treatment, other steps can be taken to improve the outcomes of HCV-infected patients with psychiatric and substance abuse disorders. Discussions with the patient and caretakers/family can be initiated well before treatment begins to explain the potential side effects of the antiviral treatment so that plans can be made to increase the psychosocial support of the patient. Optimal timing of the treatment can be discussed in order to reduce stress on the patient and caretakers. Close mental health monitoring and co-management of patients with HCV clinicians, including screening questionnaires, interviews, medication management and cognitive therapy are strategies that will assist in successful treatment of patients with mental health issues who are undergoing interferon and ribavirin therapies.

Availability of Facilities for Management and Care

The single population most afflicted by viral hepatitis is found in the methadone maintenance treatment facilities (MMTFs), which are the end point for many opioid dependence issues. Estimates of prevalence in this population are surprisingly consistent, with point prevalence of hepatitis B in 2007 at 20%, and hepatitis C at 80%.[9] However, institutional and systemic responses have been restricted by diminishing reimbursement for such facilities and the resultant diminution of counseling, rehabilitation, and allied health services. As a result there is limited availability of adequate substance abuse disorder treatment facilities for the identified chronic hepatitis population. In 2007 there were two MMTFs in Honolulu on O'ahu and one in Hilo on the Big Island, and day treatment programs on Kaua'i and Moloka'i, with limited residential treatment on Maui. Thus, geographic proximity to such a center is a major factor in getting proper treatment. The increasing availability of buprenorphine, a new narcotic agonist therapy that has been shown to be useful in managing the dependence needs of an opioid addict, is an accessible improvement that provides support for methadone treatment, although some individuals on high doses of methadone may be resistant to this therapy.

Although substance abuse treatment programs are an important point of contact to provide health services to diagnose, treat, and prevent transmission of hepatitis, one study found that only 28.9% of programs in the United States offered HCV treatment either on-site or via referral, and that very few offer comprehensive hepatitis vaccination services.[10] A chronic hepatitis diagnosis for many individuals produces grief equivalent with anticipated death, which can lead to pathological mourning, and absence or reduction in hope. The efficacy in obtaining substance use disorder treatment for patients with chronic hepatitis lies in the potential for increased adherence to medications and to epidemic control measures. An individual whose expectation of death is high may place more reliance on the quality of the remaining life; and if convinced that life will be both short and unpleasant, there is little basis for treatment adherence. Treatment of the substance use disorder can improve both, and in so doing, enhance HCV treatment adherence. One proposal to consider is providing head of the line privileges for substance abuse disorder treatment for those with hepatitis, analogous to that provided for those with HIV disease. Equally, the role of social engagement cannot be over-emphasized. As depression is the most prevalent disorder in management of both the HCV population and those who are dependent on opioids, and as the behavioral management of depression emphasizes counterphobic behaviors (e.g. getting out of bed early despite somnolence, interacting with people in spite of social avoidance and isolation) a great opportunity is missed if these patients are not actively engaged in community recovery programs. Whether through 12-step-based recovery groups, social enterprises by allied agencies, or occupational rehabilitation and training, interaction with a healthier population of goal-directed individuals is central to chronic disease management. It addresses the spiritual core of the human animal, the requirement for human relatedness. An operational example would be walking through an Alcoholics Anonymous or Narcotics Anonymous weekly schedule with the patient, identifying likely compatible groups, and groups close to home or work, and marking routes of travel to attend the meetings.

Coordination of care between psychiatrists and hepatitis clinics is the standard of care at the Veteran's Administration Hospital, and ideally the mental health provider or addiction specialist screens patients before treatment and meets with patients at each hepatitis clinic visit. This model can be seen in a number of Hawai'i community health centers, including Waikiki Health Center, Kalihi-Palama Health Center and the Queen Emma Clinics which all have Infectious Diseases specialists and often Gastroenterologists available. Private clinics such as the Liver Center also offer combined support. All successful settings seem to require one champion for integrative management who correctly perceives the issue as a chronic disease with multi-systems expression, inclusive of behavioral, neurological, and social elements. This advocate need not be a psychiatrist, or even a physician.

In summary, public health interventions to improve access to hepatitis testing, treatment, and prevention are needed at the community level to provide assistance and incentives for patients with psychiatric and substance use disorders.

IV. Perspectives of Administrators and Health Care Plans

This section outlines the perspectives of several different administrators who manage hepatitis, including representatives from the State of Hawai'i Department of Health, State of Hawai'i Department of Public Safety (prison system), and private insurance carriers Kaiser Permanente and the Hawai'i Medical Service Association (HMSA).

A. Viral Hepatitis and the Hawai'i State Departments of Health and Public Safety

Kay Bauman, MD and Heather Lusk

The primary challenges identified when working with hepatitis from the state-sponsored health department and department of public safety (prison system) perspectives include: lack of funding and cost of providing services; integration of services; and increasing capacity within private and public systems to meet the needs of persons at-risk for and living with viral hepatitis.

Funding

The annual budget for the Centers for Disease Control (CDC) Division of Viral Hepatitis for fiscal year 2010 is $18.3 million, with approximately $5 million allocated to various states for the Adult Hepatitis Prevention Coordinator Program. These funds are distributed to 51 jurisdictions with the goal of developing and implementing comprehensive viral hepatitis prevention and control programs at the state, county, and city levels by providing one full-time salary position and limited travel funds. At the Hawai'i Department of Health (DOH), the hepatitis program has an Adult Viral Hepatitis Prevention Coordinator who is functionally located within the STD/AIDS Prevention Branch of the Communicable Disease Division. Because the CDC funding only allows for salary, there are very little additional funds available for viral hepatitis activities and general program support. Despite these challenges, creative solutions have been successful in circumventing limited funding resources. Because training and education are relatively inexpensive, these areas have been heavily utilized, with over 1,000 people trained annually in recent years through presentations conducted as part of larger conferences, workshops, and integration of information on viral hepatitis into existing trainings for different agencies. In 2007, four "Training the Trainers" programs were conducted statewide to increase the cadre of persons who can authoritatively educate about viral hepatitis in settings such as high school workshops, prisons and jails, and drug and alcohol treatment centers.

In addition to education programs, in kind staff and funds from the HIV prevention program have been used to provide free hepatitis C testing and counseling at all DOH HIV/STD sites and some community-based organizations with approval from the HIV Community Planning Group as allowed by the CDC. Since 2004, over 2,000 tests have been conducted with an approximately 16% positivity rate. Free hepatitis A and B immunizations for adults at-risk as identified by the Advisory Committee on Immunization Practices (*ACIP*) have been provided by the DOH Immunization Program at all HIV/STD sites for those who can't afford them, with on-site vaccinations made available at the Pride Festival and injection drug user events. As a result of these group efforts, infrastructure has been established with the standardization of policies and procedures, forms, and data tracking systems in place for future funding and improvements. Collaborations with organizations such as the Hepatitis Support Network of Hawai'i have also been vital tools in coordinating a statewide viral hepatitis program with little in the way of funding or resources. Given the lack of federal funds dedicated to combating the viral hepatitis epidemics, it is essential to leverage existing resources. By being creative and thinking outside the box, state-sponsored programs can make a difference in affecting the hepatitis community with limited resources.

Hepatitis C is an increasing challenge for health care providers working in correctional facilities. In the US prison system, which houses approximately 2 million adults, 16% to 41% of inmates are positive for antibody to HCV, and 12% to 31% have chronic infection.[11-12] The California state correctional system found the prevalence of HCV infection among incoming inmates to be 34.3% overall.[13] These statistics are not surprising given the fact that a primary source of HCV infection is from current and former illegal injection drug users, with drug offenders comprising 20% of state and 55% of federal prison populations.[14] Within the Hawai'i prison system, there are a significant number of inmates who are HCV positive, averaging 24% in targeted testing done from 1999-2007 (Table 1). Of additional concern is a rise in the number of prisoners with recognized liver disease and a 27% death rate from liver failure within the Hawai'i prison system that exceeds all other diagnostic categories.

Table 1.— Estimates of HCV positivity in the Hawai'i prison system[58]

Years	Percent HCV Positive	Number Tested
1999-2001	29-32%	334
2002-2003	25%	555
2004	21%	716
2005-2006	18.6%	800
2007	12%	1317

Since the beginning of 2007, all inmates upon entry into prisons or jails in Hawai'i are offered HIV testing, and testing for hepatitis C is available on request and encouraged if there is a history of HIV or HBV, injection drug use, transfusions before 1992, liver disease, tattoos acquired in prison, hemodialysis, or treatment with isoniazid or agents that lower cholesterol. Patients with HCV who are candidates for treatment are treated with pegylated interferon and ribavirin. In order to qualify for treatment, sobriety and completion of a substance abuse treatment program are encouraged, but not required, and patients sign a permission form that allows for random urine drug testing with the understanding that any positive urine test is a reason for discontinuation of treatment. Treatment is initiated if more than 12 to18 months of incarceration are anticipated and approval has been obtained by a psychiatrist. Therapy is considered if the ALT is >1.5 times the upper limit of normal on a single test, or any abnormal elevation at two separate occasions for African-Americans. If a liver biopsy is done, therapy is offered if there is evidence of fibrosis (grade 2-3 by Knodell Scale). When fibrosis is advanced (grade 4), therapy is done at the physician's discretion.

The course for treating genotype 1 is 48 weeks, and 24 weeks for genotypes 2 and 3. Therapy is discontinued for any genotype if there is no response after 12 weeks of treatment, where response is defined as a negative viral load or a two-log drop from initial viral load.

The cost of providing care within the prison system as compared to the community is shown in Table 2, where cost estimates were based on the 2007 charge data for the institution with additional data provided by local pharmacies and laboratories. The combined cost of interferon and ribavirin alone for a treatment course of 48 weeks through the Hawai'i prison system was approximately $25,578 compared with $41,354 in the community in 2007. These expenses do not cover laboratory studies, provider services, staffing, administration, or other overhead charges.

Table 2.— Cost of providing care in the State of Hawai'i Department of Public Safety (prison system) compared with community in 2007[58]

Cost for 4 weeks of treatment	Hawai'i Prison System	Medicaid
Pegylated interferon alfa (weekly)	$1161	$1798
Ribavirin (600 BID)	$912	$1567
Laboratory monitoring*	$59	$82
Total for 4 weeks	$2131	$3446
Total for a 48 week course	$25,578	$41,354

*complete blood count and liver function tests on average twice per month; uric acid, triglycerides, thyroid stimulating hormone, renal panel, drug screen, and viral load approximately every three months.

In the United States, direct medical expenditures related to chronic hepatitis C are predicted to total $10.7 billion from 2010 to 2019.[15] The cost-effectiveness of treating hepatitis C in prisons has been a matter of public debate, with proponents arguing ethical duty to provide contemporary medical care to inmates, while opponents note that therapy is often interrupted by transfers or release, and that relapse into high-risk behavior is likely upon release from the system. However, Tan et al.[16] found that from a pharmaco-economic standpoint, treatment within correctional facilities was cost-effective and improved the quality of life in prisoners of all age ranges and genotypes.

The costs of hepatitis management, which includes liver biopsy, transportation for specialty care, and medications, vary among correctional systems. While the cost of providing hepatitis C treatment is still substantial, recent data indicates that in Hawai'i it is considerably cheaper to treat hepatitis C infections in prisons than in the community. Correctional systems are often able to negotiate cost-effective contracts for pharmaceutical and laboratory expenses, which are often 40% of the retail cost, although cost of physician and nurse time is likely comparable.[17] Because the data shows excellent response rates compared to treatment in the community, treating eligible inmates makes both economic and public health sense. Prisons hold high risk populations, some of whom are likely to resume risky behaviors upon release and become infection risks to current or future drug users if the hepatitis C goes untreated. With the availability of interferon and ribavirin, it is possible to cure the infection, although adverse effects, prolonged courses of therapy, cost, and success rates are significant limiting factors when considering treatment. Despite the challenges to treatment, correctional facilities offer an opportunity to screen and treat this infection in a controlled environment, and prevent its spread within the facilities and to others in the community upon release.

Integration of Services

Integrating viral hepatitis into existing community services that may already be accessed by people at-risk for and living with viral hepatitis is a functional method of merging resources and talents, although it is not always practical or accessible due to legal barriers, existing case loads, contractual obligations, funding issues, and problems with general infrastructure. However, settings such as correctional facilities, drug and alcohol programs, schools and educational programs, HIV/STD programs, churches and faith-based agencies, community health centers, homeless services, veterans services, family planning, cultural programs, mental health programs, and complementary and traditional medical are all practical targets for integration of hepatitis services. This can be accomplished by: providing training to staff; educational materials; examples of language; client intake and assessment forms; and by sharing data, evidence, and federal recommendations that support integration. Respectfully building relationships and finding individuals within organizations that are interested in viral hepatitis leads to successful outcomes when coordinating the integration of services.

In 2003, more than 6,000 people in Hawai'i were thought to be homeless with over 155,000 at risk of becoming homeless. A high proportion of the homeless have a history of drug abuse, incarceration, and prostitution.[18] Common tools of hygiene such as razors and toothbrushes may be unavailable or become a vehicle of transmission if shared. Hepatitis C virus has been found in up to one-third of tooth brushes and 38% of razors used by those infected.[19-20] A recent study suggests that the homeless people of Hawai'i are more likely to have viral hepatitis than the general population, as expected and reported by others and that they appear to be lacking in awareness of possible therapy for their infections as well as prevention of secondary infections through hepatitis vaccination.[21] Interventions through health care programs designed for homeless shelters offer a good opportunity to educate, test and offer treatment and safety kits to stem the spread of these infections within and outside the homeless communities.

Taking advantage of the healthcare programs already in place within the state prison system is an effective way to share resources and support state-wide hepatitis efforts, however, there are unique challenges to treating an incarcerated population. There are significant legal and moral questions associated with providing hepatitis treatments in prisons, including whether inmates can be required to stay within the prison system for the length of treatment necessary regardless of their judicial sentence, whether incarcerated patients should be required to complete substance abuse programs prior to HCV treatment to improve compliance, or if inmates should be eligible for organ transplantation in the event of end stage liver disease as a result of HCV infection. As such, centers of care in the community including government institutions and correctional facilities must balance treatment recommendations with the threat of legal recourse.

Increasing Capacity

Similar in scope to improving integration of services, services and awareness for persons with hepatitis C can be greatly improved by

identifying existing resources and collaborating with various agencies. Hepatitis is often not addressed because it seems overwhelming for organizations that are already supporting other, even related, causes. By providing tangible steps and support, and by utilizing everyone's strengths, these issues can be overcome. Although there are a variety of challenges to providing a comprehensive state hepatitis program, by working together we can effectively strategize and maximize the resources that are available to raise hepatitis awareness and provide essential services within the community.

Despite the challenges in working within the prison population, the state of Hawai'i has maintained a successful HCV treatment program with data that matches or is superior to published data. Successful components to the system are close monitoring of inmate patients, including well-trained nurses, which ensures excellent adherence to required testing and monitoring. An HBV treatment program within the prison system is currently in the planning stages.

B. Hepatitis and Private Insurance Companies

Tarquin Collis MD and Joseph Humphry MD

Although there are significant administrative differences when working with various private insurance providers, the common goal from a physician's standpoint is to provide excellence in patient care. Access to care, working effectively with primary care providers, maximizing cure rates, and developing data management and decision support tools were identified as important issues in treating patients with hepatitis from different private insurance perspectives (Kaiser Permanente and HMSA). Table 3 summarizes the various administrative and health plan perspectives regarding hepatitis treatment options.

Access to Care

Access to and delivery of care is a significant problem in Hawai'i for patients with hepatitis B and C, due in part to limited access to specialists. As previously described, this access is particularly difficult for high risk populations. Various community screening programs can increase the number of patients screened for hepatitis, including the "3 for Life" program, which has been a successful community-based HBV testing and vaccination program targeting the Asian/Pacific Islander American population. The program, which first started in San Francisco in 2004 and has expanded to other major US cities including Honolulu, is an accessible, affordable, and sustainable model to increase HBV awareness, testing, and prevention.

The Hepatitis C Clinic was established at Kaiser Permanente in Honolulu in 2003 and is currently staffed by the medical director (an infectious diseases specialist), an internist, a clinical pharmacist, a nurse practitioner, and a registered nurse. The clinic provides care for Kaiser members on O'ahu and Kaua'i with HCV infection, and will begin providing care for Kaiser members on the Big Island in 2010. The clinic has an aggressive approach to HCV treatment, which is a conscious decision based on the fact that many of the clinic's patients have significant social and economic barriers that effectively preclude liver transplantation as an option should their liver disease worsen as a result of ongoing HCV infection. The clinic employs a number of treatment approaches that help it maintain substantially higher rates of virologic cure than would be expected given the challenging treatment population that it serves. A unique aspect of working at Kaiser as a specialist is the ability to provide cutting edge care for patients outside the context of the often adversarial relationship between a doctor or patient and private insurance companies. At Kaiser Permanente, specialists have been granted the opportunity to dispense HCV-infected patients the medicine that they need, for the duration of treatment necessary, and to use the tests that in the physician's judgment are appropriate to guide patient care without the concern that a third-party payer will deem the recommended medical care inappropriate or overly expensive.

Working Effectively with Primary Care Providers

Because the field of hepatitis C, like that of HIV infection, is a relatively young one, and because advances in hepatitis C treatment have evolved at a rapid pace, many practicing primary care providers are unaware of the details of HCV related medical care and the very real possibility of cure for many patients. Most internists, family practitioners, and nurse practitioners have limited knowledge of the important roles of HCV genotypic and viral load testing in predicting response to treatment, and have little firsthand experience with hepatitis C treatment and its attendant side effects.

At Kaiser, there is a well-established framework to assist frontline caregivers in learning about HCV infection and treatment. In addition to talks and grand rounds offered to medical and nursing staff, the Kaiser Permanente Hepatitis C Treatment Guidelines is a document made available on Kaiser's intranet which provides an evidence-based, up-to-date, and extensively referenced overview of hepatitis C epidemiology and natural history, and reviews the clinic's approach to treatment and side effect management. This guideline is updated annually to reflect the newest research in the field.

Another approach the Kaiser clinic has taken to assist frontline physicians with their HCV-infected patients is through efforts at targeted population management. One of the benefits of a "closed" patient population that is cared for through an electronically integrated care delivery system such as Kaiser's is the capacity to efficiently create comprehensive databases of Kaiser members in order to improve their health care. For example, the clinic team systematically reviews a database of known HCV-infected Kaiser members who have not been seen in consultation, and identifies patients who are newly diagnosed with hepatitis C, whose labs or radiology studies suggest undiagnosed cirrhosis/advanced liver disease, or who have easy-to-cure Hepatitis C genotypes. Through Kaiser's email system, physicians caring for these patients can be contacted directly and offered consultation for the patients in question. This method has been highly successful and has already resulted in the cure of many patients who might otherwise have come to the clinic's attention only after becoming too sick to receive interferon-based care. Kaiser's hepatitis C clinic has a similar database that is used to automate the screening for liver cancer for hepatitis C-infected patients with advanced liver disease. These unique opportunities for proactive population management are a particularly exciting part of Kaiser's practice, and provide unique forms of assistance for frontline medical providers and their patients in ways that are well outside the realm of the reactive, referral-based model of specialty care as it is generally practiced in the United States.

Maximizing Cure Rates

The hepatitis C clinic at Kaiser maintains a separate, highly detailed electronic database on all of the patients who have been seen in consultation, allowing a better understanding of the demographics of patient population, and providing regular updates on clinic treatment outcomes. From the standpoint of potential virologic cure, the patient population that Kaiser manages is quite difficult to treat. For example, as of September 2007, of the patients who have completed a full course of HCV therapy at our clinic, 78% had either stage 3 or 4 hepatic fibrosis and nearly 20% had failed one or more courses of interferon HCV treatment prior to receiving care at the hepatitis C clinic. In addition significant co-morbidities including HIV co-infection, end stage renal disease, morbid obesity, and active social and psychiatric issues were present in a significant number of patients.

Despite a patient population whose profile includes many factors mitigating against the chances of cure, the intent-to-treat, genotype specific rates of cure with HCV treatment at Kaiser are equal to or better than those of the licensing trial of pegylated interferon alfa-2a, which is the form of pegylated interferon used at the Kaiser clinic.[22] In that licensing trial, the patient population represented young, treatment-naïve patients, of whom only 12% had stage 3 or 4 fibrosis. An important part of Kaiser's success in achieving rates of cure that are much higher than would be predicted for the population served involves an integrated treatment approach that includes: thorough pre-treatment counseling; aggressive, multifaceted patient support by the treatment team once treatment starts; and the minimization of dose-reductions during treatment through the use of erythropoietin and, when needed, blood transfusion and growth colony stimulating factors. Hence, the rates of treatment discontinuation and dose-reduction during therapy are extremely low, translating to much higher rates of cure than would be possible otherwise. In addition, Kaiser Permanente has given the clinic the liberty to employ several approaches to HCV treatment that are not currently reimbursed by private insurance in Hawai'i , but which are supported by recent clinical trials and are in common use in university academic HCV treatment centers. These include the use of high dose (weight-based) ribavirin for significantly obese patients,[23] the use of prolonged courses of HCV treatment based on detectable HCV viral loads at week 4 of treatment,[24-25] and the use of daily dosed "consensus" interferon (Intergen) for selected patients who are not responding to pegylated interferon therapies.[26-27]

At the Hawai'i Medical Service Association (HMSA), hepatitis C treatments for its members require prior authorization except for HMSA Quest members that have State mandated benefits. HMSA hepatitis C policy is based on national guidelines with input from local experts. HMSA's research policy allows coverage of usual covered costs for members who are enrolled in studies sponsored by recognized institutions such as the National Institutes of Health (NIH), Veterans Administration (VA), and more. All hepatitis B treatments are covered, and immunization coverage for adults currently follows CDC recommendation.

There are a number of ongoing drug trials supported by the pharmaceutical industry to test new drugs or new combinations of medication. The contribution of these clinical trials is often overlooked in our community. The medications must meet the standards of the US Federal Drug Administration and are provided at no charge by the companies. Clinical trials sponsored by centers such as the Liver Center and Infections Limited Hawai'i have saved our communities millions of dollars in therapy and made treatment available for patients who might otherwise not be able to afford it.

Data Management and Decision Support

Partnering with HMSA Foundation, the University of Hawai'i Telehealth Research Institute, and community health centers, the Liver Center at Hawai'i Medical Center East is developing a hepatitis B and C telemedicine system to provide quality care in the primary care setting. The "3 for Life" and the Hepatitis Support Network of Hawai'i screening programs allowing tracking and monitoring from detection to outcome, and improves communication and coordination among the state health department, specialty pharmacies, health plans, specialists, and primary care providers. There are over 300 patients registered in the database. The objectives of this program are primary care education for hepatitis, telemedicine information and consultation services, and establishment of a comprehensive disease management program for hepatitis that includes a registry, decision support and care monitoring, tracking, reminders for hepatitis B immunizations, survey tools, educational material, report generator, graphs of labs, and secure email. Obstacles to improving these services are resistance from primary care providers to change their systems, HIPAA privacy rules, multi-system integration, software development, overall implementation, and adequate funding and personnel. Data collection and ongoing analysis are important aspects for the evaluation and management of hepatitis. There is an ongoing need for comprehensive registries or electronic medical records reporting systems that would allow for rapid analysis of patient databases for hepatitis and its complications.

Table 3.— Comparison of selected administrative and health plan perspectives and hepatitis C

	HMSA	Kaiser	State of Hawai'i Department of Public Safety	State of Hawai'i Department of Health
% of treatment-eligible population with hepatitis	1-2%	1-2%	20%	2%
Availability of hepatitis screening programs	Supports community programs	Yes	Yes	Limited
Availability of hepatitis treatment options	Requires approval for standard treatment	No pre-approval required; treatment plan decided on by patient and treating physician	Standard treatment with some exclusions	None

V. The Future of Hepatitis in Hawai‘i

A. Advocacy Programs

Kenneth Akinaka

The Hepatitis Support Network of Hawai‘i (HSNH) is the oldest hepatitis prevention, education, treatment and advocacy organization in Hawai‘i. With fourteen active programs and over 100 volunteers, the program provides free community presentations by experts in the field of hepatitis and other infectious diseases and free hepatitis B and C screenings and hepatitis B vaccinations to hundreds of people every year. The goals and objectives of the program are to provide prevention, education, treatment, support, medical case management, and counseling for those who are infected with chronic viral hepatitis including those who are co-infected with HIV. The HSNH has outreach services that target the underserved including Native Hawaiians in rural areas, the poor, immigrants, homeless, prisoners, substance users, and those who are uninsured as well as those with medical insurance.

Hawai‘i has the highest rate of liver cancer in the United States.[28] It is a leading cause of cancer death among Native Hawaiian, Filipino, and Chinese men in Hawai‘i.[28-29] The average rate of hepatitis B in the United States is 0.5% to 1%, while Asian and Pacific Island countries generally have greater than 10% of their populations affected (Table 4). Hawai‘i’s immigrant population, largely derived from these affected areas, makes up 17% of the total population, and accounts in part for the high rate of HBV in Hawai‘i. These patients require monitoring every six months for liver cancer even if their viral load is low, and it is recommended that family members are vaccinated to protect them from infection. It is suggested that physicians and local health care clinics start following CDC recommended guidelines, which is to screen all immigrants and migrants from countries that have chronic viral hepatitis B rates of over 2%.[30]

There are a number of problems that need to be addressed by healthcare advocates if the course of these silent epidemics in Hawai‘i is to change. These primary problems include a lack of public education and awareness and issues with accessing testing and treatment.

Public Awareness and Education

Because there is a significant delay in the signs and symptoms that accompany viral hepatitis infection, many individuals who once may have led a risky lifestyle may not realize that they are infected until many years later. Nursing education often does not include adequate courses on hepatitis B and C, and physician education classes may also be outdated. A specific focus on these epidemics in Hawai‘i is necessary, as prevalence is higher than that on the continental US. Testing, case management, and earlier medical interventions are necessary for infected individuals including the working poor who often do not have medical insurance or are homeless. Medical case management is needed for referrals for services and to dispel some of the myths and fears about treatment side effects that often prevent people from seeking treatment. The HSNH sponsors a number of programs to address these issues, including outreach office sites and prison classes as well as the Save-a-Life Safety Kit Campaign which encourages healthcare service organizations, civic clubs, and churches to distribute free razors, toothbrushes, nail clippers, and prevention education materials to the homeless population. The network also supports community education by presenting at health fairs, sponsors speakers at various medical venues, and assists in the training of volunteer case managers and medical education training programs. Educational campaigns and outreach programs sponsored by pharmaceutical and local advocacy groups targeted at the general public have also resulted in increased screening by printing material in several languages, advertising on the radio, television and internet, and more.

Testing and Treatment

Advocacy in Hawai‘i needs to encourage physicians, nurse practitioners, and physician assistants to test, counsel and consider treatment for people who have risk exposure histories. Often primary care physicians do not test for hepatitis, or wait until a patient has complaints or symptoms of liver disease to refer for treatment. Quite frequently patients do not feel ill until it is too late to successfully treat the infection. Often there is no funding to provide medical case management or treatment for people infected with HBV and HCV who do not have health insurance or who cannot afford the co-payment cost of treatment. The HSNH provides community education, testing, and vaccination programs, as well as an HIV/hepatitis C co-infected support group and a Micronesian outreach healthcare

Table 4.— Hepatitis B infection rates in Asian and Pacific Island nations[59]

Country	Population	HBsAg+	% Infected with Hepatitis B
American Samoa	50,923	3,565	7%
China	1,299,180,000	155,901,600	12%
S. Korea	46,403,000	5,568,360	12%
Marshall Islands	56,417	6,770	12%
Micronesia, FSM	190,000	22,800	12% to 15%
New Zealand	3,662,000	29,296	0.8% (10% of Maori)
Palau	16,386	1,966	12% to 15%
Philippines	77,473,000	7,747,300	10%
Western Samoa	190,000	15,200	8% to 10%
Tonga	92,000	18,400	20%
Vietnam	82,427,000	9,891,240	12%

program to assist in this effort. Telemedicine and accessing rural populations is another issue, as many people cannot afford to travel to Honolulu for treatment. Currently the HSNH, in partnership with Access Care Today Clinics, is working to improve their Telemedicine and Rural and Neighbor Island Infectious Disease Treatment Expansion Program to accommodate these populations.

B. Hepatitis and Impact of Immunization

Neal Palafox MD

Two different perspectives about hepatitis B vaccination programs are presented. The first highlights the data and epidemiology of hepatitis B in US associated Pacific nations, and the second addresses implementation of childhood vaccinations in the United States specific to Hawai'i.

Hepatitis B in the US Associated Pacific

The Compact of Free Association (COFA) defines the relationship that three sovereign nations, the Federated States of Micronesia (which include Chuuk, Kosrae, Pohnpei, and Yap), the Republic of the Marshall Islands, and the Republic of Palau, have entered into as associated entities of the United States. In exchange for certain defense rights, the United States provides guaranteed financial assistance to the COFA nations, representing a total of 475,000 people.

Health outcomes such as increased infant mortality and reduced longevity in these nations are directly related to amount of healthcare spending by the US government, where approximately $5,700 was spent per capita in the United States, while nations such as Chuuk and Pohnpei received only $80 and $117 per person per year respectively in 2006 (Figure 2).[31-32]

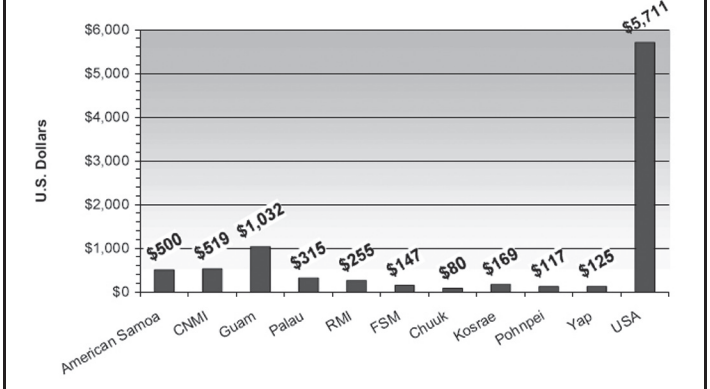

Figure 2.— Per capita total health expenditures in the Western Pacific Region compared to the United States in 2006.[31-32]

In addition, there are an estimated 14,500 COFA Micronesians living in Hawai'i with a growth rate of 6.2% annually. Of those individuals, an estimated 18% are hepatitis B surface antigen positive. Two-thirds of the homeless population in Hawai'i are Micronesians and may be at increased risk for HBV infection due to poor hygiene, skin injuries, and related lifestyle components. As such, there is a vested interest in caring for this population both in Hawai'i and within their own nations. As shown in Table 5, despite introduction of the HBV vaccine in the late 1980s, the percentage of individuals in Chuuk with positive HBV markers prior to 1985 was 80%, and in 2007 the percentage was 76%, with chronic rates of infection actually increasing in both Chuuk and Pohnpei.[33-35]

Table 5.— Prevalence of HBV infection among adults born prior to routine childhood hepatitis B vaccination[33-35]

COFA Nation	Positive for any HBV marker		Chronic HBV HBsAg +	
	1965-1985	2000-2007	1965-1989	2000-2007
Chuuk	80%	76%	7%	9%
Pohnpei	68%	52%	2%	4%
Marshall Islands	88%	44%	16%	10%

Although the rates show decline in other nations, the overall infection and exposure rates are extremely high. In the Marshall Islands, 4.6% of total deaths reported in 2005 were due to chronic liver disease.[36] Similarly, in Pohnpei and Palau, chronic liver disease represented 7% of the total deaths occurring in those nations.[37]

When the hepatitis B vaccine is given properly, it is 95% effective in preventing chronic infections. Hepatitis B was added to the routine childhood immunization schedule in most Pacific Island nations in the late 1980s, and multiple seroprevalence surveys were conducted to measure the impact of introduction of the vaccination. In Chuuk it was shown that prior to the immunization program in 1988 15% of two year old children had chronic hepatitis B infection, but that by 1992 the number was down to 3%, demonstrating that the vaccination programs are indeed capable of being effective. However, the biggest predictor of HBV in these areas is vertical transmission at birth from mother to infant, and vaccination within 24 hours of birth is an important factor in prevention. In Chuuk in 2000, only 61% of infants received a dose at birth, with similar numbers reported in Pohnpei and the Marshall Islands. It was reported that none of the chronically infected children in Chuuk received a birth dose of the vaccine, and none of the infected children received all three doses of the vaccine on schedule. Because the hepatitis B vaccine needs to be implemented at birth for maximum efficacy, accessibility and availability of vaccines to the remote outer islands needs to be addressed and improved. A recent advance includes the introduction of the 'Uniject' system which provides for the stable storage of the hepatitis B vaccine at up to 90º F for up to 30 days without losing immunogenic properties.

In contrast to HBV transmission in the United States where adolescents and adults more commonly test positive, the primary populations infected with HBV from Pacific nations are infants and young children. This is due primarily to both perinatal and horizontal transmission (child to child or among family members), as HBV is stable in the environment for up to seven days and is capable of transmitting via contaminated objects, particularly in crowded communities and shared households. Vastly improved systems of diagnosis, treatment, and management need to be put into place both in Hawai'i and within the COFA nations, with targets of immunization programs being infants and children since age of infection is biggest predictor of chronic HBV infection. Primary goals for improving HBV infection rates in these areas include expanded education programs, proper prenatal care and testing,

increased availability of vaccines particularly for areas outside of the hospital setting, and routine vaccination of children within 24 hours of birth up to age five.

Implementation of Hepatitis B Childhood Vaccinations

Since 1991 a key strategy to eliminate hepatitis B transmission in the United States was to administer the first dose of the vaccine at birth, preferably within 12 hours to ensure that the mother does not leave before the infant has a chance to get immunized. Implementation of the hepatitis B birth dose provides early protection to infants at risk for infection after the perinatal period without knowing HBV status of birth mother. This leads to an overall higher rate of on time completion of the HBV vaccine series. Through the immunization program, the incidence of HBV among children and adolescents in the United States declined 89% between 1990 and 2002. However, parents often have philosophical or religious objections to vaccines or have read conflicting media reports about vaccine safety and child development, and raise questions for the practitioner to address.

Parents commonly question whether their children should be vaccinated against hepatitis B when they don't feel as if their children or families are exposed to any of the risk factors. These concerns can be addressed by emphasizing the importance of getting vaccinated despite the absence of obvious risk factors in that 16-30% of all hepatitis B cases have no known source of infection. Unvaccinated children in families with no known risk are still at some risk for infection through normal play activities, and teenagers have an increased risk of exposure when they become sexually active. The most common source of infection is from mothers who may not know that they are hepatitis B infected. Despite being a vaccine-preventable disease, HBV is still responsible for death in 2% of cases.[38]

There are also concerns that children are too young to receive the large number of shots they are given as infants through early childhood. It is true that 20 years ago there were seven routine vaccines given compared to 11 routine vaccines given now, with some 20 total injections by the time a child is two years old, yet the number of total vaccine proteins and polysaccharides is less than it was in the past. Young infants are capable of responding antigenically to about 100,000 different organisms at one time. There was some confusion surrounding whether to administer both the birth dose of hepatitis B vaccine as well as the combination shot, Pediarix, which combines the DTAP, polio, and hepatitis B vaccines. In some cases practitioners were deferring the birth shot in favor of the combination shot administered at two months of age, however, it is advised to not eliminate the birth shot, and studies have shown that administration of the combination shot does not constitute an extra dose nor does it cause an increase in side effects. In addition to childhood screening, all pregnant women should have hepatitis B surface antigen (HBsAg) testing so that immunoprophylaxis can be given to infants with HBsAg positive mothers. Results of prenatal testing should be both given to the mother as well as communicated to the facility where the mother is expected to give birth.

The relatively new hepatitis A vaccine is an added immunization at 12 months and 18 months, although not all health plans cover it. In 2005, 4,488 cases of hepatitis A were reported to the CDC, although there were an estimated 42,000 new cases overall. The CDC recommends individuals ages one year and older should receive the HAV vaccine as a routine vaccination and that this will likely be added to the vaccination requirements for entry into school.

Vaccinations are the cornerstone for prevention of disease. Use of information and educational strategies can enable parents to follow through and ensure completion of their child's vaccines.

C. The Future of Hepatitis Therapy

C. Bradley Hare MD and Carroll Leevy MD

Hepatitis B

In the last decade, therapeutic options for treatment of hepatitis B have improved significantly. Despite these advances, the treatment options are not optimal. It was originally thought that hepatitis B had three sequential phases: immune tolerant, which is characterized by the detection of the hepatitis B 'e' antigen (HBeAg) with no evidence of anti-HBe antibodies (anti-HBe), immune active or chronic phase in which the host immune system recognizes the HBeAg and anti-HBe appears, and a non-replicative phase, or inactive HBsAg carrier. However, these groups are in fact interchangeable and reactivation can occur as long as an individual has HBeAg surface antigen present. One of the primary goals of HBV therapy is to suppress HBV replication and reduce DNA to undetectable levels, as incidence of hepatocellular carcinoma and cirrhosis increases with increasing HBV DNA baseline viral levels.[39] Because the natural course of the disease is typically asymptomatic, detecting HBV in patients who need treatment is crucial. Indications for treatment are based on serum ALT levels, serum HBV DNA levels, and histological grade and stage of fibrosis.[40]

There are two distinct patient populations targeted for antiviral and immunomodulatory therapies. In HBeAg-positive (wild-type) patients, therapy is aimed at suppressing DNA to low or undetectable levels. Data indicating discontinuation of therapy after seroconversion and ALT normalization is strongest following treatment with interferons; however, because there is less data available to support discontinuation of therapy following treatment with newer, safer nucleoside and nucleotide analogs, experts are beginning to consider longer, even indefinite durations of treatment rather than complete discontinuation.

For HBeAg-negative patients, therapy is indicated for an unending period of time, as seroconversion does not represent an endpoint. Characteristics of HBeAg-negative chronic hepatitis B, which has an increasing prevalence, include: more common in Asian immigrants, with liver disease that is typically advanced; more common in males in the 36-45 year age range; fluctuations in ALT and viremia levels; severe liver necroinflammation; and progressive fibrosis with a poor prognosis.[41-42]

In terms of need for long term therapy, recognition of naturally occurring and treatment-induced genotypic HBV mutations is a key component to drug development and application. While these mutations are spontaneous and are capable of reverting back to the wild-type, when drugs are targeting and selecting against the wild-type, mutations and resistance are able to take hold. Although some HBV treatment and management leaders recommend using pegylated interferon alfa-2a as a first course of treatment due to its efficacy in getting rid of the virus, in reality it only works successfully in less than 50% of patients and has the potential to produce serious adverse side effects, and is not cost effective. Factors associated

with choosing interferon as initial therapy include favorable genotypic predictors of response, low baseline HBV DNA levels, high baseline ALT, younger patient demographics, no co-infection with HIV, and concomitant HCV infection.

On the other hand, oral antivirals are often better tolerated and more convenient to administer, but are prone to the development of resistance. The primary drugs recommended as the first lines of therapy include tenofovir and entecavir. Although lamivudine, a well-tolerated oral L-nucleoside analogue that interferes with HBV DNA polymerase activity and inhibits replication, has similar results to peginterferon with minimal side effects, it has the least favorable resistance profile with up to 70% of patients becoming resistant within 36-48 months. Because of this, lamivudine monotherapy is not currently recommended as a first line of treatment. Entecavir has reduced activity against lamivudine-resistant HBV when compared to wild-type HBV, and as such, tenofovir is recommended for use by the vast pool of lamivudine experienced patients.

Several other agents in development but not currently approved for use in the United States include clevudine and emtricitabine in combination with FDA approved tenofovir, although resistance, side effects, and efficacy data from phase III clinical trials vary.[43-45] Phase II investigational trials for pradefovir, valtorcitabine, amdoxovir, ANA 380, and racivir are also underway. Nucleoside and nucleotide therapies are generally designated for patients with low baseline HBV DNA, high ALT, older patient demographics, concomitant HIV infection, and no HCV co-infection. For patients with HIV co-infection, the HBV-active drugs lamivudine, tenofovir, and adefovir (as well as emtricitabine) have activity against the HIV virus as well and should be used as part of a fully suppressive HIV regimen.

Current therapies approved by the FDA are listed in Table 6. While having multiple treatment options for chronic hepatitis B represents a step forward, some clinicians view the expanding array of therapeutic choices as further complicating the challenging process of choosing the appropriate drug for use. There are existing consensus treatment guidelines, but there is insufficient data to identify in whom and when to use them.[46] Drugs in the future will need to have better reduction in HBV DNA due to increasing genotypic resistance rates of current HBV antivirals. Avoiding sequential monotherapies and using agents with similar cross-resistance profiles can help prevent drug resistance. In addition, combination therapy is becoming popular by pairing the best nucleoside and the best nucleotide together for treatment. The downside to this potentially bright scenario is that there have been few thorough combination studies done to date, and the necessary clinical trials for FDA approval of dual or triple therapy will likely not be completed for several years.

Hepatitis C

The primary goal for hepatitis C therapy is to eradicate the HCV infection. Secondary goals as outlined by Lindsay et al.[47] are to slow the disease progression, improve histology, reduce the risk of hepatocellular carcinoma, and improve health-related quality of life. Although it has been 20 years since the first identification of HCV, therapeutic options remain limited. Treatment of chronic hepatitis C has evolved from interferon alfa (IFNα) monotherapy to the current standard as defined by the National Institutes of Health in treatment-naïve patients which is the use of a polyethylene glycol modified form of IFNα (pegylated IFNα) paired with the nucleoside analogue ribavirin, which leads to a sustained viral response in approximately half of treated patients.[22,48-49] Because pegylated IFNα has an extended half-life, it can be administered once a week. Treatment duration depends on the HCV genotype and response to antiviral therapy as determined by serum viral load after four and 12 weeks of therapy. Genotypes 1 and 4 are treated for 48 weeks. Genotypes 2 and 3 are treated for 24 weeks, and a 12 week regimen has been shown to be effective in patients who achieved a rapid viral response.[50] In the coming decades, hepatitis C treatment will likely be even more tailored depending on the genotype and rapid response. The use of mathematical models and algorithms are increasingly useful in defining the mechanism of action of antivirals, guiding duration of therapy and duration of undetectability, predicting development of resistance, and answering questions regarding pathogenesis. Predictors of response to therapy are primarily dictated by viral genotype and viral load, as well as the HIV status, age, extent of cirrhosis, race, gender, and body weight of the host, among other factors.

The IFN family of cytokines affect the immunoregulatory and

Table 6.— FDA approved therapies for chronic HBV

Generic Name	Trade Name	Manufacturer	Date Approved for Hepatitis B
Interferons			
Interferon alfa-2b	Intron-A®	Schering Corporation	1992
Interferon alfa-con1	Infergen®	Three Rivers Pharmaceuticals	1997
Peginterferon alfa-2b	Peg-Intron®	Schering Corporation	2001
Interferon alfa-2a	Roferon-A®	Roche Laboratories	2003
Peginterferon alfa-2a	Pegasys®	Roche Laboratories	2005
Nucleosides and Nucleotides			
Lamivudine	Epivir-HBV®	GlaxoSmithKline	1998
Adefovir dipivoxil	Hepsera®	Gilead Sciences	2002
Entecavir	Baraclude®	Bristol-Myers Squibb	2005
Telbivudine	Tyzeka®	Idenix and Novartis	2006
Tenofovir	Viread®	Gilead Sciences	2008

antiproliferative properties of target cells, and are capable of inducing intracellular signaling through various pathways, including the Jak-STAT pathway.[51] In addition, IFNα plays a role in antiviral actions through transcriptional activation of IFN-stimulated genes, which can lead to blocked viral transcription, degradation of viral RNA, and inhibition or interference with viral replication.[52] Most effective against genotypes 2 through 6, pegylated interferon is best to use in difficult responders. Ribavirin, when given without IFN shows no antiviral effects; however, its ability to enhance the efficacy of IFN treatment is accepted, although not fully understood. Similarly, the exact mechanisms by which IFNs are effective against HCV remain poorly understood due in part to lack of HCV cell culture and small animal models. Recently, a genetic polymorphism near IL28B which encodes for interferon lambda-3 was found to be strongly correlated with patient sustained viral response when treating with pegIFNα/ribavirin in individuals with HCV genotype 1.[53] This interferon lambda-3 pathway may constitute a potential novel target for HCV antiviral therapies.

There are new drugs currently being derived against protein targets such as polymerases and protease inhibitors that block HCV replication, although timelines for FDA new drug approval are generally five years or longer. There are currently two HCV NS3-4A protease inhibitors, telaprevir and boceprevir, that are being evaluated in phase III clinical trials,[54-55] and it is expected that novel small molecule antiviral compounds, or STAT-C compounds, will eventually be part of standard HCV therapy. STAT-C drugs have been shown to improve the first-phase HCV RNA decline by shutting down virus production, and may yield early viral suppression and improved sustained viral response rates with shorter treatment durations.[55-56]

Other therapies also under investigation include caspase inhibitors, therapeutic vaccines, longer acting interferons, and a variety of nucleoside analogs. However, the highly replicative nature of HCV infection coupled with error-prone viral RNA synthesis and considerable genome diversity pose challenges to drug development. Although novel therapeutics might shorten the duration of treatment, they will not likely replace the use of pegylated IFNα and ribavirin, which will remain a mainstay of therapy for the foreseeable future, or until such time that multiple direct-acting antiviral inhibitors are available and proven to provide a sufficiently high barrier to resistance when used in combination.[57] Despite the potential for future advances in therapy, we must have an aggressive approach and treat hepatitis now.

VI. Summary and Conclusions

Alan Tice MD

Understanding the varied perspectives of patients, physicians, administrators, and community advocates who are closely involved with different aspects of hepatitis are important steps toward the development of effective, collaborative management strategies. Although viral hepatitis has been termed the 'Silent Epidemic' due to infection that too often goes undetected and untreated because patients and physicians may be unaware of who is at risk or may fail to pursue testing, the communities in which the virus is prevalent cannot afford to be silent any longer. It is reminiscent of the parable of the blind man and the elephant wherein different opinions and expertise were compiled in an effort to determine an appropriate course of action. In this case, the 'elephant' is hepatitis, and the yearly symposia sponsored by the Hepatitis Support Network of Hawai'i are one tool being implemented in order to bring many backgrounds and perspectives together for a single purpose, which is to highlight and share the challenges and solutions of living with and treating viral hepatitis. With the help and support of the medical community and individuals who have been personally affected by viral hepatitis, the future of hepatitis detection, therapies, cure rates, and other challenges unique to the disease is promising.

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Figure 3.— The Blind Men and the Elephant – an Oriental rendition.

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