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The 25th Anniversary of the Discovery of the Hepatitis C Virus: Looking Back to Look Forward

Dr. Matt Birnholz:

Welcome to the Grand Rounds Nation on ReachMD, presenting the best Grand Rounds from across the country. I'm Dr. Matt Birnholz. This week's Grand Rounds comes to us from the Centers for Disease Control and Prevention in Atlanta, Georgia, and is titled The 25th Anniversary of the Discovery of the Hepatitis C Virus: Looking Back to Look Forward. Here's Dr. Thomas Frieden, Director of the CDC.

Dr. Thomas Frieden:

Okay, good afternoon everyone, and thanks very much for being here for the Public Health Grand Rounds on the 25th Anniversary of the Discovery of Hepatitis C Virus: Looking Back and Looking Forward. Twenty-five years ago CDC played an integral role in identifying what was then known as non-A, non-B hepatitis and became hepatitis C virus.

Since then there have been really important public health milestones including the development of a screening test for hepatitis C, the screening of blood, making our blood supply safer and dramatically reducing the number of new infections in this country. And now we have a new milestone, which is effective better-tolerated and shorter-duration treatment for hepatitis C. We have the potential to cure a lot of people who are infected with hepatitis C and who otherwise will go on to develop severe disease, cirrhosis, liver cancer, and other severe complications.

There are significant concerns about both cost and access to medical treatment for hepatitis C, and I think that we in the public health world can't afford to be naïve either about the need to stand up for what's right in terms of getting access to lifesaving treatment or about the concerns that are valid about the affordability and profit margins of treatments that are essential and that may exist.

And I think one of the things that means for us is that we need to be extremely careful about any conflict of interest or potentially perceived conflict of interest in any of our recommendations and actions, particularly when there are large economic interests at stake. We'll also need to address the whole cascade of treatment. And we've seen this in condition after condition, whether it's hypertension or HIV, going from how many people are out there to how many people are actually effectively treated.

And to do that is going to require our engagement with the health care system, where we in public health can bring a laser focus on thinking about denominators. How many people do we really need? But it will be the clinical providers who need to figure out how to get that proportion effectively treated up. That cascade has so many points of falloff it's not enough to increase testing rates.

We have to figure out how to make sure that the providers and the systems out there have systems in place to give consistently good results and get a very high proportion of people effectively treated. We'll also need to understand the long-term consequences of treatment and confirm that sustained virological response is truly sustained. I want to think our speakers and introduce Dr. Phoebe Thorpe.

Dr. Phoebe Thorpe:

Thank you, and thank you Dr. Frieden for your thoughtful comments. I'm Dr. Phoebe Thorpe, Deputy Scientific Director of the Public Health Grand Rounds. Continuing education credits for Public Health Grand Rounds are available for physicians, nurses, pharmacists, health educators, and others. Please see the Public Health Grand Rounds website for additional information. And now I'd like to introduce the first speaker, Dr. John Ward.

Dr. John Ward:

Thanks, Phoebe. Good afternoon, everyone. I am John Ward, I'm the Director of the Division of Viral Hepatitis here at CDC. Hepatitis C virus was first discovered 25 years ago in 1989. We're privileged today that two of the key leaders in that discovery have joined us, Dr. Dan Bradley, formerly of CDC and the hepatitis branch, and Dr. Harvey Alter from the National Institute of Health. Hepatitis C is an

enveloped RNA virus. The genome consists of 96 hundred nucleocytos that encodes a polyprotein that's cleaved into structural proteins and nonstructural proteins.

The nonstructural proteins are the targets for antiviral therapy, as you'll hear later on in this session. Because the RNA polymerase lacks proofreading activity millions of viruses with minor genetic changes known as quasispecies arise in each host. Based on major differences in genetic structure HCV is grouped into seven genotypes which respond differently to antiviral therapy and cluster geographically globally. In the United States approximately 70 percent of infected persons had genotype 1, a genotype typically difficult to treat.

This genetic diversity coupled with a host relatively weak immune response increases the likelihood of chronicity as well as poses formidable barriers for the development of a protective vaccine. Globally hepatitis C is a major problem. Based on data from the World Health Organization an estimated 135 million persons are living with hepatitis C with the areas colored in red having the highest prevalence. Egypt is considered to have the highest prevalence with one out of every 10 persons chronically infected.

It's estimated that approximately a million persons die each year from complications of HCV infection. In the United States an estimated one percent of the civilian population or approximately 2.7 million persons are infected with HCV. This estimate is based on the National Health Survey, which excludes populations such as the homeless and the incarcerated, which are known to have increased prevalence for hepatitis C. Adjustments of the estimates for these exclusions increase this prevalence by upwards of 350 to 850 thousand persons.

Before its discovery, when it was then called non-A, non-B hepatitis, as mentioned by Dr. Frieden, epidemiologic studies had already revealed that this was a blood-borne disease most common among transfusion recipients and persons who had injected drugs and that there was an evolution over time as various prevention strategies were put into place even before the virus was discovered in 1999 such as various surrogate markers for non-A, non-B hepatitis introduced into blood banking as well as HIV prevention measures which began to ramp up in the late 1980s, particularly those directed toward injection drug users.

Thereafter with the discovery of the virus serologic tests were developed which further improved blood safety and proved the precision of prevention measures, and coupled again with other measures such as efforts to improve patient safety have led to decreased incidence to the point where in 2012 after years in the '80s where there were hundreds of thousands of cases of infection, 22 thousand cases were reported in the most recent year. Between 2007 and 2012 reports of new HCV infection increased 50 percent nationally with 17 states reporting an increase of 200 percent over that time period.

Our epidemiologic studies conducted to date indicate that at least 70 percent of these infections are related to drug use which often begins with the abuse of oral prescription narcotics among older adolescents and young adults. These individuals are predominantly white, residing in suburban and rural areas. HCV is more transmissible than HIV through blood contact. Risk factors for HCV transmission include the duration of injection, frequency of injection, and equipment sharing, not just sharing needles but also preparation equipment used to prepare the drug for injection.

So as a result interventions such as syringe exchange which have been highly effective in preventing HIV transmission are only moderately so in preventing HCV. So despite declines in HCV incidence the prevalence among persons who inject drugs remain high in the United States, ranging from 27 to 50 percent. There are other exposures to contaminated blood which contribute to incidence. This includes the health care setting where the risk of HCV transmission from a needlestick is greater than that for HIV, in part because of the higher viral concentration of HCV versus HIV.

From 2008 to 2013 CDC participated in the investigation of 18 health care associated outbreaks, which were linked to 200 new infections and the notification of over 90 thousand patients. These transmissions occurred in multiple settings in both inpatients and among outpatients related to syringe reuse, other poor infection control, and drug diversion by health care workers. There is a risk of transmission from mother to child, particularly if the mother is HIV-infected.

Sexual transmission tends to be rare except among HIV-infected men who have sex with men, where incidence has been found to be high in both Europe and the US, and other exposures which place people in contact with contaminated blood. Once infected with HCV the risk of chronic infection ranges between 55 to 85 percent. Thereafter disease progression is typically silent.

That's why hepatitis C is often called the silent epidemic, while an HCV infection leads to liver damage progressively over the years with over a 20-year period 15 to 30 percent of persons developing severe fibrosis known as cirrhosis and then thereafter a two to four percent annual risk of developing _____ (10:09) liver disease and liver cancer. There's also a risk for other extrahepatic diseases that contribute to this morbidity. Despite the drop in incidence mortality from HCV increased from 1999 to 2010 by 50 percent with a mean age of 59 years, several decades younger than the average life expectancy of Americans.

Black non-Hispanics, American Indians, and Alaskan Natives have twice the mortality as white Americans. These mortality figures are

conservative as the valuation studies indicate that only about a third of liver-related deaths among HCV-infected persons are reported on bio records. Further, other studies have indicated that about 45 to 60 percent of persons are unaware of their HCV infection.

Given the rising morbidity and mortality, given the large proportion of persons currently unaware of their status, we began to look for other options for interventions beginning with testing. And that search began with looking at the data where it reveals that the wave of incidence that was observed in the '70s and '80s and early '90s persists as a wave of prevalence with infection among young adults in those earlier years now persisting as prevalent infection among middle-age and older adults currently.

And indeed the birth cohort of persons born between 1945 through 1965 or the so-called baby boom population has the highest prevalence by birth year compared to other adults, indeed a sixfold higher prevalence than other adults, representing 81 percent of all persons living with HCV in the US and three out of every four persons dying of this condition. As you'll be hearing from Dave in just a moment, we have entered into a whole new highly effective era for HCV therapy, but we're not going to be successful if we don't link the patients who need testing, care, and treatment to those interventions.

And as was published by CDC authors and our partners last year, the care cascade for HCV is absolutely dismal. So where are we now? The burden of HCV-related disease is large. Reports of new HCV infections are increasing. CDC and the US Preventive Services Task Force have issued new recommendations calling for HCV testing for persons born during 1945 through 1965, for persons who inject drugs, and others at risk.

At least half of HCV-infected persons are unaware of their status, and access to HCV testing, care, and treatment must improve for patients to benefit from therapy. Now I'll turn it over to Dave Thomas to describe the evolution of HCV therapy and the arrival of a curative era for HCV. Thank you.

Dr. Dave Thomas:

Thanks very much, John, Dr. Frieden. It's a pleasure to be here. I'm so honored to be able to speak about hepatitis C treatment, arguably one of the most exciting and rapidly-changing fields of medicine. To understand hepatitis C treatment you need to think about three terms defined by what happens to the HCV virus load after treatment. In some individuals thorough treatment is given and there's little to no reduction in the HCV viral load, a condition referred to as nonresponse.

In others HCV RNA is suppressed below the level of detection, but then after treatment is discontinued the infection rebounds, and those persons are called relapsers. In a third group of individuals HCV RNA is suppressed below the level of what can be detected in the blood, and then even after therapy is discontinued remains undetectable. Now the FDA has decided that the goal of successful therapy is being undetectable 12 weeks after therapy is discontinued, so-called SVR 12.

Now we refer to an SVR as a cure for really three reasons, one of them durability. SVR is considered a cure because it's durable. In thousands of individuals followed after successful treatment after SVR 12 or 24 there's few to no individuals in whom infection is detected again in the blood, and in some in whom it is it's impossible to rule out that they were reinfected rather than that their original infection relapsed. So first of all SVR is considered cure because it's durable.

Secondly, it's considered a cure because it most importantly reduces the incidence of hard clinical outcomes. Third, HCV sustained virologic response is considered a cure because as Dr. Coffin will emphasize later it reduces the risk and eliminates the risk of the virus being transmitted to another person.

We've been able to achieve that cure with a variety of different approaches over the years beginning in 1991 with the approval of interferon, which had progressive improvements in the frequency with which cure can be produced by adding ribavirin, by changing to long-acting interferon, and most importantly by adding to the interferon and ribavirin molecules that directly interfere with various nonstructural proteins, as John mentioned in his first talk.

In particular the HCV protease and the HCV polymerase have been important drug targets with molecules already approved by the USFDA for use in clinical practice. As exciting as the improvements in efficacy are we've also experienced substantial improvements in safety of treatment. There are a large number of regimens that are already filed, many cases with expedited review approved by the USFDA, and some interferon-sparing regimens that are already FDA-approved for use in the United States.

With each of these, many of which have already been published, there are high rates of sustained virologic response, in other words high cure rates, and very high tolerability just as what I've shown you. Well, in this rapidly changing era typical methods of establishing guidelines, if you will, for how to use medications really are insufficient.

Accordingly, the Centers for Disease Control has cosponsored along with the American Association for the Study of Liver Disease and the Infectious Disease Society of America in partnership with the International Antiviral Society of the USA guidance for how to use these medications and other aspects of hepatitis C management. There's information on testing, there's information on linkage to care,

and there's information on what regimens are recommended for particular situations.

In addition the all-important question of which patients should be treated and when. Now, it used to be that we answered that question when we had medications with lots of side effects by weighing the risks of treatment over and against the potential benefits. And oftentimes the balance favored the use of medications only for persons with advanced liver disease. But now we're looking at medications with few to no measurable adverse events, and that shifts this dynamic and opens up the opportunity for treatment for far more individuals.

That also raises the question of how that expanded access to treatment, if you will, will be paid for. Hepatitis C treatment's always been expensive. The regimens that were standard care from 2011 to 2013 could be 50 to 100 thousand dollars. There's already been studies that have shown that medications in that price range and with that efficacy would be consistent with what we usually consider to be cost effective in the United States.

The new regimens are more expensive but they're also more efficacious, and preliminary observation suggests that there's incremental cost effectiveness achieved, that in other words the increase in efficacy counterbalances the increase in cost, from a cost perspective that is. Nonetheless, the issue of cost has clearly come into the hepatitis C treatment discussion and has entered in and shifted the dynamic

Whereas we once talked about essentially what was the advisability if you will of treatment or the advisability for a given patient determined by risk and benefit we're now concerned with this broader perspective and a physician's not only thinking about the advisability but in some instances having to defend the necessity of treatment, something that we haven't had to do in the past.

There's no question that we've experienced remarkable progress on the efficacy of hepatitis C treatments, beginning with interferon and now with the all-oral regimens really realistically being able to achieve a cure in more than 90 percent of the persons who come in for care. It's tremendous progress that we need to celebrate and applaud.

However when we take a broader perspective and consider that progress on the y axis, if you will, the percent who are cured, over and against the percent of the 135 million people around the world that know they have hepatitis C and haven't had an opportunity to be treated, not to mention be cured, we get a very different perspective. And this starts to show us what the challenge is for the next 25 years.

Whereas we've been able to move up the y axis because of the progress in virology, clinical testing, and the progress brought about with clinical trials and the innovations from that work, in the next 25 years we're really going to have to make progress on this x axis, expanding the percentage of persons who know they have infection, and somehow getting treatment to them and paying for it.

So what I've done in my talk is establish that hepatitis C can be cured. I've used the word cure because the sustained virological response is durable, because it reduces hard clinical outcomes including improving mortality, because it prevents transmission from one person to another. I've also emphasized that the efficacy of hepatitis C treatment has risen considerably in association with improvements in the safety of hepatitis C treatment.

But then I've also pointed to challenges that remain, and when we think about the next 25 years the kinds of science, the kinds of implementation science that will be necessary to have the same sort of impact that we're celebrating today. Thanks very much for your attention. Now it's my privilege to introduce Phil Coffin to present the next talk.

Dr. Phil Coffin:

So as we've heard so far, we've entered an era where we have the tools to end hepatitis C in the United States, and there are two major goals to achieve this. The first is to treat those already infected, and then the other is to prevent new infections from occurring. The new screening guidelines targeting those most at risk of advanced liver disease, particularly baby boomers, can allow us to cure a substantial portion of the population and lead to enormous reduction in the morbidity and mortality from chronic hepatitis C.

To prevent new infections we need to implement ways to interrupt transmission among those who are most at risk, in particular people who inject drugs. Although there are multiple risk groups, these two groups represent the bulk of established and incident cases of hepatitis C. Some parts of public health models that have proven useful to complement or enhance the management of HIV can be applied to formulate a public health response to hepatitis C.

This continuum starts with primary prevention, goes to screening, diagnosis, management, treatment, viral suppression, and then hopefully reduction in prevalence and incidence of disease. It's useful not just for improving clinical outcomes and identifying gaps, but also in helping public health in tracking lab-based outcomes.

If we apply it to hepatitis C primary prevention includes interventions like syringe access and access to other injection equipment, safer

sex particularly among HIV-positive men who have sex with men, and improved access to substance abuse disorder treatment medication-assisted therapies. Screening in this setting could be tracked by health care systems which have access to both positive and negative test results. Electronic health records can be used by establishing automated alerts or reminders to screen based on public health recommendations by both risk factor and birth cohort.

Screening would optimally be designed as opt-out as it should be for HIV, and local and health systems would need to develop guidelines in terms of how frequently you need to screen those who are at ongoing risk of transmission. Diagnosis unfortunately still requires both a screening and then a subsequent confirmatory RNA test for hepatitis C. This is a two-step process that can sometimes be confusing, and patients oftentimes don't know if they have RNA-confirmed hepatitis C or are simply seropositive.

There's some movement towards reflex testing, which would be an automatic confirmatory RNA test done in the setting of a positive antibody, as is done for HIV and syphilis. This would be a huge benefit as of course would be a point-of-care RNA assay. Public health's role in this setting could be to track if those who with a positive antibody have received RNA testing, however it would have to change the required reporting.

Currently negative RNAs are not reportable to public health surveillance systems, so there's no way to track if all the hepatitis C seropositive persons have received RNA confirmatory testing. Another role for public health in this setting is to evaluate the effectiveness of screening interventions. Like with HIV, if we're effectively screening we'd expect to detect people at higher CD4 counts. In hepatitis C we'd expect to detect people with earlier stages of fibrosis.

The initial management of hepatitis C includes screening for syndemic infections, hepatitis A and B, HIV, vaccinating for hepatitis A and B and pneumococcus, counseling regarding risk reduction and transmission. Brief clinician interventions around alcohol have been shown to be effective in this setting. And you need to assess for treatment both in terms of getting a genotype and evaluating liver disease. So the liver evaluation includes a physical exam, liver function tests, platelets, sometimes imaging and even pathologic evaluation to estimate the degree of fibrosis in the liver.

Clinically health care systems could do this with sort of a simple laboratory-based proxy of transferase levels after diagnosis just to ensure people will have had evaluation of their liver and genotypes to ensure that patients have been considered for treatment. Additional steps in management are getting patients into substance use disorder treatment, particularly methadone and treatment and psychiatric management, although that is less critical as we move away from interferon, which is the primary reason that psychiatric disease has historically been a contraindication to hepatitis C treatment.

So these traditional barriers to hepatitis C treatment, the toxicity of interferon, the duration of treatment, the low likelihood of cure, these are not as relevant now as we move away from interferon and the much more challenging treatments. However we have new barriers, in particular cost, which we all expect is going to limit access to hepatitis C treatment for some time to come. The proportion cured by hepatitis C treatment with cure rates over 90 percent should be pretty close to the proportion that are actually treated.

This depends a little bit on which regimen's offered and on adherence of course. Unfortunately the cost of new therapeutics is expected to result in restrictions on who can receive them. A common way to restrict this has been based on degree of fibrosis. The new therapies are fairly straightforward, so primary care providers who couldn't offer the old therapies due to complexity of the regimens now potentially could.

Only 5,200 individuals were prescribed hepatitis C therapeutics in the first quarter of 2014. If we expand this to primary care providers and others with expertise in managing viral infections we can greatly increase the number of providers who can offer treatment and the geographic distribution. Federally qualified health care centers already care for many hepatitis C-infected persons, and they are available all over the country.

Moving on to the second goal, preventing new or incident infections, we need to focus on high-risk groups. Currently drug injectors account for the vast majority of new infections. Strategies to reduce their risk include syringe access programs, medication-assisted treatment, treatment as prevention, and prophylactic vaccines. Medication-assisted treatments, particularly with agents such as buprenorphine and methadone are well-known to reduce disease incidence, but they're not universally available and are often restricted to detoxification short-term treatment regimens that are markedly less effective.

A prophylactic vaccine would be fantastic, but we're unfortunately in the very early stages of development for that. Syringe access programs, which offer clean syringes and other injection equipment and teach hygiene such as not handling equipment with contaminated hands, are still not widely available in many parts of the United States. These charts show the impact of syringe access programs on hepatitis C prevalence and incidence. The black dots on the left chart represent actual prevalence, and the gray-shaded area is the estimated prevalence if syringe access programs had not been available.

Similarly on the chart on the right with incidence the gray area represents what it would have been without syringe access programs. As you can see, there is an effect, and it's an important effect, however it's simply not enough to achieve reduction in hepatitis C prevalence and incidence in a timely manner. The ease of novel therapies makes the concept of treatment as prevention or TasP for hepatitis C feasible. Successful TasP programs would interrupt secondary transmission and lower incident infections.

These programs would have the most impact by focusing on people who are actively injecting drugs in areas with a high prevalence of hepatitis C. But implementing TasP among injectors may be a little bit complicated. Concerns about adherence to treatment might lead some to want to limit access to treatment to injectors who are in substance use disorder treatment programs such as methadone programs. That would of course lessen the impact, because those individuals would be at less risk of transmitting hepatitis C while they're in the program.

Patient navigation programs, conditional cash transfer or contingency management and directly-observed therapy may be other approaches we need to consider for maximizing adherence. It's critical to remember, and I can't overemphasize, that there's no single intervention for preventing HIV or hepatitis C. So in summary there are multiple very positive signs and an array of serious challenges.

The public awareness campaigns and community mobilization have generated broader recognition that hepatitis C needs to be addressed now, not tomorrow but today. The CDC and US Preventative Services Task Force recommendation for baby boomer screening should be implemented such that opt-out screening happens. This would both improve screening and reduce the stigma that has been a barrier to hepatitis C screening and care.

Hepatitis C screening can be more simple than the current two-step process of diagnosis that is confusing to many patients and even some providers. Policy changes that for example make negative RNAs accessible and reportable to public health agencies could improve the ability of surveillance to track how we're doing, and we all hope that these new therapies will bring competition and improve the price issue that we're running into currently. Thank you very much.

Dr. Matt Birnholz:

You've been listening to Public Health Grand Rounds from the Centers for Disease Control and Prevention, presented on ReachMD's series Grand Rounds Nation. Be sure to join us again for the next episode of the nation's best grand rounds. Until then, I'm Dr. Matt Birnholz, and thanks for listening.