

One Small Step for Rhode Island Medicaid, One Giant Leap Towards Hepatitis C Elimination

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On Aug. 1, 2021, Rhode Island (RI) Medicaid removed prior authorizations (PAs) for two direct-acting antiviral (DAA) regimens for hepatitis C virus (HCV), glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir, following seven other states. Removing PAs will increase access to HCV cure for thousands of RI Medicaid beneficiaries. Treatment is indicated for all HCV-infected adults (except those with short life expectancy that DAAs cannot remediate and in pregnancy) because cure improves quality of life; slows liver disease progression; reduces risk for cirrhosis, liver failure, hepatocellular carcinoma, extra-hepatic complications, transplantation and all-cause mortality; and thwarts transmission.¹⁻³ Treatment scale-up can decrease prevalence and incidence, and makes possible elimination of the United States' (U.S.) biggest infectious disease killer (aside from SARS-CoV-2), saving \$3.3–3.8 billion in future health care costs.⁴⁻¹⁰

This step represents the culmination of eight years of advocacy to ensure equitable access to these life-saving medications that can safely cure 99% of HCV infections in eight to 12 weeks. During these years, for many untreated Rhode Islanders, hepatic fibrosis progressed. Some died unnecessarily of HCV. Transmission skyrocketed, creating greater medical and economic burdens.¹¹

Treatment chronology

Rescinding the PA must be understood in its historic context. In 2001, the FDA approved the first pegylated interferon (PEG) for HCV. Attaching a polyethylene glycol compound to interferon-alpha prolonged its half-life. Thrice-weekly standard interferon could be injected weekly for the year. In 2002, after seeing many patients go untreated at RI's syringe services program and HIV clinics (as was common in those days), I started the Miriam Hospital Immunology Center's Coinfection Program for patients with coexisting HIV and viral hepatitis, supported by Drs. Timothy Flanigan, Edward Feller and Pierre Gholam.¹² The goal was to treat HCV in people living with HIV/AIDS (PLWHA), including those with substance use and/or psychiatric disorders, based on lessons learned from Dr. Flanigan's modified directly observed therapy approach (DOT) to deliver antiretrovirals (ARVs), and our experience with HCV care of incarcerated persons.¹³⁻¹⁴

Interferon was ineffective and toxic, potentially causing fatigue, flu-like and neurocognitive symptoms, depression, suicidality, homicidality, other reversible and sometimes

long-term consequences. Side effects of this immunomodulator could be more common and severe for PLWHA. The addition of ribavirin, a teratogenic oral nucleoside analogue, improved response rates. Ribavirin causes hemolytic anemia exacerbated by interferon's bone marrow suppressant effects, and can precipitate myocardial infarction, respiratory distress and other harms. Yet HCV was emerging as a leading cause of morbidity and mortality as better ARVs improved HIV control. Dr. Charles Carpenter's Monday morning Immunology Center meetings, traditionally beginning by honoring those who died of AIDS in the prior week, increasingly commemorated patients who died of HCV.

So began a program of weekly PEG administration coinciding with Monday's HIV/HCV support group. All week I micro-managed patients experiencing unintended effects, modifying doses and prescribing adjunctive therapies. Cindy MacLeod, RN, helped forge weekly multi-disciplinary meetings with Family Service of RI for home-based mental health care and case management during the year of PEG/ribavirin (PR). Stacey Chapman, RN, then stepped in. For the next decade we combatted PR hazards day and night. Miriam hematologists provided erythropoietin for PR-induced anemia, granulocyte colony-stimulating factor for neutropenia, and interleukin-11 platelet growth factor. Dr. Gene Jacobs provided psychiatric expertise. Robert Janigian, MD, evaluated high-risk patients' retinas, examining patients with ophthalmologic symptoms same-day lest interferon induce vision loss.

In 2005, I began prescribing buprenorphine to stabilize opioid use disorder as bridge to PR.¹⁵ I became managing physician of RI's only HIV/AIDS assisted living establishment, to facilitate residence for PR patients living alone, unstably housed, or at high risk. When needing help, I contacted experts around the world treating PLWHA and patients with psychiatric illness and addiction.¹⁶ In 2009, European physicians providing guidance started the International Network on Hepatitis in Substance Users (INHSU). I travelled to Zurich for the first of many INHSU meetings, bringing best practices back to RI.

Development of DAAs

Despite optimizing safety and adherence, genotype 1 (the most prevalent strain) cure rates for PLWHA remained under 20%. Progress stagnated while courageous individuals braved months and sometimes two years of PR, given

virologic relapse after year one. Then a better understanding of HCV's life cycle resulted in the development of DAAs, which stop HCV's ability to replicate. FDA-approved in 2011, protease inhibitors (PIs) telaprevir and boceprevir were first, used with PR, else resistance mutations developed. Dosed three times daily, they improved cure rates but were only active against genotype 1, caused more severe anemia than with PR alone, and could trigger desquamating skin rashes. The second-generation once-daily PI simeprevir, approved in 2013 for use with PR, could also cause severe rash.

Physicians began recommending PR deferral for patients at low risk to progress to significant fibrosis, in favor of waiting for two DAAs, each blocking a different viral replication step. Baby boomers' high HCV prevalence plus noxious, ineffective pharmacotherapies contributed to the peaking burden of advanced liver disease. The backlog of interferon-experienced treatment failures, interferon-intolerant, and those with PR contraindications, grew.

Turning point in DAAs/Medicaid hurdles

On Dec. 6, 2013 the FDA approved sofosbuvir, an NS5B polymerase inhibitor – a new DAA class. This pan-genotypic game-changer made HCV curable without interferon. While at that time sofosbuvir had to be combined with simeprevir (for genotype 1), or ribavirin (for any genotype), sofosbuvir-based treatment could be life saving for PR treatment-failures, decompensated cirrhotics and others with PR contraindications, plus treatment-naïve patients. Finally, we had tools to avert the suffering and premature deaths, remove HCV's painful stigma and stop interferon's harm. We had cared for patients through years of ARV progress, which transformed HIV from a death sentence to a chronic, manageable illness. Here was the opportunity to transform HCV into our first curable virus, a pivotal moment in medical history!

What a shock to learn that sofosbuvir would not be added to RI's Medicaid formulary. Drs. Thomas Sepe, Alan Epstein and I met with Medicaid officials repeatedly to discuss a PA, share evidence, review treatment as prevention...while winter became spring...then summer. Patients pleaded to know when it would be their turn; we had no answers. What could we say to our cirrhotic patients running out of time – one with a painful, 20-centimeter spleen, another with interferon-induced hypertriglyceridemia and diabetes by week two, not cured after two PR courses; a non-PR candidate with thalassemia trait, arteriovenous malformations and coronary artery disease; another with a painful cryoglobulin-induced rash, coagulopathy, epistaxis and new-onset ascites?

In August 2014, eight months after FDA-approval, RI Medicaid issued its PA. Months of discussions were ignored. RI Medicaid would restrict sofosbuvir to those with advanced fibrosis, meaning that patients had to wait until serious hepatic disease developed, possibly a pre-cancerous liver, before treatment. RI Medicaid also instituted sobriety,

prescriber, and HIV-related restrictions despite simplified therapy with efficacy irrespective of disease stage, substance use or HIV status.¹⁷

The PA dealt a blow to individual and public health. This was the heyday of Dr. Carpenter's Immunology Center. We strove for comprehensive care for PWLHA throughout the adult lifespan, nurturing close patient-doctor relationships, with incremental care over time. We remembered those struggling through interferon, beating their HIV and sometimes substance misuse after years of toil, only to die of HCV; those dying too young following transplant failure as their new livers became reinfected; and Vietnam veterans dying of HCV after so many battles. Many feared PR would compromise their work performance. Many travelled from other states for PR so that no one near home would know of their HCV.

Medicaid recipients started undergoing costly and at times needless work-ups, sometimes with universal screening for rare liver diseases and elastography and/or liver ultrasound – even for young people with normal results of serum biomarker fibrosis scores calculated from routine blood tests. Those without advanced disease were told they were not 'sick enough,' for DAAs. Many emerged without DAAs if they had used any alcohol or drugs within six months. Many sought second opinions. Often the same evaluation was repeated. Medicaid required no elastography PA. Duplicative evaluations increased the ultimate cost per cure.

We raced to treat those with advanced scarring while new diagnoses surged. There were improvements in Medicaid restrictions – for example, nurse practitioners (NPs) were allowed to prescribe DAAs – but many endured. We published on Medicaid's response to this historic breakthrough, which exacerbated health care disparities.¹⁷ Restrictions violated federal Medicaid law, which requires states to cover medications consistent with their FDA labels. After four years of forums, radio shows and negotiations to no avail, stakeholders informed RI's Executive Office of Health and Human Services (EOHHS) that they were prepared to litigate against EOHHS.¹⁸ On July 1, 2018, the remaining DAA restrictions were lifted under threat of lawsuit.¹⁸

The arduous PA remained a barrier. This pre-approval process to determine if a patient met payer-specific DAA criteria differed across four RI Medicaid plans (and seven other payers), each with unique requirements, taking 45–120 minutes per patient.¹⁹ We completed and faxed a payer-specific PA document, plus laboratory results, to each plan. PAs required repeat blood tests – HCV RNA and genotype within 90 days even for patients with documented viremia for years and recent genotyping, prescribed pan-genotypic regimens – and myriad administrative elements (phone calls, peer-to-peer discourse, denials, appeals). Each plan dictated a preferred pharmacy, some mail order only, and a preferred formulary. Many practices lacked staff for this. The process delayed treatment initiation, prevented

test-to-treat strategies, and contributed to loss to follow-up.

And oh, the administrative waste. How much time did we spend on this bureaucratic task rather than with patients? The U.S. spends more on health care than any other nation, with the cost of waste accounting for 25%–30% of total health care spending.^{20,21} The administrative complexity category is associated with the greatest contribution to waste, even more than the inflation of medication pricing.²⁰

There was collateral damage. PAs contributed to misperceptions about HCV. Some clinicians interpreted fibrosis documentation to mean that they could not treat without radiologic evaluation of liver stiffness (not the case). Others inferred that they could not treat people who use drugs, while evidence demonstrates comparable cure rates with and without substance use with appropriate supports, and that reduction in the viremic pool is imperative. Appreciation of the opportunity for quantum progress was lost.

Even without PAs for two preferred regimens, challenges persist. Both contain PIs (glecaprevir and voxilaprevir). For beneficiaries with PI contraindications, Medicaid does not include alternatives, compelling PAs. PIs and thus both regimens are unsafe in decompensated cirrhosis. Rarely, PIs may induce drug-induced liver injury in patients with Class A cirrhosis or alcohol misuse.²² Drug-drug interactions are common. For example, glecaprevir and voxilaprevir may not be used with certain ARVs (e.g., ritonavir-containing regimens), nor with dabigatran, while PI-sparing sofosbuvir/velpatasvir may be co-administered. Atorvastatin, lovastatin and simvastatin, contraindicated with glecaprevir, and rosuvastatin and pitavastatin, contraindicated with voxilaprevir, may be prescribed at low doses with sofosbuvir/velpatasvir. Importantly, sofosbuvir/velpatasvir/voxilaprevir, salvage therapy for DAA failures (combining three DAAs blocking three distinct replication steps), should not be used for reinfections, which should be treated as naïve. RI Medicaid wants patient-level virologic response data submitted if requested (I decline). We are not obligated to provide treatment outcomes to prescribe medications for other diseases; this is particular to HCV and unwarranted.

Neighborhood Health, UnitedHealthcare Community and Tufts Health Public, the three plans offering coverage to RI Medicaid recipients, deem DAAs “specialty medications” provided through one pharmacy only. Their pharmacists must talk to patients via phone before dispensing DAAs. The scripted conversation, not tailored to the individual, stresses adverse events, rare with correctly prescribed DAAs. Only one month’s DAAs are provided at a time; refill delays can decrease cure rates. UnitedHealthcare’s pharmacy in Indiana, Optum, ships DAAs to a home address once a patient and Optum’s pharmacist schedule delivery via phone; expect long telephone wait times. Tufts’ pharmacy, CVS Caremark Specialty Pharmacy in Illinois, follows the same mail-only practice, hindering treatment for patients with unstable housing or telephone access.

RI lags in elimination projections

In part due to this history, RI’s HCV prevalence exceeds national averages.²³ RI joins seven states projected to eliminate HCV latest, beyond 2050.⁸ It will be said that Medicaid programs, caring for a disproportionate share of HCV, struggle to treat their enrollees. While rationing and an onerous PA pathway curbed DAA prescriptions, RI Medicaid’s largest provider recorded \$1,366,000,000 revenue in 2017, 35.1% growth percentage, and \$354,625,064 revenue growth, as RI’s second fastest growing private company.²⁴ It is well established that universal, immediate DAA treatment in Medicaid populations is cost effective and decreases downstream costs, due to avoidance of liver-related complications (not including prevention benefits which decrease risks to the community). As untreated persons reach age 65, costs are shifted to Medicare. Here, medication discounts do not exist, but universal treatment does nationally, increasing DAA expenses for the population not treated earlier.¹⁰

Sofosbuvir’s production cost is approximately \$1.50 per pill.²⁵ Initially, manufacturers set U.S. prices unduly high. However, list prices bear little resemblance to what Medicaid pays. DAA makers provide substantial discounts to Medicaid and pharmacy benefits managers. While DAA wholesale acquisition costs have dropped dramatically since sofosbuvir approval, lack of transparency about current pricing and discounts continues. I estimate RI’s current Medicaid price for eight weeks of glecaprevir/pibrentasvir at \$10,000. Hopefully with this writing, we get the facts. Let us consider lessons learned in the care of people experiencing poverty and other marginalized populations, work together for solutions prioritizing the needs of individuals and public health, and do better with the next therapeutic revolution.

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Epilogue

Decades of scientific work culminated in the 2020 Nobel Prize in Medicine being awarded to **Harvey Alter, Michael Houghton** and **Charles Rice** for their 1989 discovery of HCV. Several years ago, I had the privilege of meeting Dr. Alter at an HCV meeting. After his keynote address, Dr. Alter read an original poem. I summoned the courage to thank him and ask for a copy. I was elated to receive the following email on Aug. 2, 2021:

“Lynn: It has only been about two years since you asked for this poem (maybe three). I usually like to wait five years before responding, but consider this a priority. Seriously, your note to me got lost and somehow just reappeared. Very sorry for the delay. Hope things are as well as they can be in these crazy times, Harvey.”

Dr. Alter, Distinguished NIH Scientist Emeritus, gave permission to publish his poem here.

I Can't See the Forest for the Hb Ags?

*I think that I shall never see
This virus called non-A, non-B
A virus I cannot deliver
And yet I know it's in the liver
A virus that we often blame,
But which exists alone by name
No antigen or DNA
No little test to mark its way.
A virus which in our confusion
Has forced us into mass collusion
To make exist just by exclusion
But is it real or an illusion?
Oh great Liver in the sky
Show us where and tell us why
Send us thoughts that will inspire us
Let us see this elusive virus
If we don't publish soon, they're going to fire us*

*Let us find this little beastie
Give us a sign - a star from the Easty
Well today we're together
And our quest we'll begin
For this agent that plagues us like original sin
And perhaps someday, we all will agree
That indeed there exists a non-A, non-B*

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