Public health impact of a population-based approach to HCV treatment in Kentucky

This is a summary of the key outcomes of a hepatitis C virus (HCV) disease burden analysis undertaken by the Center for Disease Analysis Foundation's Polaris Observatory, in collaboration with ASTHO, CDC, the Kentucky Department for Public Health, Louisville Metro Public Health and Wellness, Kentucky Department for Medicaid Services, and providers from the University of Kentucky, Hepatitis C Treatment Centers, the University of Louisville, and UK HealthCare.

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Executive Summary and Key Recommendations

Hepatitis C virus (HCV) is a bloodborne infectious disease that causes substantial liver-related morbidity and an increased risk of liver cancer and liver-related death.[1] HCV is often known as a "silent disease," as there are few noticeable symptoms, especially in early stage infection.[2] Because of this, many infected individuals are unaware of their HCV status until more serious, late stage complications arise. Treatment is available for HCV, with success measured by the sustained viral response (SVR) rate at 12-24 weeks post-treatment. Prior to 2014, an average of 48-70% of patients achieved SVR with the available therapies; however, recent therapeutic advances mean that SVR rates in 2017/2018 have increased to more than 95%.[3] Achieving SVR can reverse the effects of early stage fibrosis and slow the progression of cirrhosis, which may avoid decompensation or hepatocellular carcinoma (HCC).[4,5] This reduces liver-related mortality by twenty-fold and all-cause mortality by four-fold.[6] Transmission of HCV can be prevented by avoiding direct exposure to contaminated blood or blood products, including objects that may have come in contact with contaminated blood, such as needles and syringes.

Over the last 14 years, the HCV epidemic has drastically changed in the US. Originally a disease affecting "baby boomers" (people born between 1945 and 1965), HCV has reemerged as a syndemic with opioid misuse, overdose and HIV.[7] In 2010, approximately 3.5 million Americans were infected with chronic HCV[8] and, according to CDC data, HCV now kills more Americans than any other infectious disease.[9] Additionally, HCV is the leading cause of cirrhosis and liver cancer, and the most common reason for liver transplantation in the US.[10] In 2013, HCV-related deaths surpassed the total combined numbers of deaths from 60 other infectious diseases reported to the CDC, including HIV and tuberculosis, and in 2014, HCV-related deaths reached an all-time high with more than 19,600 deaths reported.[11] At the same time, there has been a marked simultaneous increase in the number of persons newly diagnosed with HCV across the US, particularly among people with a history of injection drug use.[12] Increases in acute HCV and hospital admissions for opioid injection were seen between 2004 and 2014, with the number of persons newly diagnosed with HCV more than doubling between 2010 and 2014.[13]

National-level programs to control the burden of HCV have focused primarily on the older cohort of previously infected individuals. These programs include screening for HCV in the baby boomer birth cohort (1945-1965) as well as programs through the Veteran's Administration (VA) to diagnose and cure all veterans infected with HCV. Despite these efforts, barriers to treatment still exist at the state Medicaid level, as evidenced in many states by fibrosis requirements that preclude treatment for patients with early stage liver disease.[14] Universal procedures exist to prevent HCV transmission in medical settings across the US (though localized outbreaks may still occur when procedures fail). However, the recent opioid crisis presents a new challenge for HCV prevention efforts. At present, policies to prevent transmission among drug users are entirely state-specific, and in many states these policies are non-existent.[15]

This report presents the outcomes of a multi-stakeholder collaboration to assess the HCV disease burden in the Commonwealth of Kentucky. This work follows a standard methodology (modified Delphi process) developed and facilitated by the CDA Foundation's Polaris Observatory staff. It engages local stakeholders including the Kentucky Department for Public Health, the Louisville Metro Public Health and Wellness, providers from the University of Kentucky and the Hepatitis C Treatment Centers, Kentucky Medicaid and the University of Louisville, to ensure the best available data are used in the analysis and to develop momentum and consensus toward a common goal. A Microsoft Excel based Markov model, populated with consensus estimates, was used to address the basic questions needed for HCV policy development in Kentucky.

Key Insights and Recommendations

Who is affected in Kentucky?

- At the beginning of 2018, there were 78,300 HCV-RNA+ (viremic) infections in Kentucky. Approximately 88% of infections were diagnosed previously (n=68,700), with 23,100 infections diagnosed annually, and 5% of persons infected were initiated on treatment annually (n=4,200). There were an estimated 4,300 new infections annually, an incidence rate of 97 per 100,000 in 2018. As well in 2018:
    - 26% of total infections were in the 1945 to 1965 birth cohort*
    - 26% of total infections were among women of childbearing age*
    - 12% of total infections were among people who inject drugs*
    - 13% of total infections were among the incarcerated population*
    - 20% of infected individuals were enrolled in Kentucky Medicaid*[+]

  *Percentages do not sum to 100% because overlap exists across groups and not all subpopulations are considered here

  [+]The true prevalence in Kentucky Medicaid was unknown, but 15,400 persons are estimated to be currently infected

What is the impact of current policies?

- If currently policies continue and there is no change to the HCV treatment paradigm in Kentucky, the total number of HCV infections will increase by 1% by 2030. Liver-related deaths, hepatocellular carcinoma (HCC), and cirrhosis will decrease by 8-15% as the infected population ages.

What needs to be done to eliminate HCV in Kentucky?

- Eliminating HCV (defined by the World Health Organization (WHO) as 90% diagnosis of all infections, 80% reduction in new infections and a 65% reduction in liver-related mortality) by 2030 can be achieved in Kentucky using the following approach:
    - Prevention efforts will need to be increased to lower the incidence rate from 97 per 100,000 cases in 2018 to 18 per 100,000 cases by 2030. Additionally, the number of patients treated each year must double; increasing to 5,400 patients treated annually, starting in 2021. New diagnoses can decrease to 1,000 during this time period.
        - Strategies such as providing access to sterile syringes and treating persons who are actively injecting drugs for their HCV could all contribute to this prevention effort.

Background

HCV globally

Today, an estimated 71 million individuals globally are infected with hepatitis C, a curable disease that can lead to cirrhosis, liver cancer and liver-related death. Approximately 400,000 people die each year from causes related to HCV, which can be eliminated through coordinated efforts for prevention and treatment. Unfortunately, as of 2017, only 20% of those infected patients have ever been diagnosed, and currently only 2% of total infected patients are being treated for the disease annually.

The CDA Foundation and the Polaris Observatory

The Center for Disease Analysis Foundation (CDAF) is a non-profit organization specializing in the study of complex and poorly-understood diseases to provide countries and states with the data and information to create and implement successful elimination scenarios. The Polaris Observatory, an initiative of CDAF, provides epidemiological data, modeling tools, training and decision analytics to support eliminating HCV and hepatitis B (HBV) globally by 2030. The Observatory offers the most up-to-date estimates for HCV and HBV disease burden and economic impact, and offers strategies for elimination, along with financing options. An independent advisory board with representatives from global health organizations, academia, civil societies and donors oversees the activities of the Observatory. The Observatory's teams of epidemiologists work directly with stakeholders in over 100 countries to assess the current and future disease burden of hepatitis, model economic impact and develop strategies that can achieve country- or state-defined targets for elimination. By developing partnerships at country and local levels, the Observatory collects and analyzes data for its platform and publishes key findings to enable policies around hepatitis elimination.

How this model has been used globally

This work has resulted in the adoption of national hepatitis elimination strategies in countries such as Egypt and Mongolia. In Egypt, this included an economic analysis that accounted for both direct costs (healthcare, screening, diagnostic and antiviral therapy costs) and indirect costs (based on disability-adjusted life years). The analysis showed that it would cost Egypt US$90 billion over a 15-year period if the government kept the status quo. A plan of action was then developed beginning in 2014 with a goal of treating 300,000 patients annually, including cost subsidies for four years. After seeing successes, the plan continued each year. In 2016, Egypt treated 577,000 patients, and the plan expanded to include patients at all stages of disease, even those without any HCV-related consequences.

In Mongolia, CDAF and its Polaris Observatory team worked with the World Health Organization's Regional Office for the Western Pacific (WPRO) to first design an economic analysis and understand the disease burden. Working with partners including WPRO, the president of the Mongolian Association on Study of Liver Diseases, a physician professor and a group of other researchers, the team developed the co-payment method based on income level. The Mongolian government subsidized part of drug treatment and as prices declined, treatment became even less expensive for patients. CDAF also worked with the WPRO to develop a national screening program in urban and rural areas after reaching the conclusion that, even if the prevalence of HCV goes down in the next decade, there will still be more transmission and deaths unless there is an increase in screening and diagnosis.

How this model has been used in the United States

In 2014, this work expanded to include state-based analyses within the US. Through collaborations with a combination of state health departments, the CDC Foundation, Association of State and Territorial Health Officials (ASTHO) and state collaborators this model has been used to encourage the removal of Medicaid fibrosis restrictions (Colorado), to publish the HCV epidemiology and an elimination scenario (Rhode Island) and to inform the development of state elimination scenarios (District of Columbia and New York, *in progress*). These results can be found on the Polaris Observatory website (http://cdafound.org/polaris-hepC-dashboard/). Analysis have been completed in ten states (California, Colorado, Georgia, Iowa, Louisiana, New Mexico, Pennsylvania, Rhode Island, Tennessee and Washington) and ongoing analyses include collaborations with ASTHO, CDC and state partners to identify the disease burden and associated elimination strategies in Kentucky.

Hepatitis C-Related Disease Burden – Kentucky

Kentucky is ranked as one of the top states most affected by HCV. The rate of acute HCV is more than double the national average and has been driven by increases in unsterile injection drug use in rural Appalachia.[16,17,18]

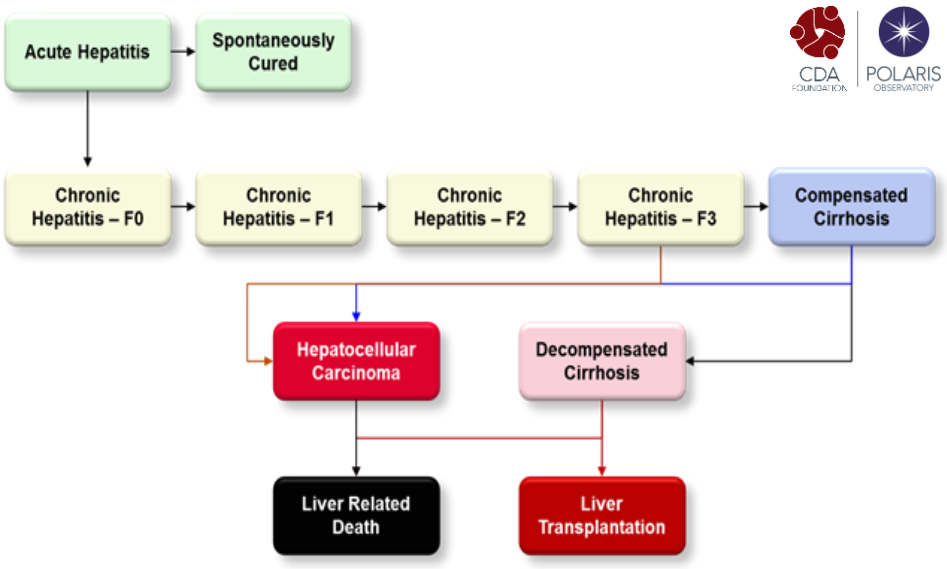
Based on Kentucky-specific adjustments to risk factors, it was estimated that 1.6% of the Kentucky population was chronically infected (RNA positive) with HCV in 2010. This equates to approximately 70,000 infected individuals in 2010.

Similar to the US, in Kentucky, more than 70% of individuals infected have genotype 1.[19] Though previously genotype 1 chronic infection was the most difficult to treat, pangenotypic DAAs allow for successful and safe treatment of all genotypes. Based on expert input, we assumed an SVR rate of 95% for all genotypes in this modeling exercise.

The Model

The mathematical model is an Excel-based disease progression model that was calibrated using reported, state-specific, epidemiologic data. The progression is as follows (Figure 1):

Figure 1.



The details of the model have been described previously in Blach 2016.[20] Briefly, a Markov disease progression model grounded in population, mortality and state-specific HCV data was developed. The model captures new (acute) infections by age and sex starting in 1950, and then follows the annual progression from acute to spontaneous clearance or through the stages of chronic infection. Additionally, the model accounts for age-specific mortality as well as patients who maintain an SVR. Based on state-specific inputs, the model is used to forecast the disease burden by HCV-sequelae, including fibrosis, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC) and liver-related death from 1950-2030.

Input Data

The following epidemiologic data were input into the Kentucky model (Table 1):

Table 1.

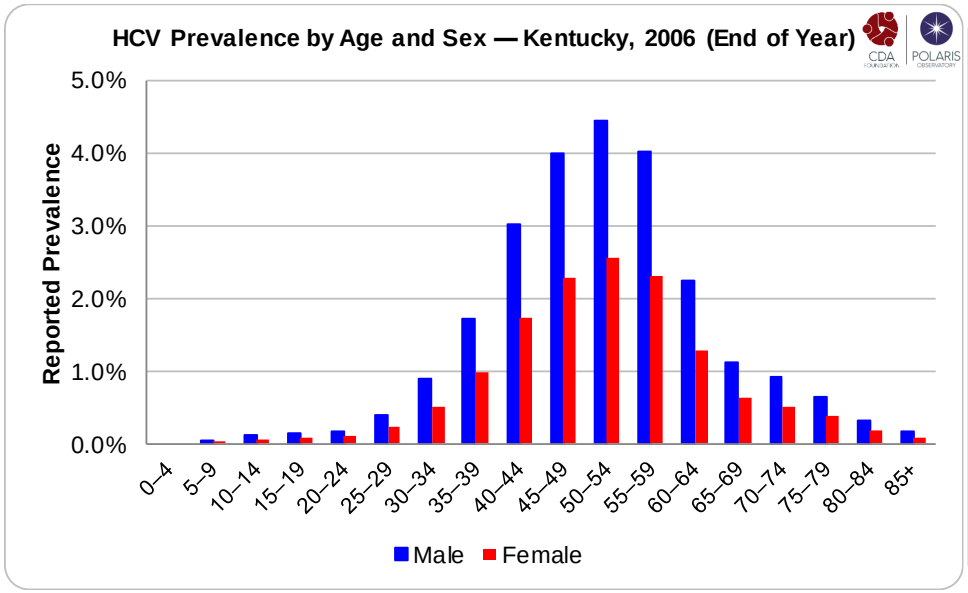
Historical Input	Estimate (Range)	Estimate Year	Source	Source Description
HCV-RNA+ Infections	70,000	2010	Expert input	Expert input based on Kentucky-specific risk factors, incidence, and trends in laboratory reporting
Anti-HCV Prevalence by Age and Sex	See Figure 2	2006	[21, 22]	Denniston 2014
HCV-RNA Prevalence by Age and Sex	See Figure 3	2018	[23]	Denniston 2014, scaled to the KY prevalent population and aged through the model, accounting for incident cases, deaths, and treatment/cures
HCV Genotype	See Table 2	2015-2018	[24]	Unpublished commercial laboratory data.
Total Diagnosed (HCV-RNA)	45,600	2017	[25,26,27]	State electronic laboratory reporting (ELR) RNA positive and anti-HCV positive results. A viremic rate of 75% in 2012 and 59% in 2013 was applied to annual anti-HCV positive results.
Annual Newly Diagnosed (HCV-RNA)	23,100	2018	[28, 29, 30]	State ELR RNA positive and anti-HCV positive results. A viremic rate of 75% in 2012 and 59% in 2013 was applied to annual anti-HCV positive results.
Annual Number Treated	4,200	2018	[31, 32, 33]	For 2008-2013, drug sales & Gilead investor reports for the US scaled to Kentucky. For 2015 and 2016, local data. For 2014, 2017 and 2018, adjusted Medicaid data.

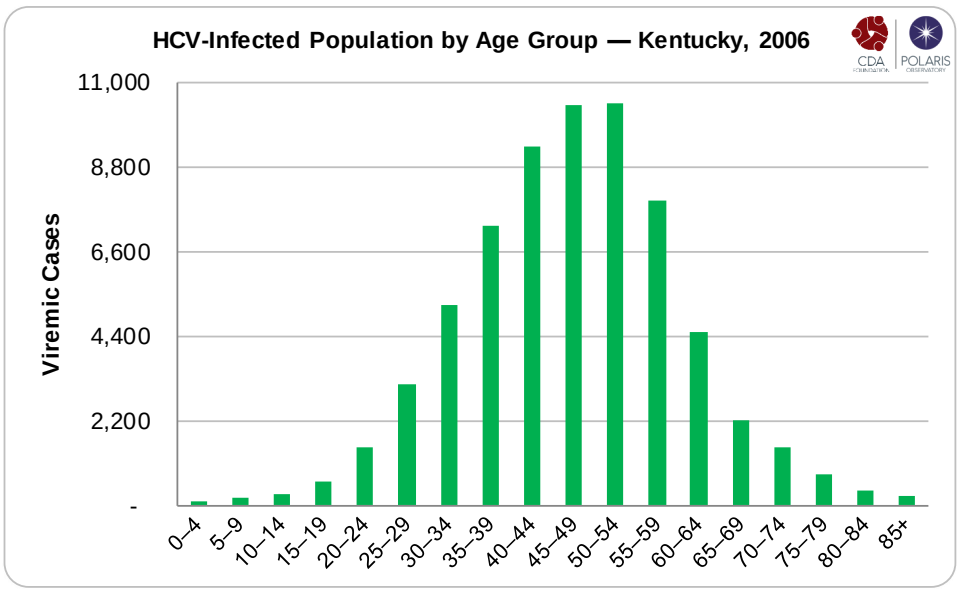
Prevalence

The expert panel reviewed multiple sources that estimate prevalence by adjusting national data from the 2003-2010 National Health and Nutritional Examination Survey (NHANES) for the population of Kentucky [34,35,36]. However, the group agreed that additional factors, including early onset of the opioid epidemic in Kentucky, are not accounted for in the NHANES dataset, and therefore these estimates are too low. After adjusting for a trend of increasing incidence and laboratory reporting of RNA positive tests, 70,000 individuals were estimated to have viremic CHC in 2010; a prevalence rate of 1.6%. CHC is not a reportable condition in Kentucky, therefore surveillance data were not available to conduct sensitivity analyses.

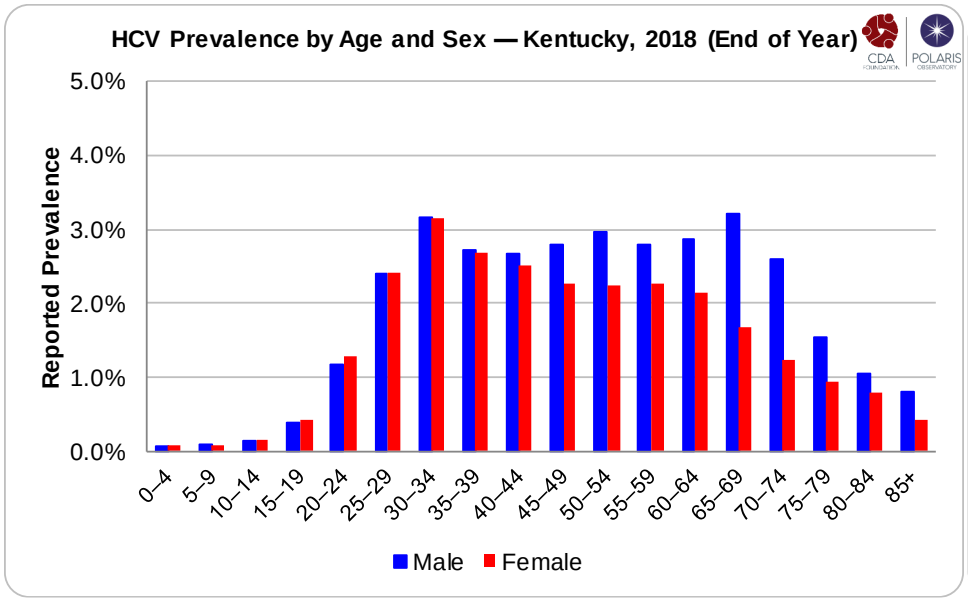
The historical age and sex distribution of the infected population in Kentucky was assumed to be similar to the US. Data reported from NHANES 2003-2010 were therefore used as the baseline prevalence by age and sex in 2006 (Figure 2a and 2b).[37] Specifically, published US prevalence by age and sex was multiplied by the Kentucky population by age and sex in 2006, with extrapolations for younger age groups not represented in NHANES (ages <6 years). The HCV infected population was then aged through the model by 12 years to estimate the age and sex distribution of the infected population in 2018 (Figure 3a and 3b).

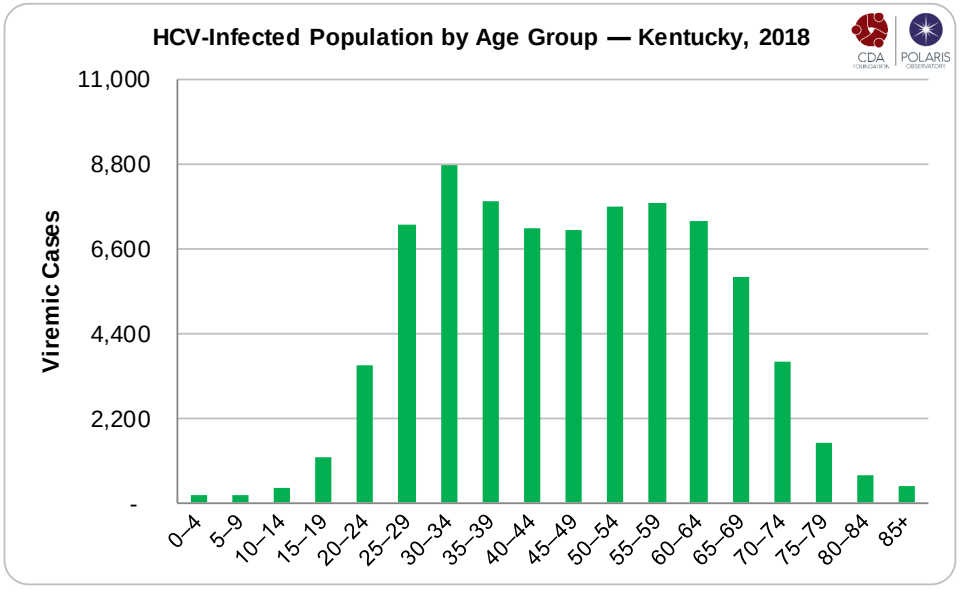
Figures 2a and 2b.





Figures 3a and 3b.





Genotype

The genotype distribution in Kentucky is based on unpublished commercial laboratory data collected from 2015-2018 (n=11,315).[38]

Table 2.

Genotype	G1a	G1b	G1	G2	G3	G4	G5	G6
Kentucky DOH	63%	7.0%	<0.1%	11%	18%	0.3%	-	<0.1%

Incidence

Incidence was back calculated to fit the total number of infections in 2010 and adjusted to best match state electronic laboratory reporting (ELR) RNA positives in those aged 40 years and younger. In terms of trending, prior to 2006, HCV incidence in Kentucky was assumed to mirror that of the US.[39] Starting in 2006, it was assumed that incidence increased to reflect growing use of injection drugs and sharing of injection equipment in the state. Experts believed that the number of incident cases in recent years have not been as high as the peak in the early 1990s that was due to transfusions and unregulated blood screening. Acute notification data from the Kentucky Department for Public Health (KDPH) showed increasing rates in the early 2000s.[40]

Diagnosis

Chronic hepatitis C is not a reportable condition in Kentucky. State ELR data, which covers the major healthcare systems and smaller practices across Kentucky, was used to evaluate the number of diagnosed cases.[41] A total of 42,700 RNA positive cases and 23,900 anti-HCV positive cases were recorded between 2012 and 2018. Assuming a viremic rate of 75% in 2012[42] and 59% beginning in 2013[43], applied to the anti-HCV results, 45,600 total viremic HCV patients are assumed to be diagnosed in Kentucky through 2017.

In 2018 alone, Kentucky received 14,500 RNA positive and 14,500 anti-HCV positive ELR results. Assuming a viremia of 59% (applied to the anti-HCV+ cases), 23,100 Kentuckians were newly diagnosed with viremic HCV.[44]

Treated

Between 2008 and 2013, annual US treatment rates were applied to the Kentucky population to estimate the number of treated patients per year. Local data from the University of Kentucky, Louisville clinicians, Pikeville Medical Center, and the Department of Corrections were aggregated to approximate the number of patients treated in 2015 and 2016.[45] According to expert input, about 70-80% of all patients treated in Kentucky in 2014, 2017 and 2018 were treated through Medicaid. For those years, Medicaid treatment counts were scaled up accordingly, estimating about 4,200 treated patients in 2018. [46]

Subpopulations

Approximately 1.2 million people or 20% of the total population of Kentucky is enrolled in Medicaid.[47] Medicaid recorded a total of 26,200 diagnosed acute and chronic cases of HCV from 2014-2018, of which 25% (6,500) were treated with DAAs in this 5-year time period.[48]

Currently, there is no program for universal HCV screening of incoming or resident inmates in the Kentucky prison system. Of the estimated 41,000 total incarcerated individuals in 2018, the Kentucky Department of Corrections (KDOC) reports an anti-HCV prevalence of 30%. [49,50] The annual number of inmates receiving treatment is unknown.

According to expert input, there were an estimated 20,000 people who inject drugs (PWID) actively (injecting within the last year) in Kentucky in 2011 (0.6% of the total population). Based on multiple studies conducted in Kentucky, approximately 55% of this population was anti-HCV positive.[51,52,53]

The model also calculated HCV prevalence among women of child bearing age (WoCBA) and among the baby boomer cohort (persons born between 1945 and 1965). The model estimated about 27,100 WoCBA and 20,800 baby boomers in 2018.

Results

Past and Present Burden of Disease

Annual incidence was modeled with to peak in 1989, around the time systematic blood screening began. It was then modeled to increase again in 2006 to capture the increase in transmission due to high rates of unsterile injection drug use in Kentucky. In 2018, it was estimated that there were approximately 4,300 Kentuckians who acquired HCV (97 per 100,000).

By the end of 2018 (after accounting for cures), 88% or 68,700 of the 78,300 viremic infections were diagnosed. Of the 4,200 treated, 95% (n=4,000) were cured. This cascade of care in 2018 is shown in Figure 4. The distribution of Kentuckians with HCV by fibrosis stage, calculated by the model, can be seen in Figure 5. A quarter of patients in 2018 were estimated to be fibrosis stage F1, while about 40% were F2, F3 or cirrhotic.

HCV prevalence in subpopulations was also considered. The 30% anti-HCV prevalence rate reported by the KDOC[54] was applied to the 2018 incarcerated population (n=41,000)[55] and adjusted for 80% viremia (expert input),[56] estimating 9,840 viremic infections in 2018. In 2018, 13% of all viremic infections were among incarcerated persons.

As of 2018, 15,400 patients enrolled in Kentucky Medicaid were estimated to be diagnosed with viremic HCV (calculated by applying a 59% viremic rate to the 26,200 acute and chronic cases), corresponding to a 1.6% diagnosed prevalence. In 2018, 20% of viremic infections were among Medicaid recipients.

Applying an anti-HCV positivity rate of 55% and a viremic rate of 75% to the total PWID population (n=20,000), there would be 9,000 active viremic PWID, accounting for about 12% of all viremic infections in 2018.[57,58,59]

Prevalence by age in the WoCBA population ranged from 0.41%-3.15% at the start of 2018, with the peak prevalence in those aged 30-34. In the beginning of 2018, prevalence in the baby boomer population ranged from 1.87%-2.52%. In 2018, approximately 45% of infected Kentuckians were WoCBA and 26% of infected Kentuckians were baby boomers (aged 55-75).

Figure 4.

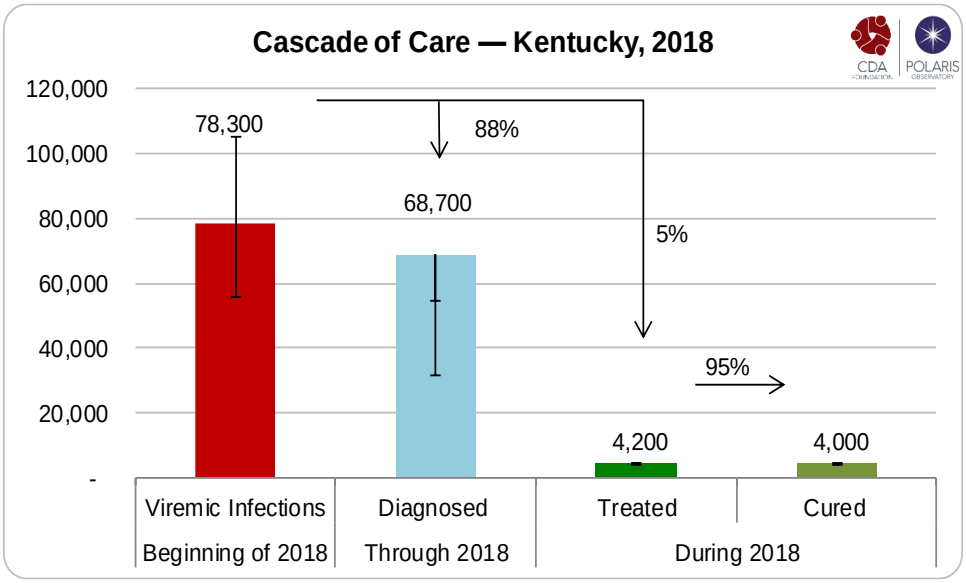
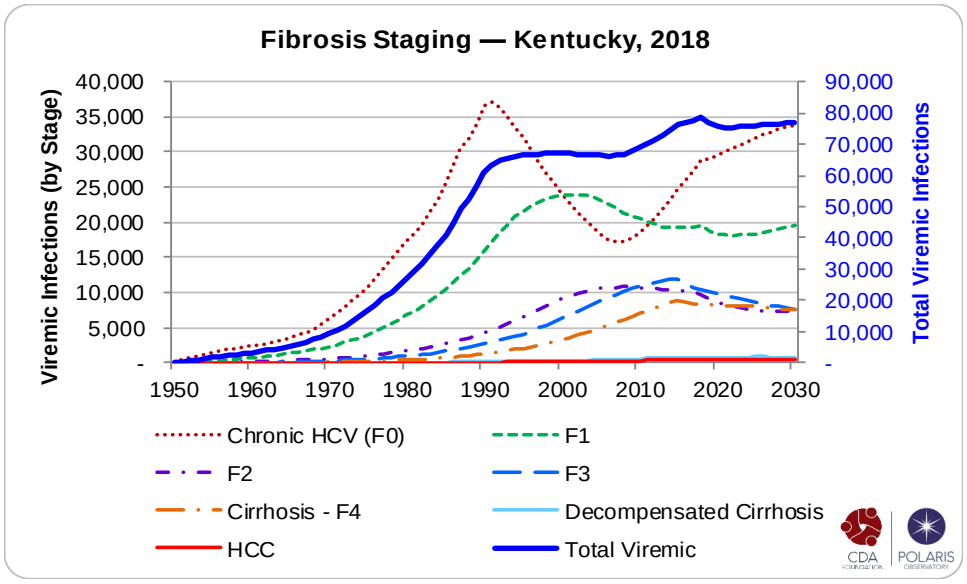


Figure 5.



Disease Burden Scenarios

We created three disease burden scenarios:

1) Base; the current standard of care assuming a 50% decrease in treatment over the next 5 years*
2) 10% harm reduction and 4,000 patients treated; experts agreed that an obtainable scale-up of prevention and care efforts would be a 10% reduction in new infections (starting in 2019) and sustained treatment of 4,000 patients annually (starting in 2021)
3) WHO elimination targets; defined as an 80% reduction in new infections, 90% diagnosis of all infections, and a 65% reduction in liver related mortality by 2030

For all scenarios and all years, it is assumed that patients over 15 years old are eligible for treatment, all fibrosis stages (≥F0) are eligible for treatment, and that treatment has an average SVR of 95%. These scenarios require the following numbers of patients to be diagnosed and treated for HCV:

Table 3.

Scenario	Model Parameter	2018	2019	2020	2021	2022	≥2023
Base	Incident Infections	4,300	4,300	4,200	4,200	4,200	4,200
	Treated	4,200	3,500	2,700	2,300	2,200	2,200
	Newly Diagnosed	23,100	9,800	5,100	3,800	3,400	3,200
10% harm reduction, 4,000 treated	Incident Infections	4,300	3,900	3,400	3,000	2,700	2,100
	Treated	4,200	3,500	2,700	4,000	4,000	4,000
	Newly Diagnosed	23,100	9,800	5,100	3,700	2,500	2,000
WHO Elimination Targets	Incident Infections	4,300	4,300	4,200	3,200	2,300	1,500
	Treated	4,200	3,500	2,700	5,400	5,400	5,400
	Newly Diagnosed	23,100	9,800	5,100	1,000	1,000	1,000

**The US National Academies report projects a 50% decline in treatment over five years following the peak number of patients treated.*

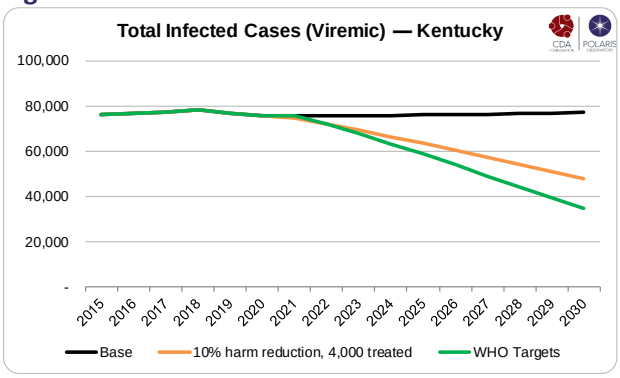
Under the base scenario, the number of Kentuckians with viremic HCV peaked in 2001 and is projected to increase by 1% between 2015 and 2030, resulting in 77,000 Kentuckians with HCV by the end of 2030. Liver-related deaths, incident cases of hepatocellular carcinoma (HCC) and incidence of decompensated cirrhosis (DC) will decrease by 8-15% over the same period (Figure 6). Incidence of HCC will decrease from 310 in 2015 to 260 in 2030 (15% decrease). Incident DC cases will decrease from 240 in 2015 to 210 in 2030 (14% decrease). Given the current standard of care in Kentucky, there would be 30 fewer liver-related deaths by 2030, an 8% decrease from 2015.

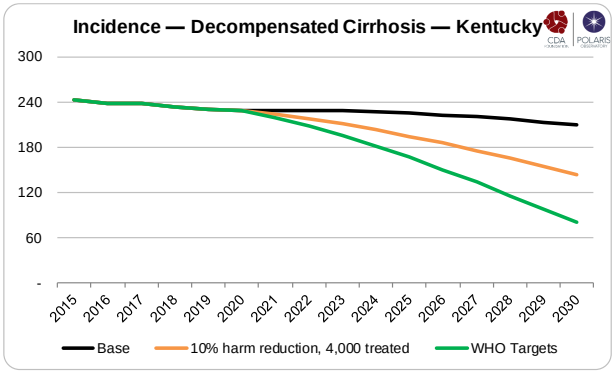
Under the harm reduction and treatment scenario, an additional 1,300 patients must be treated annually starting in 2021 and 400 new infections must be prevented annually, starting in 2019. Compared to the base, executing these changes would prevent 80 incident cases of HCC, 70 cases of DC, and save 130 lives (Figure 6).

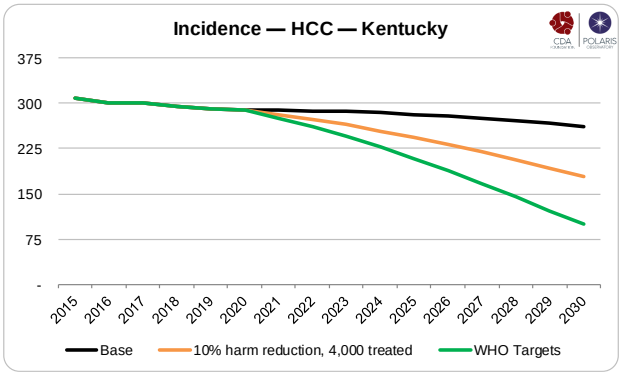
WHO Elimination can be achieved by increasing the number of treated patients to 5,400 annually and implementing harm reduction efforts that reduce the number of new infections by 24% annually.

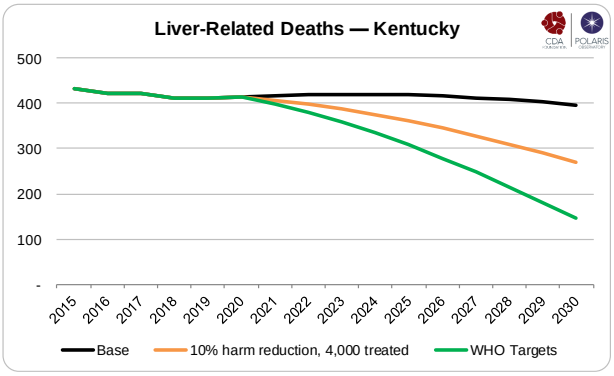
Compared to the base scenario, elimination would prevent 160 incident cases of HCC, 130 cases of DC, and would save 250 lives (Figure 6).

Figure 6.









Discussion

The ability to forecast HCV disease burden in the presence and absence of various interventions allows policy makers the flexibility to test hypotheses and quantify the impact of decisions. Using a Microsoft Excel-based Markov model, a team of state collaborators developed consensus estimates to answer three primary questions — 1) Who in the state is most affected by HCV? 2) How do current policies affect disease burden indicators such as HCV prevalence and HCV-related liver cancer and mortality? 3) What efforts will be necessary to eliminate HCV?

Currently, in Kentucky, the annual number of new cases is decreasing, however, case finding and treatment are projected to drop. Alongside increased mortality from an aging population, this means that the number of people living with HCV in the state remains high and is plateauing. At the same time, the aging population is progressing to costly advanced liver disease, which can be prevented through timely treatment. Although the number of new infections is declining, most people who are newly infected are not diagnosed for many years. Without an active screening campaign to identify these individuals, they could remain asymptomatic, but contagious, for decades and are subject to extrahepatic manifestations of CHC.

Over the past several years, Kentucky has implemented state-wide harm reduction efforts such as syringe exchange programs. Still, scale-up of these efforts would be required to achieve the goal of reducing new infections 80% by 2030. Kentucky must simultaneously begin treating HCV patients at larger volumes by sustaining treatment of 5,400 patients annually, starting in 2021. While treatment may be costly, it significantly reduces the number of patients that progress to more expensive stages of HCV. Compared to the base scenario, meeting WHO elimination targets would avert nearly 550 cases of end-stage morbidity and mortality. While more than half of the population is estimated to be diagnosed and aware of their status, this does not indicate that these patients are linked to care. Efforts will be needed to screen and diagnose new patients as well as engaging previously diagnosed patients with health services.

Currently, there are strict testing and treatment requirements within the correctional system, including fibrosis and sobriety restrictions. Despite low levels of testing, 13% of the total HCV infected population in Kentucky are estimated to be within the corrections system.[60] In recent years, the incarceration rate in Kentucky has exceed the national average. The incarcerated population overlaps with other at-risk populations, such as injection drug users, that may otherwise not seek care. The combination of high HCV rates and direct patient access provides ample reason and opportunity to provide care for incarcerated Kentuckians.

Lack of adequate funding has led to Kentucky to be slow to adopt policies and programs to address HCV care and prevention; however, treatment and prevention of new infections is integral to achieve elimination and reduce HCV-related morbidity and mortality for the citizens of Kentucky.

Appendix: Expert Panel Participants

The following individuals contributed to the content of this report through their participation in the expert panel discussions and in report revisions, and we are grateful for their efforts:

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