# Challenge and opportunities for the elimination of HBV and HCV infection in special populations

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2018

NYC

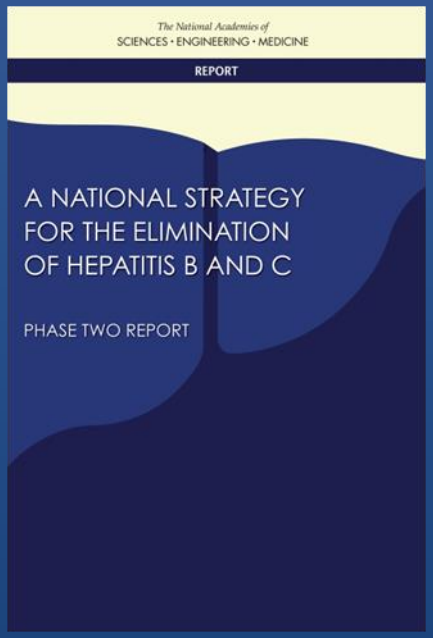
Viral Hepatitis Research Symposium

# Disclosure

- PI for research grants related to viral hepatitis with funds paid to Johns Hopkins University
  - AbbVie, Assembly Biosciences, Gilead, Proteus Digital Health
- DSMB related to HBV with funds paid to Johns Hopkins University
  - Gilead
- Scientific advisor related to viral hepatitis
  - Terms of these arrangement are being managed by the JHU in accordance with its conflict of interest policies
  - AbbVie, Arbutus, Gilead, Merck, Trek

# National Academies: Hepatitis B and C elimination in the US (2017): Elimination by 2030

- Hepatitis B
  - 50% reduction in mortality (avert ~ 60,000 deaths)
  - 90-90-80: 90% of persons diagnosed; 90% of diagnosed linked to care; 80% of those linked to care with medical necessity treated
- Hepatitis C
  - 90% and 65% reduction in incidence and mortality (avert ~ 28,800 deaths), respectively
  - 90-90-80: 90% of persons diagnosed; 90% of diagnosed linked to care; 80% of those linked to care with medical necessity treated
- Recommendations
  - The highest level of the federal government should oversee a coordinated effort to manage viral hepatitis elimination
  - DHHS should work with states to build a comprehensive system of care and support for special populations with hepatitis B and C on the scale of the Ryan White system



# Hepatitis C:  Opportunity and challenges

# Special populations are *the* populations at risk for harm due HCV

- In the United States, effective DAAs have been available since October 2013
- CHeCS cohort (2014 to 2015): 5.6% of 9,508 persons with known HCV were treated
  - Treatment associated with white race/ethnicity, private insurance, higher income, advanced fibrosis and HIV coinfection
- 2018: Untreated HCV infection is concentrated in persons who are underserved
  - Recent immigrants, people who use drugs, and justice-involved, homeless, and pregnant individuals.

Since 2014, ~ 1 million Americans have been Treated with HCV DAAs; most were cured

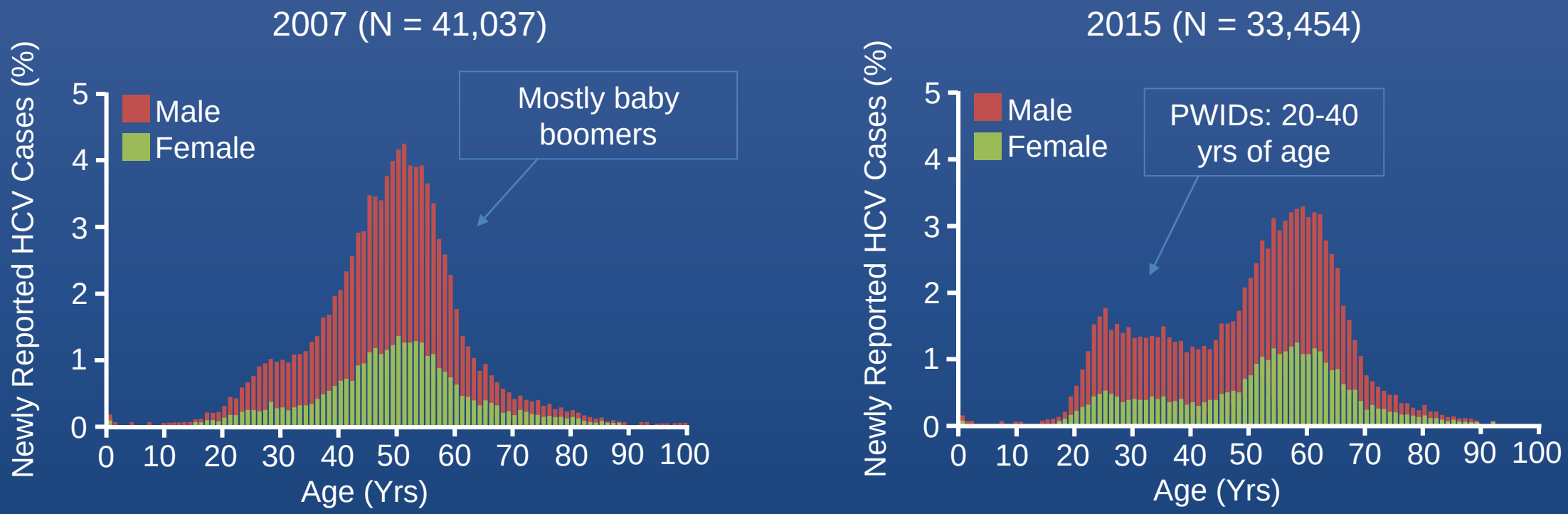

http://www.natap.org/2017/HCV/021317_01.htm; Spradling J Clin Gastroenterol 2017

# National Academies: Recommendations for Hepatitis elimination in the US (2017)

Focus on:

- CDC should support standard hepatitis case finding measures and the follow-up and monitoring of all viral hepatitis cases reported through public health surveillance.
- CDC should work with states to identify settings appropriate for enhanced viral hepatitis testing based on expected prevalence.

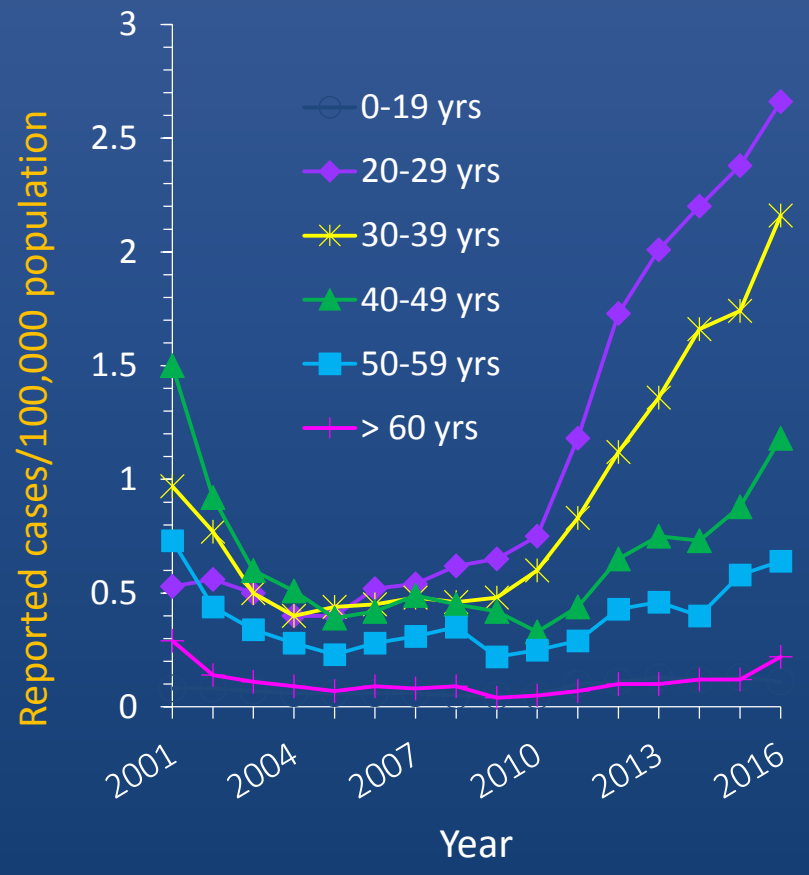
# Changing Epidemiology of HCV in the US

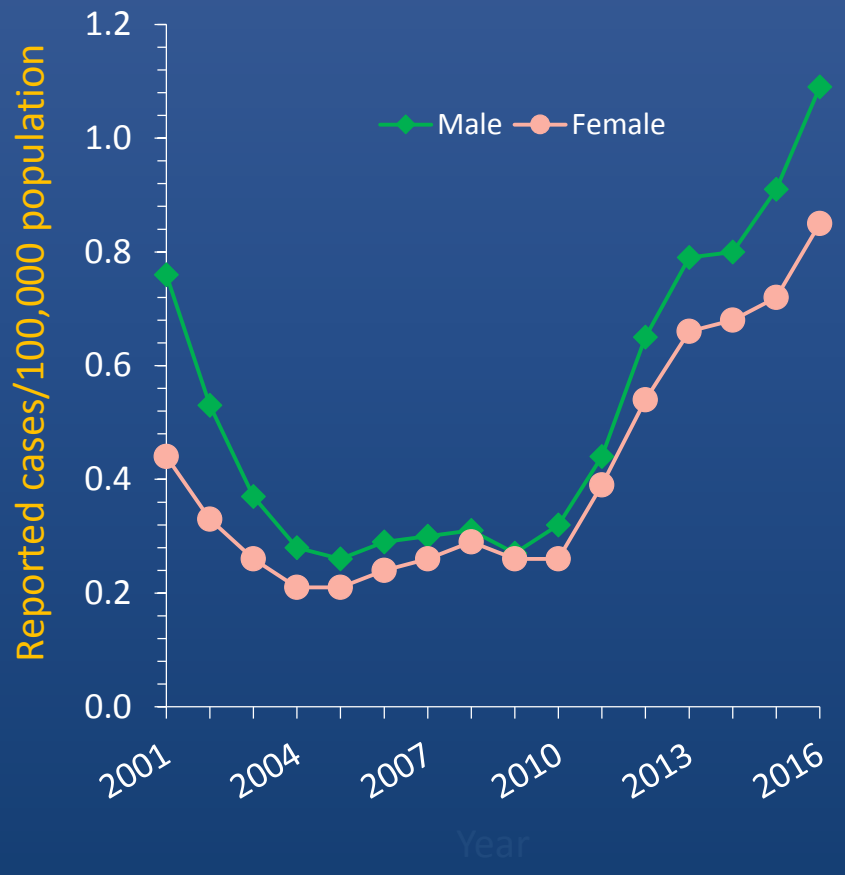



- Screening → linkage to HCV care → DAA treatment cascade must be operative in all those at risk
- Treatment of PWIDs plus harm reduction efforts essential part of elimination efforts

California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

# Incidence of acute hepatitis C by age category and sex — United States, 2001–2016




CDC Viral Hepatitis Surveillance March 2017

# AASLD/IDSA Guidance: HCV Screening During Pregnancy

- Incidence of HCV infection in children is increasing in the US
- With current increases in HCV infection among young adults, including women of childbearing age, there is considerable discussion about the possibility of universal screening of pregnant women.

| Recommendations for HCV Testing in Pregnant Women |
| --- |
| RECOMMENDED |
| There is no recommendation at this time for universal HCV screening in pregnant women, however this is under review. |
| Screening with an HCV antibody assay is recommended for pregnant women with known or suspected risk factors for HCV infection. Confirmatory HCV nucleic acid testing is recommended for women with a positive screening test. |

AASLD/IDSA. HCV guidance. September 2017.

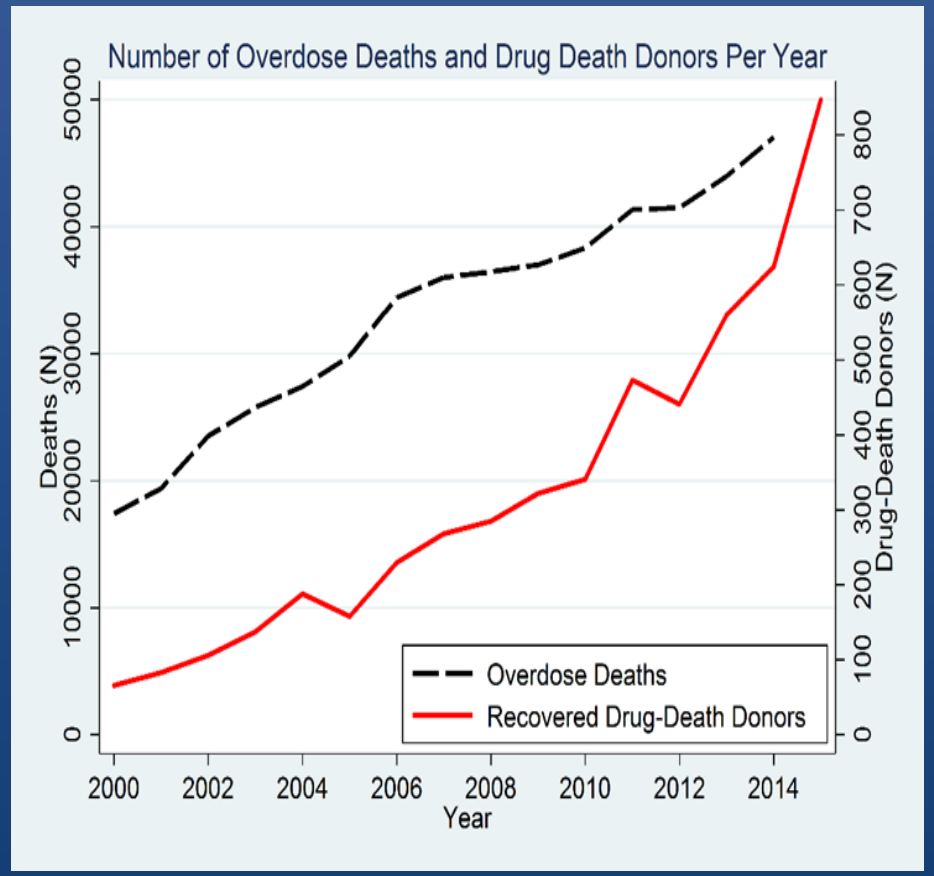
# National Academies: Recommendations for Hepatitis elimination in the US (2017)

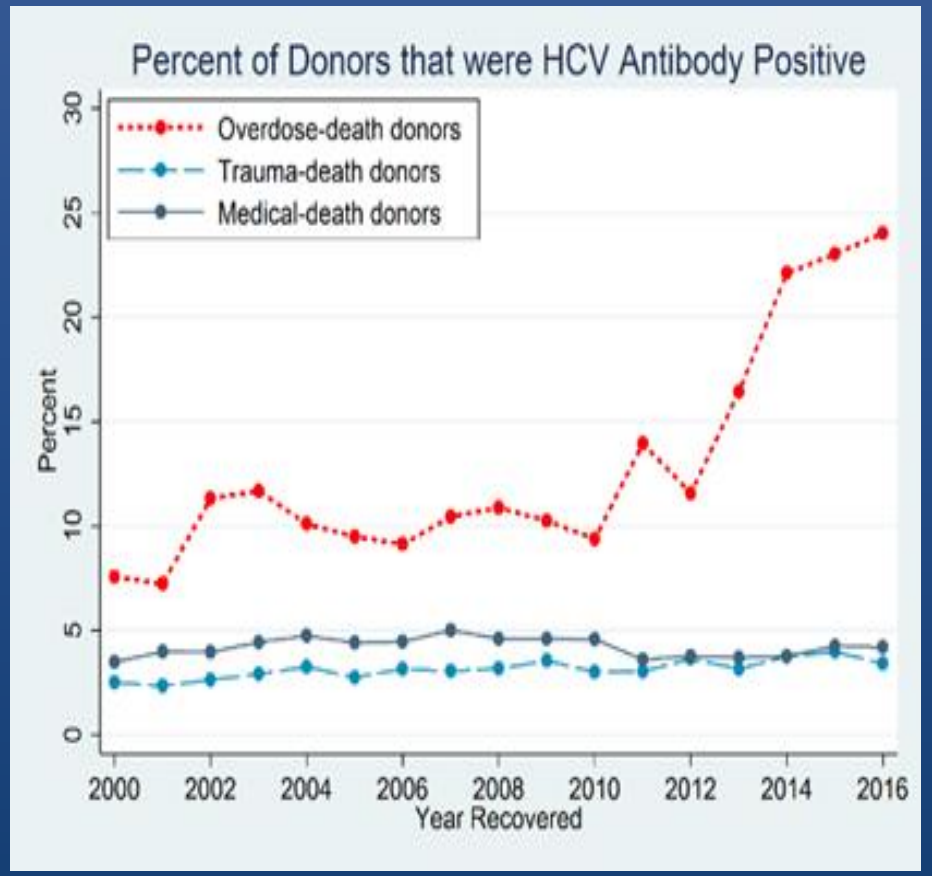
Focus on:

States and federal agencies should expand access to syringe exchange and opioid agonist therapy in accessible venues

- Prevention of overdose death should be prioritized

# Overdose deaths and increased transplantation of organs from HCV + donors



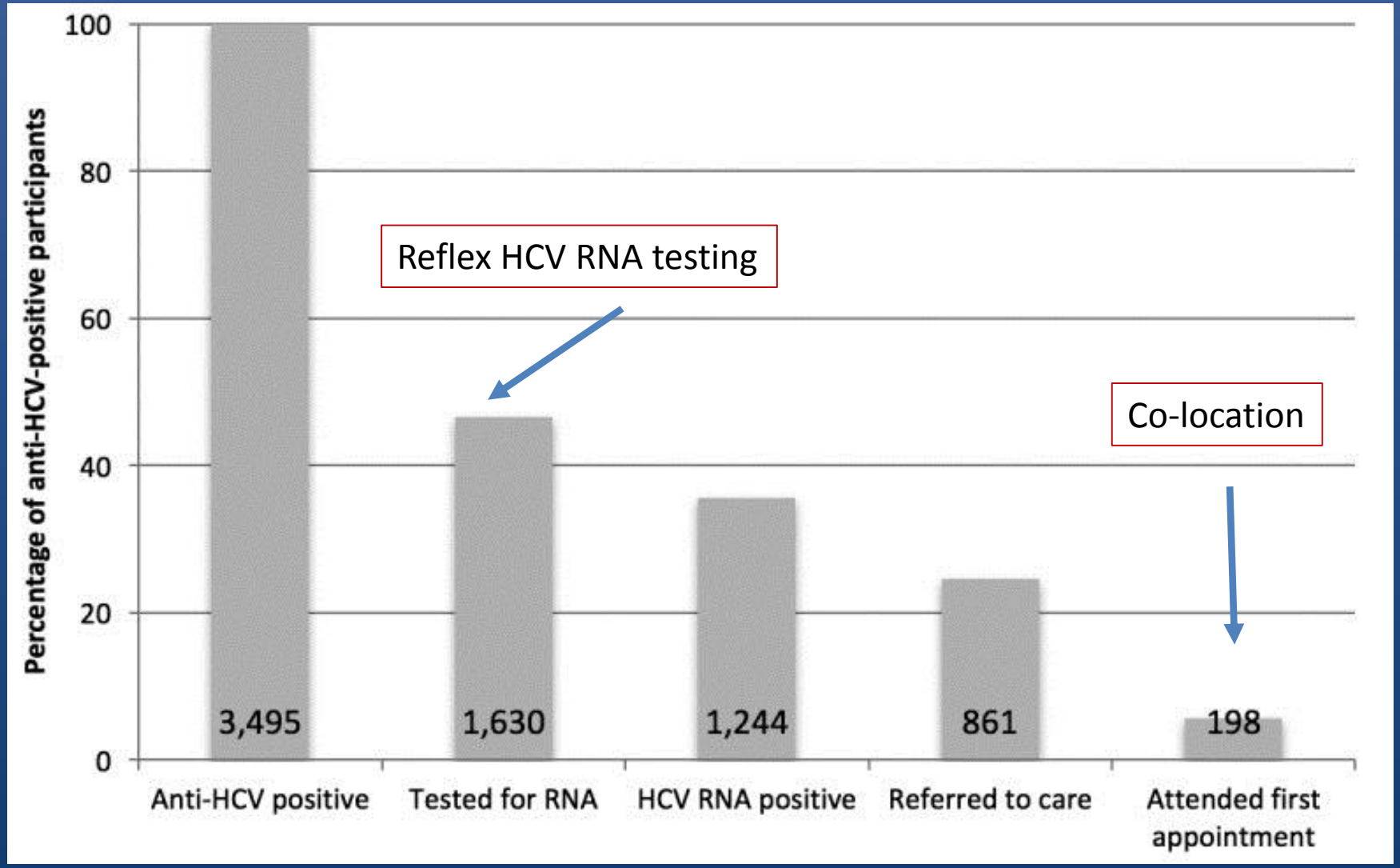




Durand et al. Annals of Intern Med 2018

# CDC-funded Hepatitis Testing and Linkage to Care at US centers that provide services for PWID

**10 HepTLC centers**

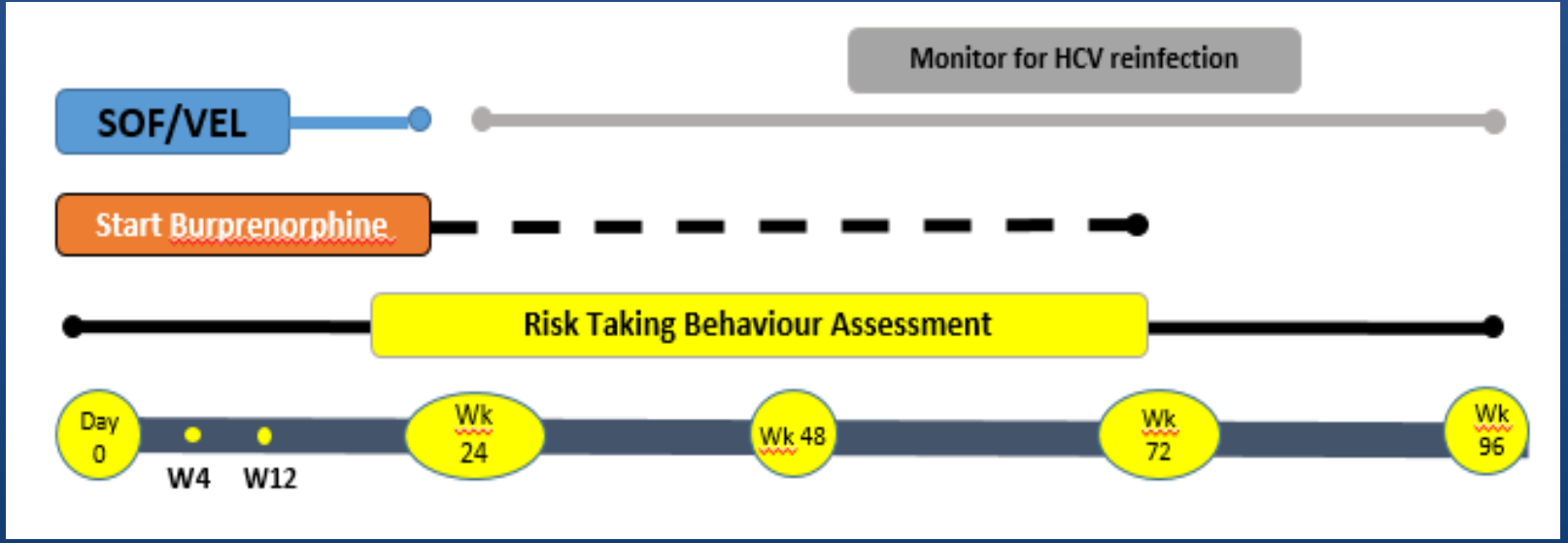
- **23% HCV seropositive**
- **HCV care cascade is has major deficits**




Blackburn Public Health Rep. 2016

# Syndemic Approach to Persons With HCV and Opiate Use Disorder

- ANCHOR study: Single-center study embedded in an urban harm reduction center providing colocalized buprenorphine and HCV treatment to improve adherence and reduce harm in PWID with HCV
- HCV treatment in PWID with chronic HCV, opioid use disorder, and IDU within 3 mos of screening




- Overdose death prevention: Naloxone
- Infectious disease prevention: Access to NSP, HIV PrEP

Rosenthal E, et al. EASL 2018, Abstract PS-092.

# Strategies to Decrease HCV Reinfection Risk After SVR in High-Risk Groups

- **Expect reinfection:** logical consequence of treating high-risk groups
- **Harm reduction access (NEP, OST):** to reduce risk of reinfection
- **Individual-level strategies:** treatment of injecting partners
- **Rapid scale-up:** initial increase in reinfections, then control
- **Access to retreatment:** without stigma and discrimination

- 18 states have highly underdeveloped harm reduction laws (including Alaska, Georgia, Michigan, Missouri, New Jersey, Texas, West Virginia)
  - No laws authorizing NEP
  - Crime to possess/distribute syringes
  - No sale of syringes without prescription
- Only 3 states (Massachusetts, New Mexico, and Washington) have laws that support full access to both syringe services programs and HCV-related treatment and preventive services for PWIDs

Campbell CA, et al. MMWR Morb Mortal Wkl Rep. 2017;66:465-469.

# National Academies: Recommendations for Hepatitis elimination in the US (2017)

Focus on:

The criminal justice system should screen, vaccinate, and treat hepatitis B and C in correctional facilities according to national clinical practice guidelines.

# HCV Seroprevalence in US State Correctional Departments, 2000-2012

| State | Sex | Period of Observations | Median HCV Seroprevalence, % |
|---|---|---|---|
| Indiana | M & F | 2003-2011 | 12.3 |
| Michigan | M<br>F | 2004-2009 | 11.0<br>27.7 |
| New Mexico | M<br>F | 2010-2011 | 44.0<br>35.4 |
| New York | M & F | 2000-2007 | 12.8 |
| North Dakota | M & F | 2008-2011 | 10.7 |
| Oregon | M & F | 2000-2005 | 26.7 |
| Pennsylvania | M & F | 2004-2010 | 18.3 |
| Washington | M<br>F | 2008-2011 | 17.6<br>24.5 |

Varan AK, et al. Public Health Rep. 2014;129:187-195.

# HCV Undertreated in Correctional Settings

- Among 41 states with reported data as of January 1, 2015:
  - 106,266 (10%) inmates known to have HCV infection
    - **Only 949 (< 1%) of HCV-infected inmates receiving HCV treatment**
- Assistance with transition to community healthcare providers upon release important for maintaining and enhancing gains achieved by HCV treatment in prison
- In Australia, HCV elimination efforts are focused on corrections as a priority population
  - SToP-C: HCV Treatment as Prevention Trial in 4 Australian Correctional Centers

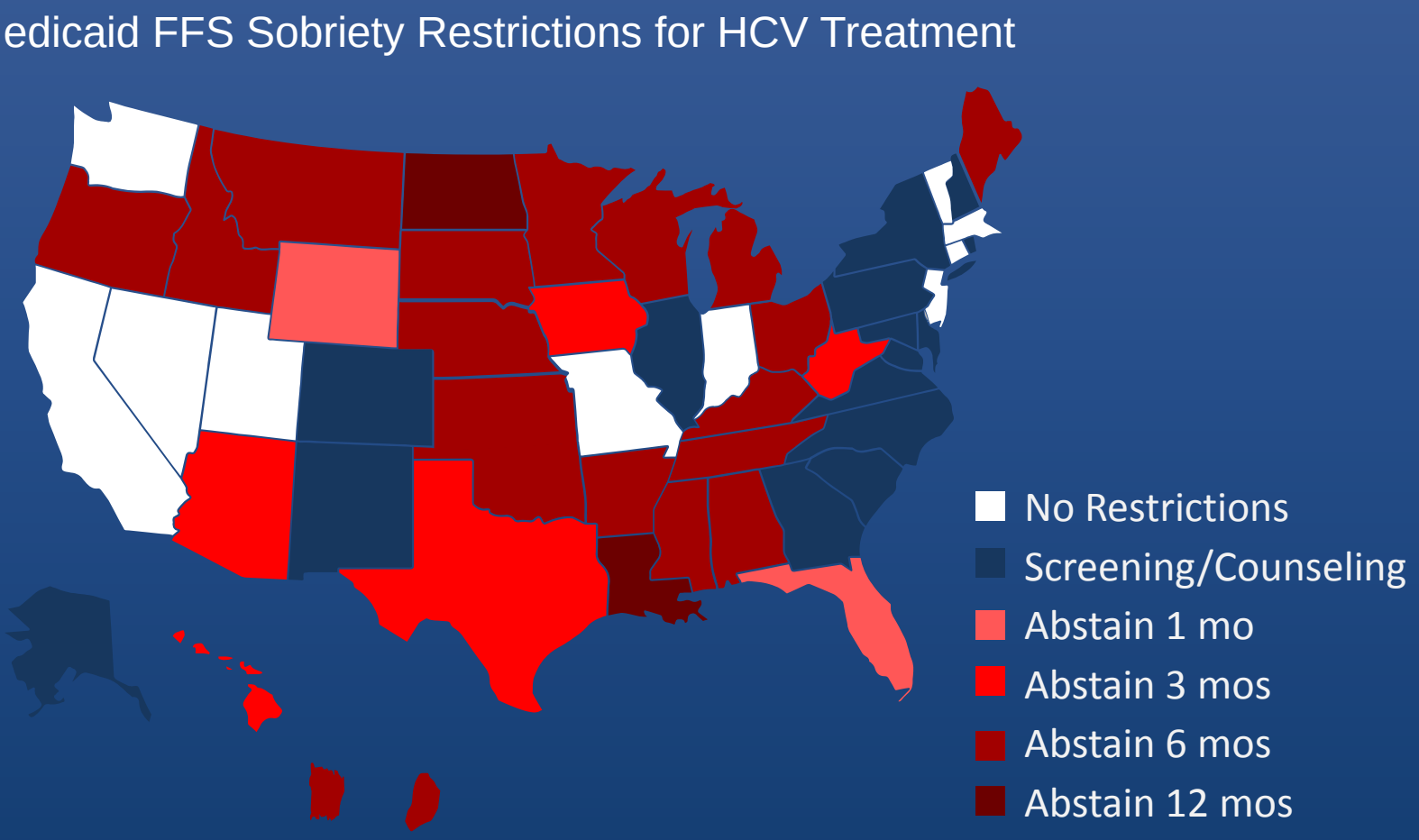
Beckman AL, et al. Health Aff (Millwood). 2016;35:1893-1901.

# National Academies: Recommendations for Hepatitis elimination in the US (2017)

Focus on:

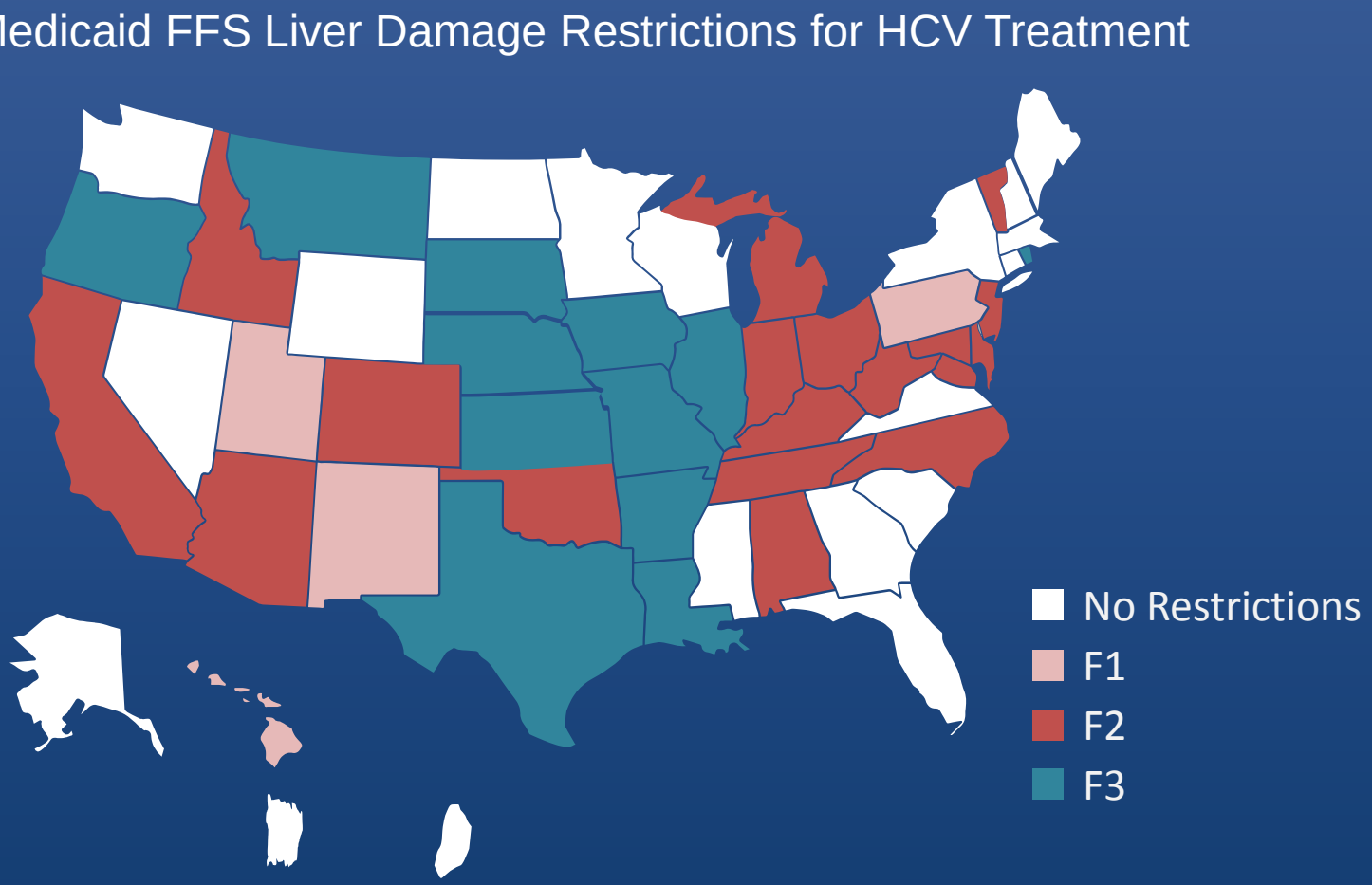
- The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America should partner with primary care providers and their professional organizations to build capacity to treat hepatitis B and C in primary care
- Public and private health plans should remove restrictions that are not medically indicated and offer direct-acting antivirals to all chronic hepatitis C patients

# 2017 NVHR Update: Drug/Alcohol Use Leads to Reduced Treatment Access in Some Settings



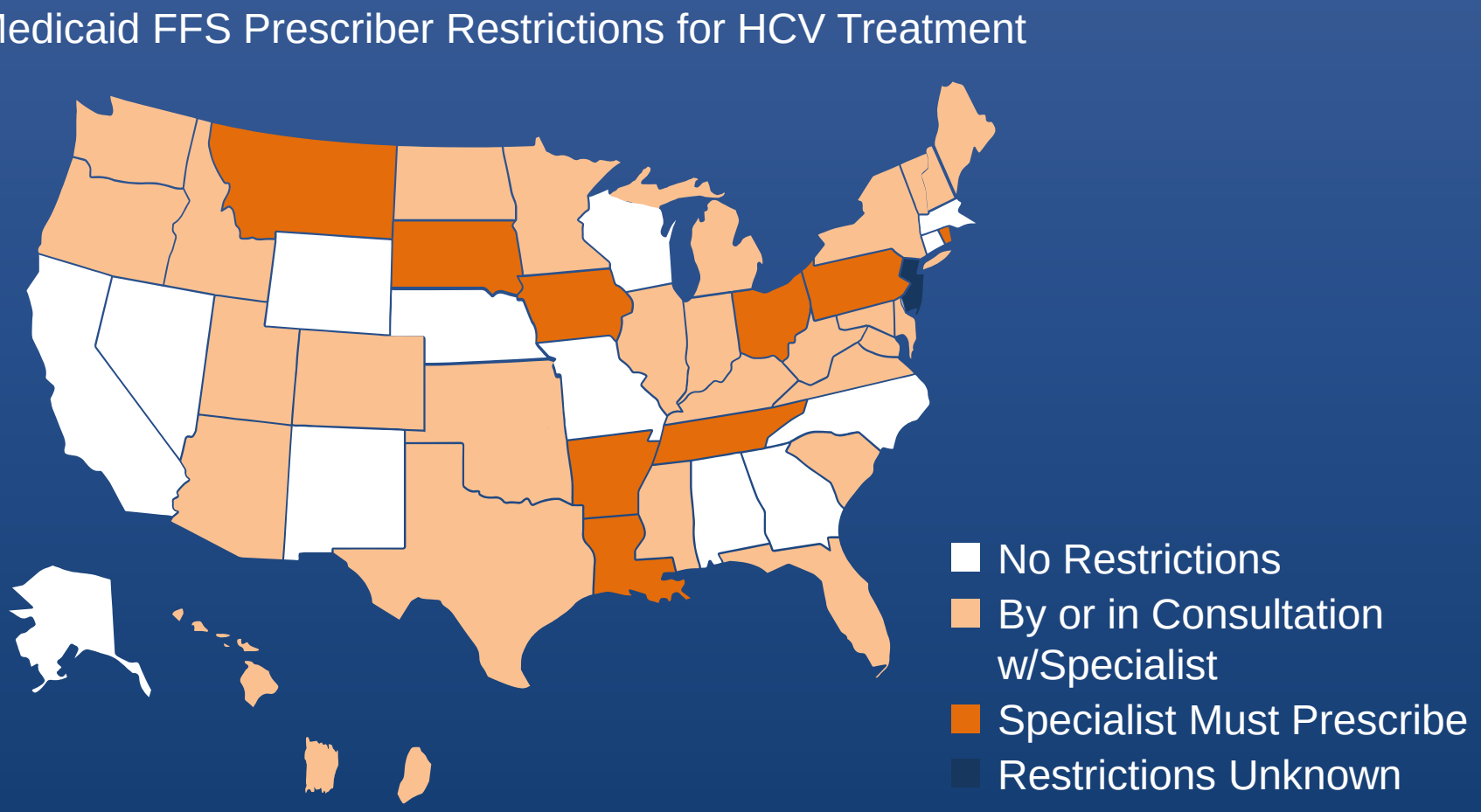

NVHR State of Hepatitis C State of Medicaid Access Report Oct 23, 2017. https://stateofhepc.org/

# 2017 NVHR: Reduced Treatment Access in Many Settings for Patients With Mild Liver Disease




NVHR State of Hepatitis C State of Medicaid Access Report. Oct 23, 2017. https://stateofhepc.org/

# 2017 NVHR: Reduced Treatment Access for Patients Receiving Care From Non-Specialists




NVHR State of Hepatitis C State of Medicaid Access Report. Oct 23, 2017. https://stateofhepc.org/

# CDC-funded program to train community based treaters

## Community-based Programs to Test and Cure Hepatitis C (CDC-RFA-PS14-1413)

| Site | # of Providers Trained | # of clinics with trained providers contributing data on HCV treatment* | # patients treated at clinics with trained providers contributing data on HCV treatment* | Methods used for training |
|---|---|---|---|---|
| Baltimore-Maryland | 25 | 6 | 300 | Didactics, in person mentorships |
| Chicago | 165 | 8 | 190 | Project ECHO |
| Seattle-King County | 252 | 6 | 207 | online curriculum, Project ECHO, large group didactics, in-clinic mentorships |

Scott J. Liver Meeting 2017; https://www.cdc.gov/hepatitis/policy/communitybasedhepcprogs.htm

# National Academies: Recommendations for Hepatitis elimination in the US (2017)

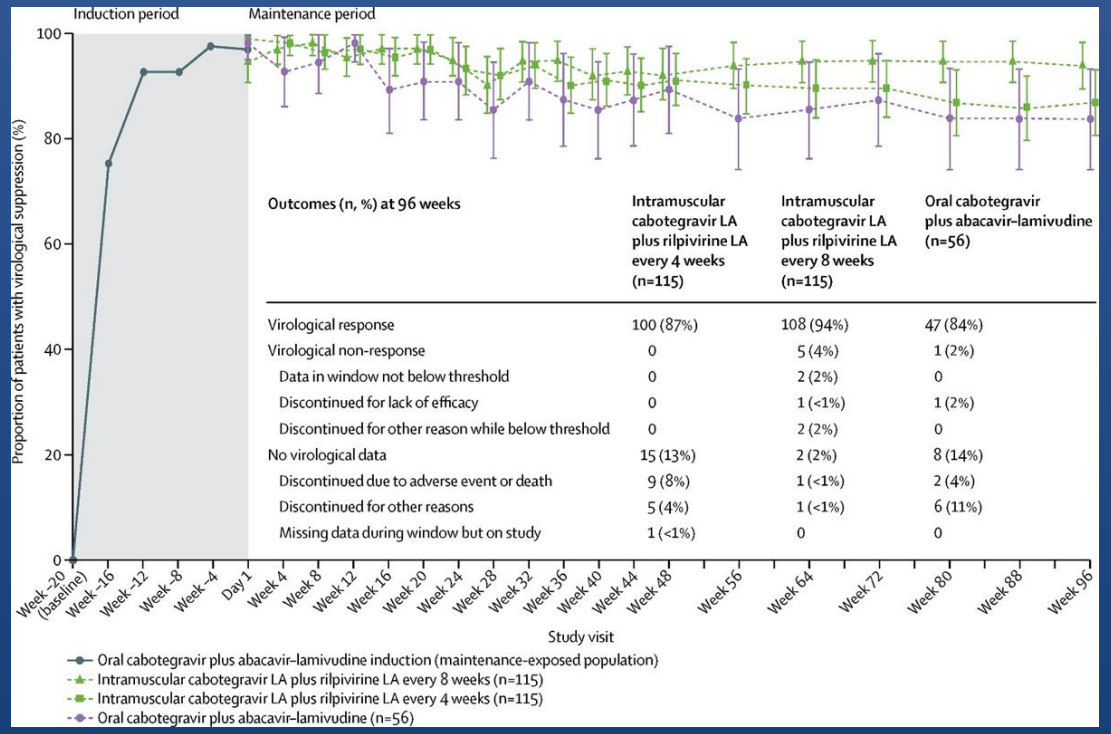
Focus on research

- There can be no elimination of viral hepatitis without better attention to research gaps.
- Mechanistic research questions include: curative therapy for chronic HBV infection and HCV vaccine
- Implementation research questions include: stigma alleviation, understanding networks of drug users, and health in incarcerated people.

# Extended release HCV treatment would transform HCV elimination: Single step test and treat

- Rapid HCV point-of-care diagnosis
- Stage with FIB-4 and physical exam
- Single dose of pangenotypic DAA regimen
  - SOF + Daclatasvir or Velpatasvir
  - Glecaprevir + Pibrentasvir
- Anticipate cure rate of > 95%

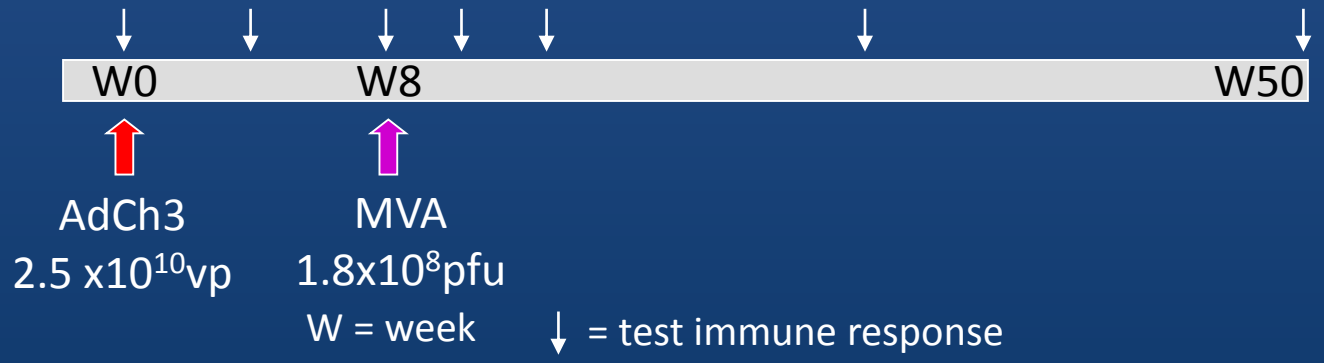
Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV infection (LATTE-2)




| Outcomes (n, %) at 96 weeks | Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115) | Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115) | Oral cabotegravir plus abacavir–lamivudine (n=56) |
|---|---|---|---|
| Virological response | 100 (87%) | 108 (94%) | 47 (84%) |
| Virological non-response | 0 | 5 (4%) | 1 (2%) |
| Data in window not below threshold | 0 | 2 (2%) | 0 |
| Discontinued for lack of efficacy | 0 | 1 (<1%) | 1 (2%) |
| Discontinued for other reason while below threshold | 0 | 2 (2%) | 0 |
| No virological data | 15 (13%) | 2 (2%) | 8 (14%) |
| Discontinued due to adverse event or death | 9 (8%) | 1 (<1%) | 2 (4%) |
| Discontinued for other reasons | 5 (4%) | 1 (<1%) | 6 (11%) |
| Missing data during window but on study | 1 (<1%) | 0 | 0 |

# HCV Prophylactic Vaccine Based on Sequential Use of AdCh3and MVA with NS

- Cross reactivity of AdCh3 with human anti-adenovirus Abs is 12%
- MVA boosts well in Phase I trials
- Double-blinded, randomized, placebo-controlled two stage study.
- Subjects: HCV Ab and RNA negative, active IDU's at high risk for HCV, 18 -45 y.o.
- Two Sites (UCSF, JH): Study is complete; data expected Fall 2018




Slide courtesy of Dr. Andrea Cox


"The opioid epidemic is a stark reminder of the consequences of a societal problem that remained hidden for years, in part because of the stigma associated with drug use and the reluctance to confront it as a public health problem. **The concurrent spread of HCV, if not controlled, will similarly have public health and financial repercussions for decades to come.**"

Liang TJ, et al. N Engl J Med. 2018;378:1169-1171.

# Hepatitis B:  Opportunity and challenges

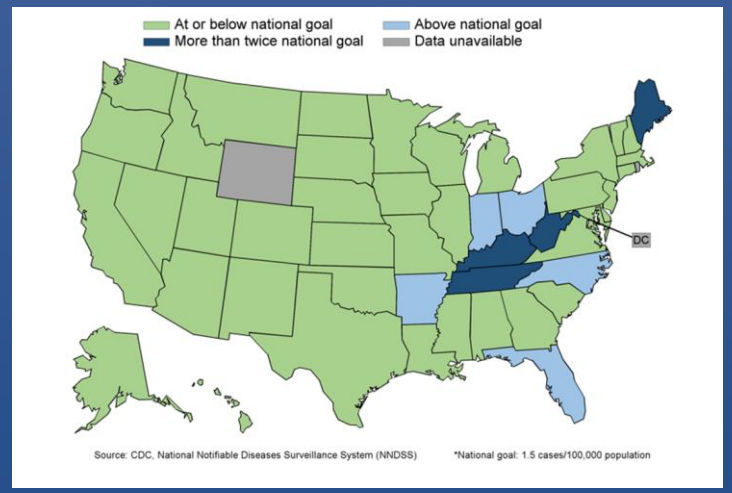
# National Academies: Recommendations for Hepatitis elimination in the US (2017)

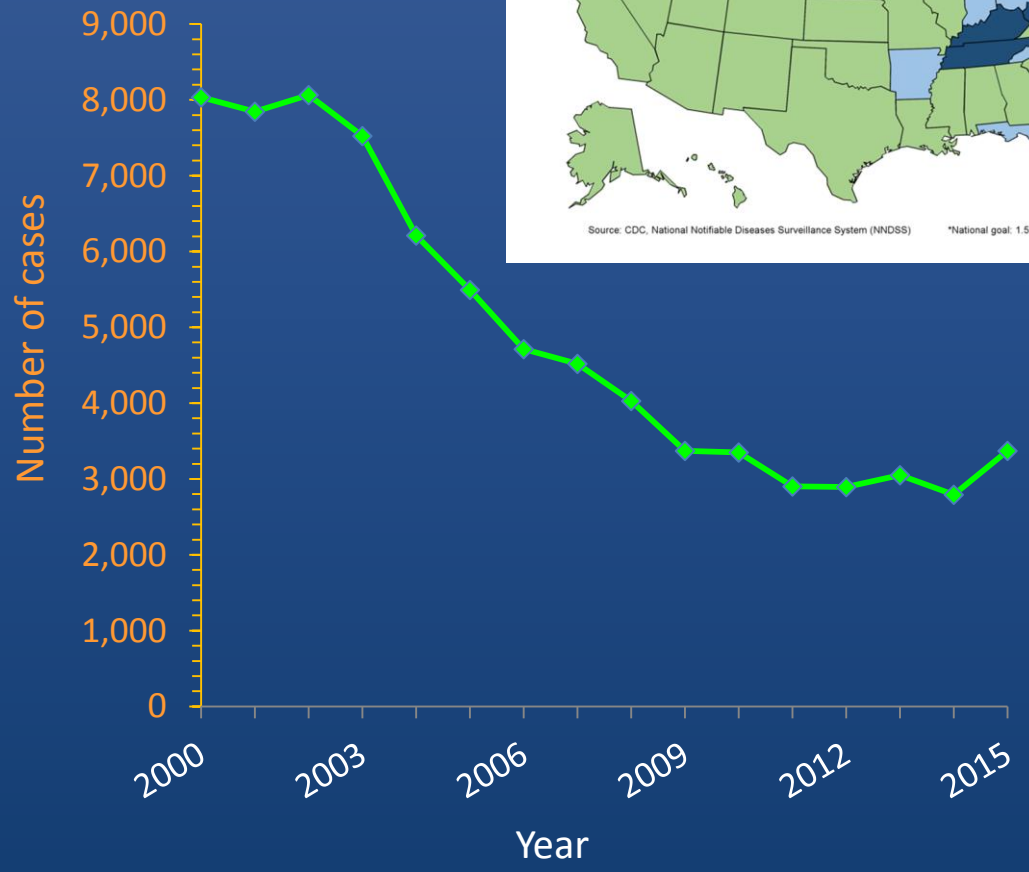
Focus on:

- CDC, in partnership with state and local health departments, should support standard hepatitis case finding measures and the follow-up and monitoring of all viral hepatitis cases reported through public health surveillance.
- CDC should support studies to measure HBV and HCV infection incidence and prevalence in high-risk populations
- States should expand access to adult hepatitis B vaccination, removing barriers to free immunization in pharmacies and other easily accessible settings.

# CDC Surveillance for Viral Hepatitis B – United States, 2016

- Acute hepatitis B virus (HBV) infection
  - After adjusting for under-ascertainment and under-reporting (2), the estimated number of new HBV infections in 2016 was 20,900 (95% CI, 11,900–51,200)
- Chronic HBV infections.
  - For 2011-2012, an estimated 847,000 (95% CI, 565,000-1,130,000) persons were living with HBV in the United States
  - A 2009 estimate, using other adjustment methods, was reported to be as high as 2.2 million

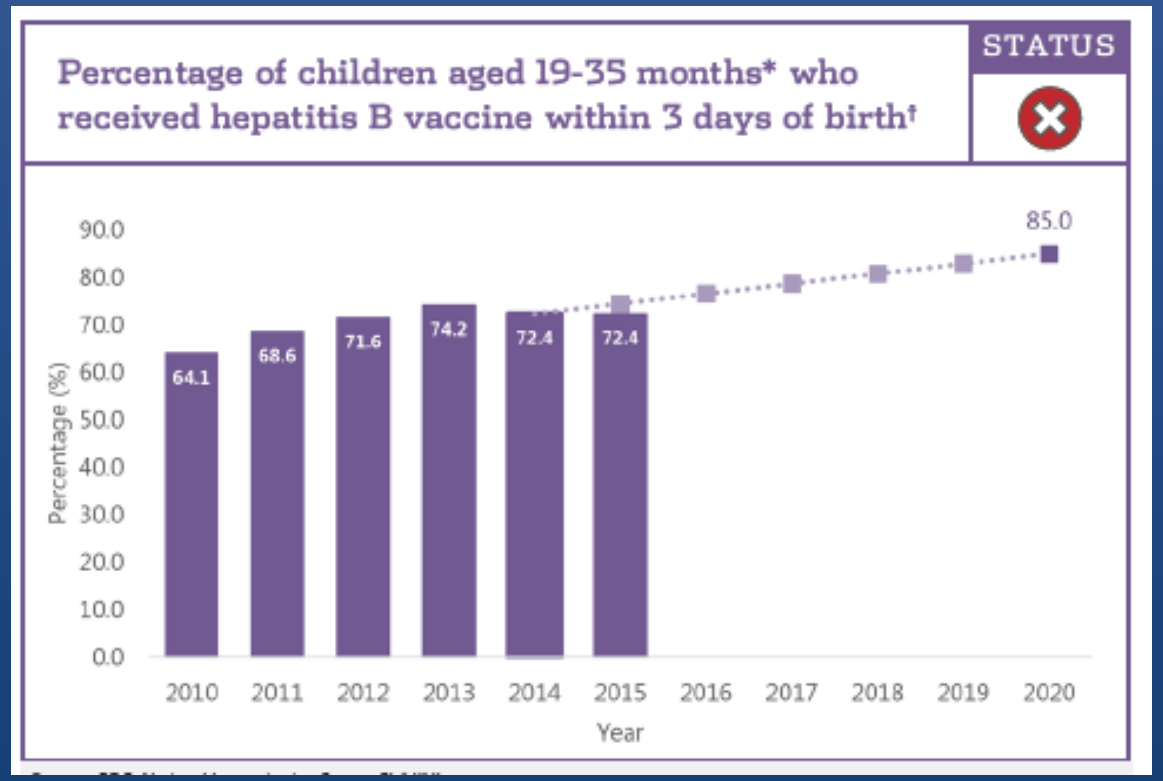


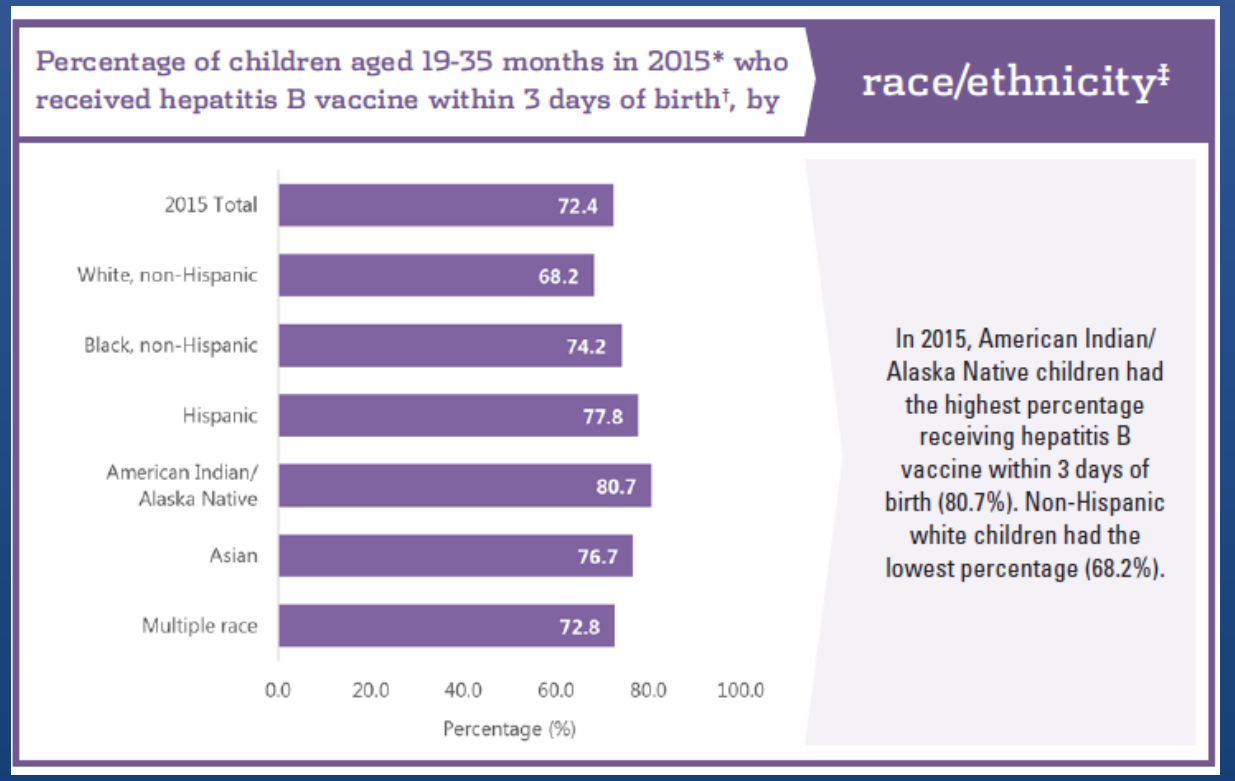



# CDC January 2018: New or updated HBV prevention recommendations

- Universal HBV vaccination within 24 hours of birth for medically stable infants weighing ≥2,000 grams
  - Removal of permissive language for delaying the HBV birth dose until after hospital discharge
- Vaccinate all persons with chronic liver disease (not limited to HCV)
- Renewed focus on PWID
  - Since 2009, there has been an increase in acute HBV infection among non-Hispanic whites aged 30–39 years residing in nonurban areas reporting injection-drug use as a risk factor

# HBV vaccination rates are falling short of 2020 goals




≥ Poverty level: 70.2%
< Poverty level: 76.3%

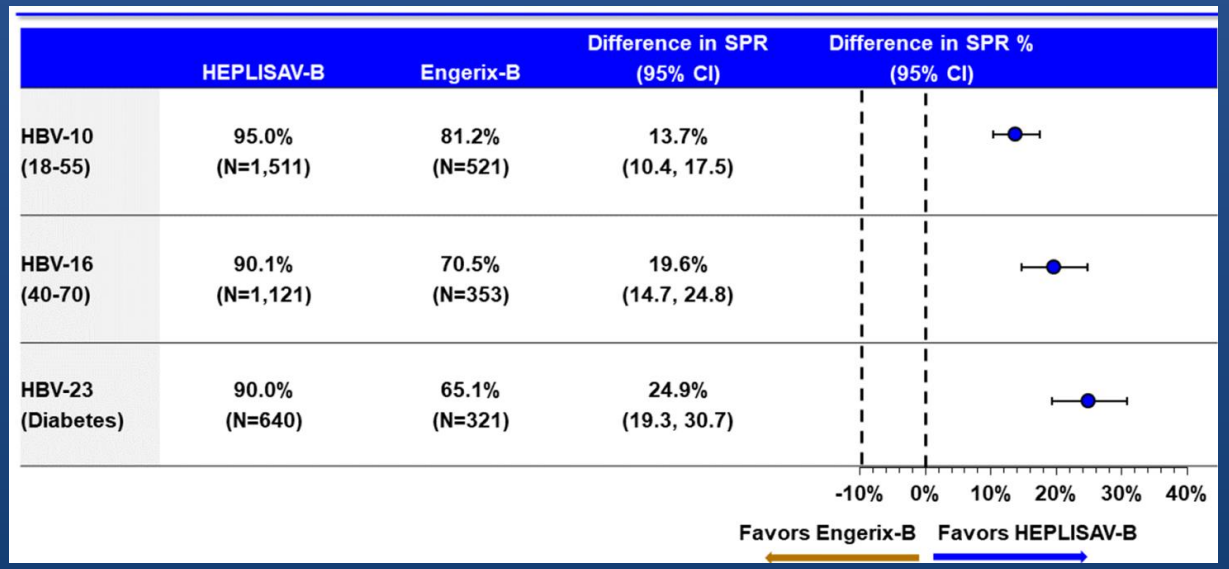
# HBV vaccination completion rates and potential impact of a new HBV vaccine

Hepatitis B Vaccination Dose-Series Completion, 2012 to 2015

| Dose | Total Doses Given | Range of percent receiving HepB series among those received 1st dose | Average percent receiving HepB series among those received 1st dose |
|---|---|---|---|
| 1st dose | 29,457 | -- | -- |
| 2nd dose | 11,897 | 18.5% - 67.6% | 40.4% |
| 3rd dose | 6,557 | 6.2% - 46.1% | 22.3% |

HepB-CpG may be used as a HepB vaccine in persons aged ≥18 years recommended for vaccination against HBV

- Novel TLR-9 agonist
- Administered as a 2-dose series (0, 1 month)




Watson, et al. 2017 National Adult and Influenza Immunization Summit Posters
Schillie S, et al. MMWR Morb Mortal Wkly Rep 2018;67:455–458.

# National Academies: Recommendations for Hepatitis elimination in the US (2017)

Focus on:

- The National Committee for Quality Assurance should establish measures to monitor compliance with viral hepatitis screening guidelines and hepatitis B vaccine birth dose coverage
- CDC, AASLD, IDSA, and the American College of Obstetricians and Gynecologists should recommend that all HBsAg+ pregnant women have early prenatal HBV DNA and liver enzyme tests to evaluate whether antiviral therapy is indicated for prophylaxis to eliminate mother-to-child transmission or treatment of chronic active hepatitis

# Prevention of HBV transmission from mother to child

- All HBsAg-positive pregnant women should be tested for HBV DNA to guide the use of maternal antiviral therapy during pregnancy for the prevention of perinatal HBV transmission
  - AASLD recommends maternal antiviral therapy if HBV DNA >200,000 IU/mL
- All HBsAg-positive pregnant women should receive information concerning HBV that discusses:
  - Potential use of antiviral therapy
  - Importance of prophylaxis for their infant (HepB vaccine and HBIG within 12 hours of birth), completion of the vaccine series, and post-vaccination serologic testing.

Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1):1–31.

# National Academies: Recommendations for Hepatitis elimination in the US (2017)

Focus on:

- The criminal justice system should screen, vaccinate, and treat hepatitis B and C in correctional facilities according to national clinical practice guidelines

# Hepatitis B transmission in the justice system

- 2000:  Hepatitis B Outbreak in a State Correctional Facility
  - Among the 907 susceptible inmates who completed the questionnaire, 473 (52%) reported at least one high-risk exposure while incarcerated
    - Injecting drugs (2%)
    - Sex with another man (4%)
    - Using a razor that had been used by another inmate (8%)
    - Receiving a tattoo (48%)
- Vaccination is recommended for  adults at risk for HBV infection which includes those in correctional facilities
  - Pprevalence of chronic HBV infection has been higher among prison inmates (1.0%–3.7%) than among the general population
    - Overrepresentation of persons entering correctional facilities with risks for HBV infection

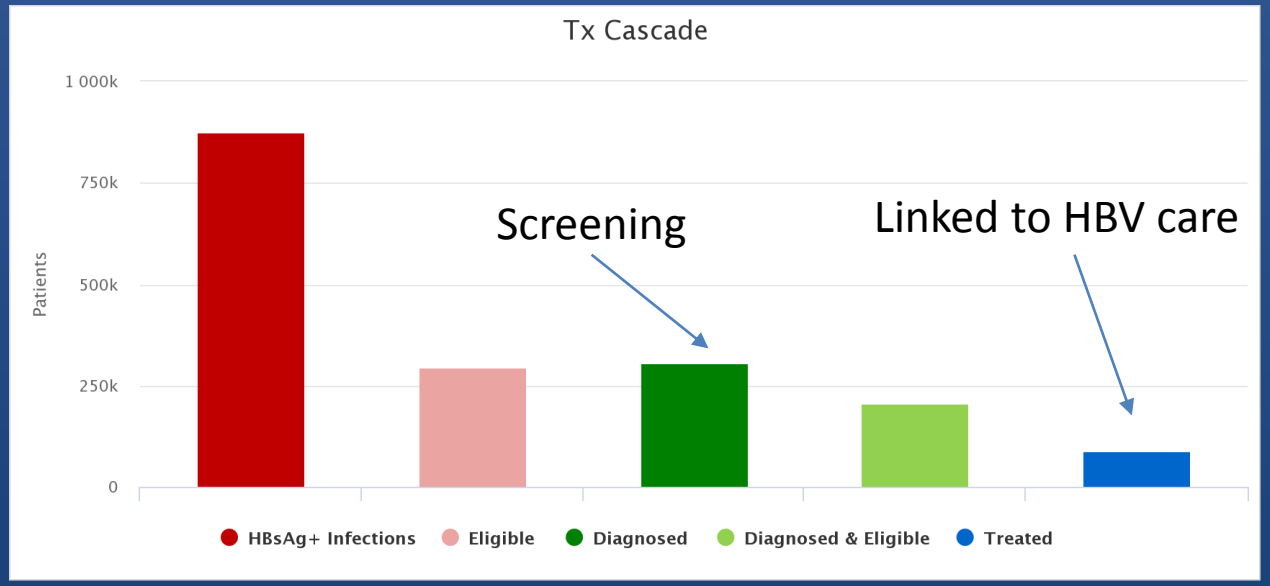
# National Academies: Recommendations for Hepatitis elimination in the US (2017)

Focus on:

- AASLD and IDSA should partner with primary care providers and their professional organizations to build capacity to treat hepatitis B and C in primary care

# HBV care continuum in the US: Polaris Observatory

HBV care continuum in the US: Polaris Observatory




2030 Goals: 90% diagnosed/90% evaluated/80% treated (medical necessity)

Barriers to Evidence-Based Practice of Vaccination, Screening, and Linkage to Care for HBV

*Table 4.* Barriers to Evidence-Based Practice of Vaccination, Screening, and Linkage to Care for Chronic HBV Infection and Approaches to Overcome Them

| Level | Barriers to Evidence-Based Practice | Approaches to Overcome Barriers |
|---|---|---|
| Patient | Lack of awareness about chronic HBV infection and the health benefits of the hepatitis B vaccine<br>Low educational and socioeconomic levels<br>Lack of health insurance coverage and difficulty navigating the health care system<br>Stigma associated with chronic HBV infection and fear of a positive test result | Increase patients' knowledge about risk for and severity of chronic HBV infection and benefits of screening, vaccination, and treatment. |
| Clinician | Lack of awareness about risk for chronic HBV infection in high-risk populations<br>Lack of routine assessment of adult vaccine needs and HBV risk during clinical encounters<br>Low level of awareness of guideline-based recommendations on treatment and monitoring of chronic HBV infection<br>Some clinical practices may not routinely store hepatitis B vaccine | Routinely assess HBV risk and vaccine needs during clinical encounters.<br>Increase clinicians' awareness about groups at risk for chronic HBV infection.<br>Vaccinate all patients at risk for HBV infection.<br>Screen all patients at high risk for chronic HBV infection.<br>Monitor patients with chronic HBV infection periodically to determine disease progression and initiate treatment when indicated.<br>Refer to a liver specialist or hepatitis B–experienced health care provider when patients with chronic HBV infection become eligible for treatment.<br>Clinical practices that do not stock the hepatitis B vaccine can refer susceptible patients to the local health department or to larger clinical practices that do. |
| System | A complex health care system that may require referral to a liver specialist can present challenges to persons who lack knowledge about how the health care system works. | Use EMR prompts and reminders, standing orders, and patient reminder systems to improve hepatitis B vaccination and screening.<br>Use culturally and linguistically competent peer navigators in health care settings to increase the number of patients who receive hepatitis B–directed care and to facilitate continuity of care. |

EMR = electronic medical record; HBV = hepatitis B virus.

Abara et al. Ann Intern Med. 2017;167(11):794-804

# HCV and HBV treatment paradigms are radically different

| | Hepatitis C | Hepatitis B |
|---|---|---|
| Oral | Yes | Yes (except interferon) |
| Safe and well-tolerated | Yes | Yes (except interferon |
| Once daily | Yes | Yes |
| Potent antivirals | Yes | Yes |
| Virus targets for which drugs are available | Three (NS5b, NS3, NS5a) | One (polymerase) |
| Novel drugs in the last 10 years | Seventeen | Zero (TAF is tenofovir) |
| Complexity of the decision to treat | Simple (all) | Complex |
| Duration of therapy | 8 to 12 weeks | Long-term |
| Treatment outcome | Viral cure | Viral suppression with hope for immune control |

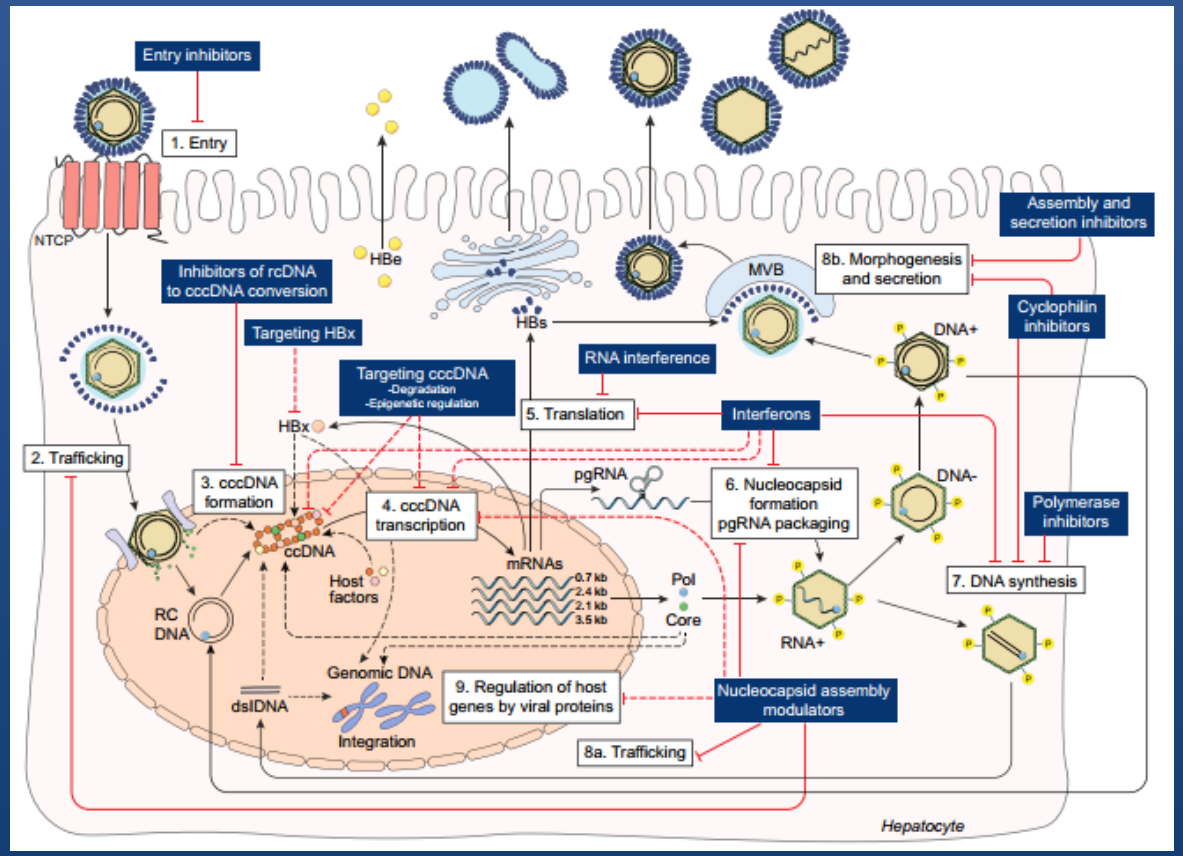
# The decision algorithm to treat hepatitis B is complex and creates a barrier to care

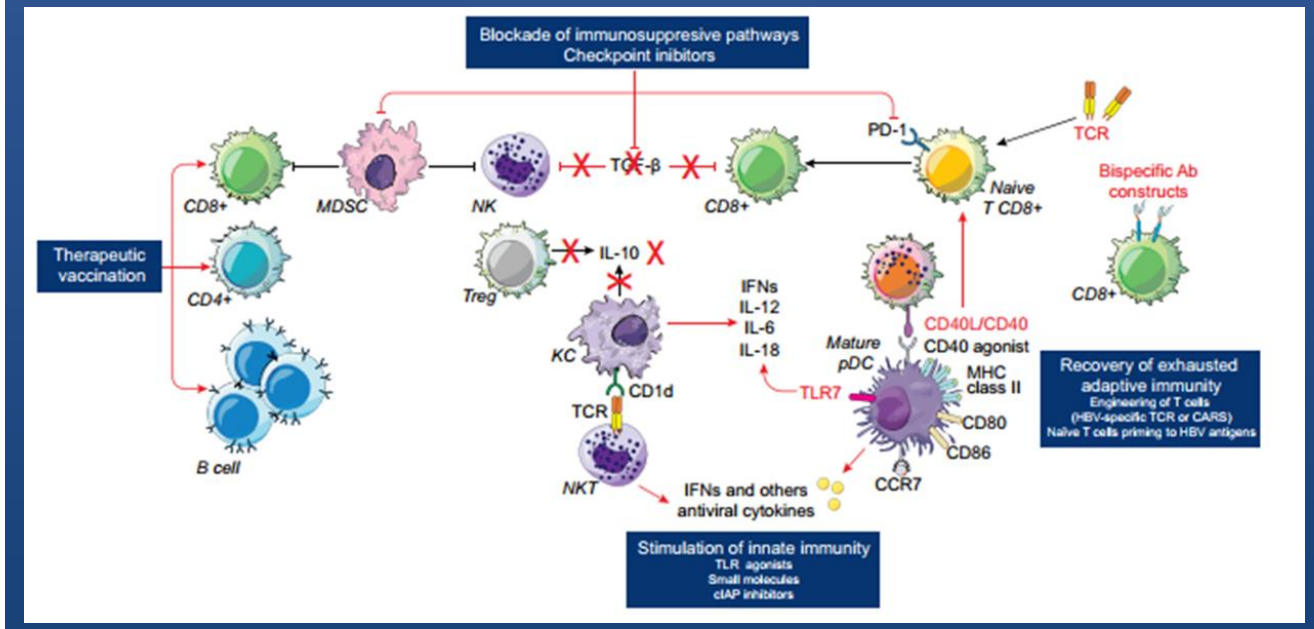
- Clinicians and patients must consider the following:
  - HBeAg status:  Negative or Positive
  - HBV DNA level:  Threshold for treatment lower with HBeAg negative
  - ALT level:  Use normal value of 35 U/L for men and 25 U/L for women
  - Liver disease severity (biopsy or non-invasive):  Cirrhosis, fibrosis, inflammation
  - Family history of HCC
  - Age
  - Transmission risk
  - HCV or immunosuppressive treatment planned
- Treat:  Long-term use of nucleos(t)ide analogue polymerase inhibitors
- No treat:  Long-term monitoring every 3 to 6 months long-term

# HBV treatment paradigm must be simplified to meet 2030 elimination goals

- Hypothesis: Persons not taking suppressive treatment when it is needed have greater risk of harm than persons taking treatment when the indication is unclear
- Optimistic view: HBV treatment is not life-long; new curative therapies will emerge within 10 years
- Cost: *G*eneric TDF and ETV can be very inexpensive
- Proposed simple treatment approach:
  - HBV DNA detected – treat
  - HBsAg + and ALT > normal – treat

# Antiviral and immunologic approaches to HBV cure



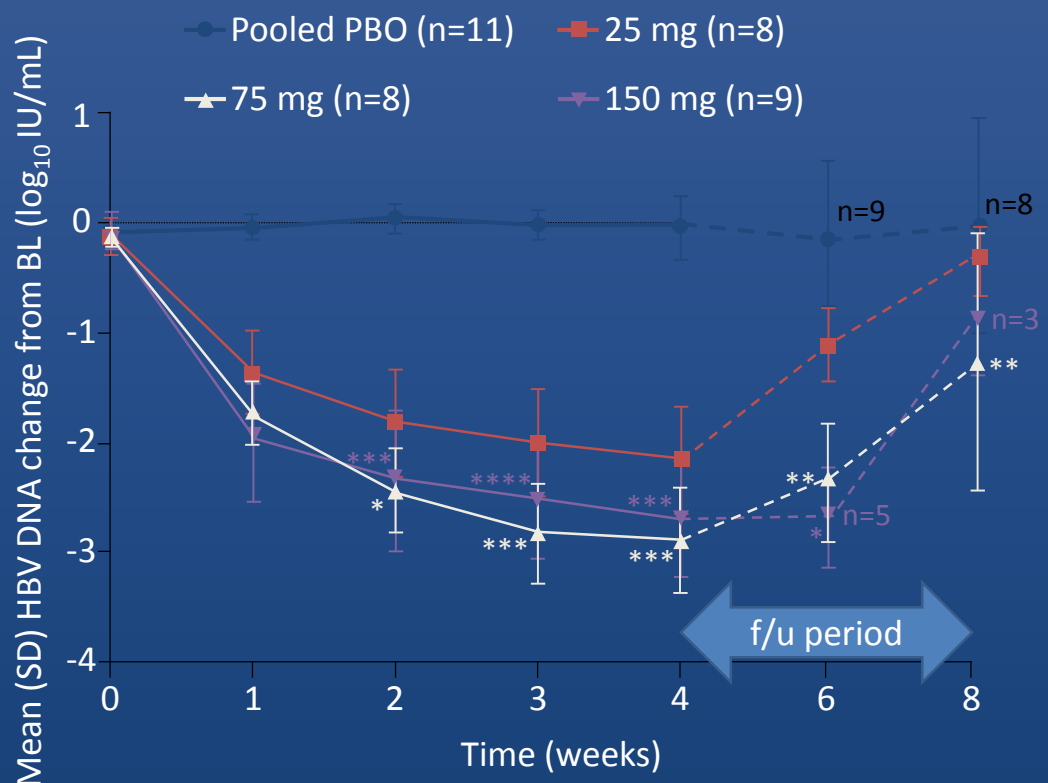
# Safety, pharmacokinetics and antiviral activity of novel capsid assembly modulator (CAM) JNJ-56136379 (JNJ-6379) in treatment-naive CHB patients without cirrhosis

## Baseline characteristics

| ITT analysis | 25 mg QD (n=12)* | 75 mg QD (n=12)* | 150 mg QD (n=12)** |
|---|---|---|---|
| **Mean age, years (SD)** | 39.5 (11.6) | 36.5 (10.2) | 45.8 (9.9) |
| **Sex – Male, n (%)** | 11 (92) | 10 (83) | 9 (75) |
| **Race – White, n (%)** | 6 (50) | 12 (100) | 10 (83.3) |
| **ALT Grade, n (%)** | | | |
| Grade 0 | 9 (75) | 9 (75) | 9 (75) |
| Grade 1 | 3 (25) | 3 (25) | 3 (25) |
| **Metavir fibrosis stage n, (%)** | | | |
| F0 | 4 (33) | 5 (42) | 5 (42) |
| F1 | 6 (50) | 4 (33) | 7 (58) |
| F2 | 2 (17) | 3 (25) | 0 |
| **HBeAg positive, n (%)** | 6 (50) | 3 (25) | 0 |
| **Mean HBV DNA $\log_{10}$ IU/mL (SD)** | 6.41 (1.99) | 5.36 (1.54) | 4.84 (1.43) |
| **Mean HBsAg $\log_{10}$ IU/mL (SD)** | 4.07 (0.96) | 3.95 (0.55) | 3.91 (0.70) |
| **HBV genotype D, n (%)** | 5 (42) | 10 (83) | 8 (67)† |

*Sessions 8 and 9: JNJ-6379 (n=8); PBO (n=4) **Session 10: JNJ-6379 (n=9); PBO (n=3)
†including one pt with recombinant genotype C/D

## Mean HBV DNA change from BL up to 4 weeks f/u

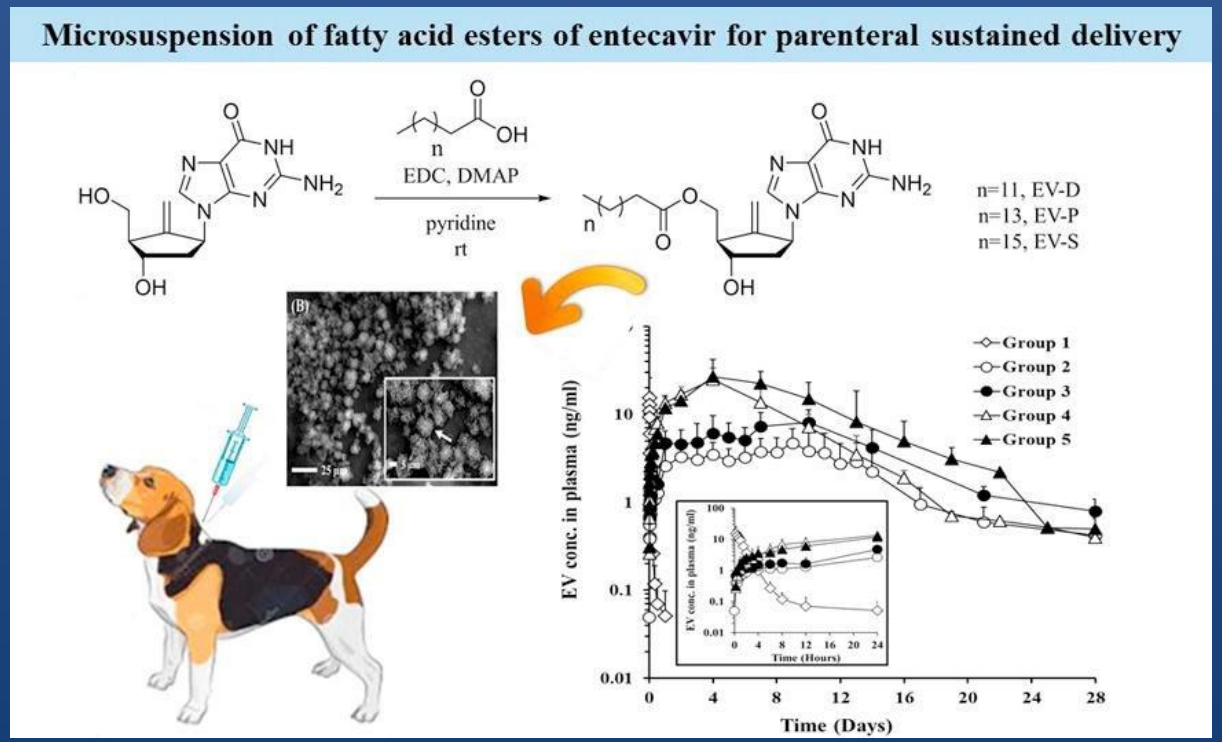



Each * refers to 1 pt with HBV DNA <LLQ

Zoulim F, et al. EASL 2018, Paris. #LBO-004

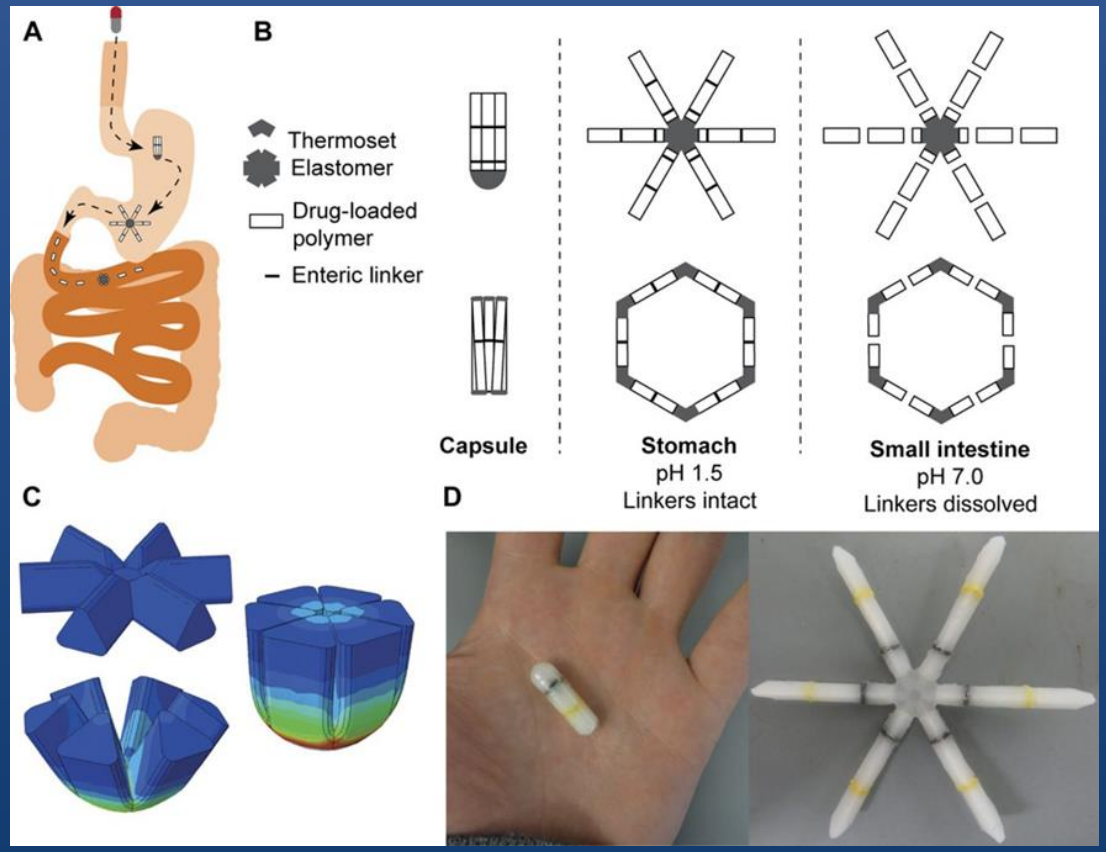
# Extended release HBV treatment could transform therapy

HBV: Microsuspension of fatty acid esters of entecavir for parenteral sustained delivery




Ho MJ et al. Int J Pharm. 2018

Malaria: Prolonged Ivermectin exposures with extended release oral formulations




Bellinger et al Science Translational Medicine 2016

# Elimination of Hepatitis B and C: Focus on Special populations

- Persons at risk for infection who are not adequately protected including those with prior HCV cure
  - HBV (and HCV) vaccine
  - Harm reduction interventions (transmission by sex and injections)
- Persons with unknown active infection
  - Screening and identification
- Persons with known active infection who have not been evaluated
  - Medical necessity for suppressive (HBV) or curative (HCV) treatment
- Persons with known active infection who remain untreated despite medical necessity
  - Treatment strategies must be adapted to the population