2019 UPDATE ON HEPATITIS B & HCV ELIMINATION IN THE ERA OF DAA THERAPY

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Disclosures

• Gilead Sciences
  • Grant funding
  • Advisory Board
Hepatitis B Epidemiology and Treatment

- 248 million HBV carriers in the world
  - 600,000 die annually from HBV-related liver disease

- Vaccination is available and effective

- Current AASLD preferred treatment for adults
  - Peg-IFN alpha 2a
  - Tenofovir Disoproxil Fumarate (TDF)
  - Tenofovir Alafenamide (TAF)
  - Entecavir (ETV)

- Goals of treatment: HBVeAg seroconversion, suppression of viral DNA

- Development of new therapeutic agents underway
HBV Lifecycle and Drug Targets

Entry Inhibitors
- Myrcludex
- Cyclosporine
- Ezetimibe

Viral Transcript Inhibitors
- SiRNA
- Antisense Oligonucleotides
- Ribozymes

cccDNA silencing

HBsAg release inhibitor
- NAP

RT poly inhibitor
- Nucleotide analogues
- Non-nuc analogues
- RNAseH Inhibitors

Core Inhibitors
- Heteroaryldihydropyrimidines
- Phenylpropenamides
- Sulfamoyl benzamides
- Aminothiazole

Immunodulators
- TLR 7 and 9 agonists
- T-cell vaccines
- PD-1/PD-L1 blockade
Pathways to Achieving Functional Cure

Inhibit Viral Replication

- Virions (HBV DNA)
- NUC
  - +/- CpAM
  - +/- RNAi
  - +/- Entry inhibitor
  - +/- cccDNA inhibitor

Lower Viral Antigen Burden

- HBeAg
- HBsAg
- siRNA
  - Oligonucleotide
  - Nucleic acid polymer
  - +/- cccDNA inhibitor

Boost Immune Response

- NK cells
- T cells
- B cells
- Macrophages
- TLR / RIG-I agonist
- PD-1; PDL1
- Lymphotoxin B
- T Cell reprogramming
- Therapeutic vaccine
JNJ-64530440: Potent Core Assembly Modulator (CAM)

- Safety, tolerability and PK data, double blind Phase 1b
- 2 cohorts of 10 tx naïve HbeAg +/- pts randomized to JNJ-0440 vs placebo
- Doses 750mg QD or BID x 28 days
- No tx discontinuation or SAEs, 8/10 QD had AE, 5/10 BID had AE
- HBV DNA declines from baseline for QD and BID dosing [mean (SD)/max] were 3.2 (0.6)/3.9 (QD) and 3.3 (0.5)/4.1 (BID) log₁₀ IU/mL.

Gane E, Abstract 89
Dual Therapy CAM (ABI-Ho731) plus NA

- Double blind placebo control trial
- Deeper DNA suppression with combination therapy
- Await data on HBeAg and HBsAg loss

Sulkowski et al Abstract LP1
Antisense oligonucleotide (GSK3389404) in NA Suppressed patients

- Phase 2a, multicenter, randomized placebo controlled, double blind
- N=66
- Proof of concept that antisense oligonucleotides can decrease HBsAg

Yuen, et al Abstract 0695
Therapeutic HBV Vaccine

- NASVAC: contains HBVsAg and HBcAg
- Administered 10 times biweekly nasally to NA suppressed patients and inactive carriers
- Open label study
- Efficacy
  - NASVAC reduced HBsAg in 70.1% of pts on NAs (avg 16.3%) and 76.5% without NAs (avg 19.6%)
  - 4 patients achieved functional cure (loss of HBsAg)

Yoshida et al, Abstract 0068
HCV Can Be Eliminated

- No non-human reservoir
- Simple and accurate diagnostic tools
- Transmission can be prevented
- Infection can be cleared from host
- Highly effective, safe drugs exist and given for a finite period
- Evidence exists that we can reduce HCV infection dramatically in the PWID population with the correct interventions
- Harm reduction will be important in this population

Two Epidemics Intertwined

HCV Infection Is a Serious Health Consequence of Injection-Drug Use

- HCV antibody prevalence among people who inject drugs (PWID) is estimated to be 70% to 77%.

1 of 3 people who inject drugs acquires HCV infection in their first year of injecting.

45% to 85% of individuals chronically infected with HCV are unaware of their status.

HCV is the most common chronic blood-borne infection in the US.

Chronic HCV Cases in Pennsylvania: 2009 and 2018

2009

2018

Case Counts

Age

Source: PA - NEDSS
Philadelphia HCV Care Cascade

This represents 50% of those estimated to be living with HCV. Are we reaching the desired communities?

Who Should Be Tested for HCV?
AASLD/IDSA Recommendations

One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.

One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV

https://www.hcvguidelines.org/evaluate/testing-and-linkage, Nov 6 2019 update
Who should be treated for HCV?
**AASLD/IDSA Recommendations**

<table>
<thead>
<tr>
<th>Recommendation for When and in Whom to Initiate Treatment</th>
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<tbody>
<tr>
<td>Treatment is recommended for all patients with <strong>acute or chronic</strong> HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.</td>
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## Management of HCV in PWID

### AASLD/IDSA Recommendations

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>RATING</th>
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<tr>
<td>Annual HCV testing is recommended for PWID with no prior testing, or past negative testing and subsequent injection drug use. Depending on the level of risk, more frequent testing may be indicated.</td>
<td>IIa, C</td>
</tr>
<tr>
<td>Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV-antibody testing with reflexive or immediate confirmatory HCV-RNA testing and linkage to care for those who are infected.</td>
<td>IIa, C</td>
</tr>
<tr>
<td>PWID should be counseled about measures to reduce the risk of HCV transmission to others.</td>
<td>I, C</td>
</tr>
<tr>
<td>PWID should be offered linkage to harm reduction services when available, including needle/syringe service programs and substance use disorder treatment programs.</td>
<td>I, B</td>
</tr>
<tr>
<td>Active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment.</td>
<td>IIa, B</td>
</tr>
</tbody>
</table>

AASLD, American Association for the Study of Liver Diseases; IDSA, Infectious Diseases Society of America.

How Do We Improve HCV Treatment Uptake Among PWID?

**WHERE**
- SUD clinics
- NSP services
- Community health clinics
- Primary care
- Sexual health clinics
- Prisons

**WHAT**
- HCV testing
- Liver fibrosis assessment
- HCV treatment
- OST
- Counseling
- Case management
- Harm reduction services

**WHO**
- Specialists
- Primary care providers
- NPs, PAs, nurses, pharmacists
- Counselors, social workers, case managers
- Peer support workers

**HOW**
Tailored processes/clinic workflows for HCV testing, linkage, treatment
Decentralized treatment of PWID

- Primary care providers trained to provide care using standard algorithm
- 3477 PWIDs initiated treatment
- 7% were cirrhotic
- SVR12 was achieved in 91% in a modified ITT analysis
  - 55% of those who completed treatment returned for SVR and 20% of those with interrupted treatment returned for SVR check
- Treatment interruptions occurred in 15% and reduced SVR 78%
- Decentralized care of PWID using DAA regimens is safe and effective even those with cirrhosis

Dhiman et al, abstract 0165, Schmidbauer et al, abstract 1561, Sulkoswski et al abstract 1554, Nallapeta et al abstract 1589
Reinfection rates after cure among PWID

- Population based cohort study estimated reinfection rates among PWID in BC, Canada
- PWID have a 3 fold higher rate of reinfection than non PWID
- Consider harm reduction and OAT post treatment

Janjua et al, abstract 282, grebely et al abstract 1584
Prevalence of HCV Viremia among PWID at Vogur Addiction Hospital in Iceland

Runarsdottir V. Journal of Internal Medicine, 2018, 283; 500–507
Harm Reduction is Needed to Address the Syndemic

SSP Coverage Across the U.S.

- 29,382 young individuals with HCV
  - 15–29 years of age
  - 80% live >10 miles from an SSP
  - Median distance: 37 miles

HCV + Donor, HCV negative Recipient

- Short course of therapy to prevent transmission
  - Ezetimibe 10mg + G/P was given 1 day before and 7 days after transplant
  - 20 HCV – recipients, 10 lung, 7 kidney, 3 cardiac, from 14 donors
  - All 20 remained RNA negative at follow up 12 weeks n=17, 4 weeks n=3

- Multicenter retrospective study of prospectively collected data
  - HCV + donors, HCV negative recipients of liver transplant, standard treatment after transplant
  - 22 HCV-seronegative LT recipients received grafts from HCV-seropositive donors
  - DAA treatment was started at the median time of 28 days (range 6-67) after LT: G/P for 12 weeks (11 patients), LDV/SOF + RBV for 12 weeks (2 patient).
  - After 4 weeks all patients had HCV RNA <40 IU/ml and were HCV RNA undetectable by week 8.
  - All nine patients who completed treatment achieved SVR 12.
PA is a leader in Viral Hepatitis Elimination in the US

- No Medicaid DAA restrictions

- Testing for and treating HCV in the PA Department of Corrections
  - All prisoners to be treated by 2022

- Testing for and treating HCV in the Philadelphia County Jails
  - Program roll out September 3 2019
  - Linkage to care services, Philadelphia FIGHT, C a Difference program

- May 1st, 2019 Harrisburg Viral Hepatitis Elimination Summit
  - Steering Committee Formed

- Get involved
  - Join the PA coalition for elimination: www.communityliveralliance.org
  - Join the Hepatitis C Allies of Philadelphia: www.hepcap.org
  - Join NVHR provider advocacy workgroup: www.voices4hep.org