Hepatitis C Virus
- the Journey from Discovery to Cure -

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Evolution of the Discovery for Viral Hepatitis

“Infectious” and “Serum” Hepatitis in 1950s and 1960s


Hepatitis A virus (HAV)
Discovered by Dr. Stephen Feinstone in 1973


Hepatitis B virus (HBV)
Discovered by Dr. Baruch Blumberg in 1968


Serological tests
HAV and HBV in mid-1970 most cases of parenterally-transmitted hepatitis were not due to HAV/HBV

Non-A, Non-B Hepatitis (NANBH)
Serial passage NANBH infection from human materials to chimpanzee by Harvey Alter in 1978


Discovery for Non-A, Non-B Hepatitis in 1980s

Non-A, Non-B Hepatitis (NANBH)
- Chimpanzee model: NANBH agents cause membranous tubules with the cytoplasm of the infected hepatocytes (TFA: tubular forming agent)

Non-A, Non-B Hepatitis (NANBH): TFA
- Inactivated by organic solvents suggesting NANBH to be a lipid-enveloped agent
- Could be filtered through 80 nM pore-size filter
- A small enveloped virus related to flaviviridae, togaviridae, or hepatitis delta proposed by Dr. Bradley in mid-1980

Natural History of Non-A, Non-B Hepatitis (NANBH)
- ~20% of infected patients slowly progressed to cirrhosis over the course of many years

Successful Molecular Identification of HCV in 1989

- **Clone 81 (overlapping with clone 5-1-1):** not hybridize with human or chimpanzee DNA by Southern blot [clone 5-1-1 and clone 81 are not derived from host genome]
- **Cloned cDNA:** hybridize with infectious chimpanzee liver, but to hybridize with uninfected chimpanzee liver or control
- **Single positive-stranded:** only one strain of Clone 81 could hybridize with infectious chimpanzee liver

Seroconversion of anti-5-1-1 and An Assay to Detect Circulating Antibodies in Hepatitis C Virus (HCV)

1. **Clone 5-1-1**: cDNA library showed one opening reading frame (ORF)
2. **Fusion polypeptide in bacteria**: superoxide dismutase (SOD)/5-1-1 (PS5)

### HCV antibody in NANBH patients from U.S.

<table>
<thead>
<tr>
<th>Transfusion</th>
<th>Total patients</th>
<th>Percent positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>No identifiable source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(community-acquired)</td>
<td>59</td>
<td>58</td>
</tr>
</tbody>
</table>

### HCV antibody in PT-NANBH patients from Italy and Japan

<table>
<thead>
<tr>
<th>Country</th>
<th>No. patients</th>
<th>Disease</th>
<th>Percent positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>32</td>
<td>Chronic</td>
<td>84</td>
</tr>
<tr>
<td>Japan</td>
<td>23</td>
<td>Chronic</td>
<td>78</td>
</tr>
<tr>
<td>Japan</td>
<td>13</td>
<td>Acute, resolving</td>
<td>15</td>
</tr>
</tbody>
</table>


SOD/5-1-1 polypeptide: 363 amino acid in recombinant yeast
Enzyme Immunoassay (EIA) for the Diagnosis of HCV Infection

<table>
<thead>
<tr>
<th>5' UTR</th>
<th>Core</th>
<th>E1</th>
<th>E2</th>
<th>p</th>
<th>NS2</th>
<th>NS3</th>
<th>NS4A</th>
<th>NS4B</th>
<th>NS5A</th>
<th>NS5B</th>
<th>3' UTR</th>
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<tbody>
<tr>
<td>IRES</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

EIA-1
- Core: c100-3
- E1: c22-3
- E2: c33c
- NS3: c33c
- NS4A: c100-3
- NS5: NS5

EIA-2
- Core: c100-3
- E1: c22-3
- E2: c33c
- NS3: c100-3
- NS4A: NS5

EIA-3
- Core: c100-3
- E1: c22-3
- E2: c33c
- NS3: c100-3
- NS4A: NS5

**Assay Sensitivity (%)**
- EIA-1: 70-80
- EIA-2: 90-95
- EIA-3: 95-98

**PPV in low-risk group (%)**
- EIA-1: 30-50
- EIA-2: 50-60
- EIA-3: 25

**PPV for high-risk group (%)**
- EIA-1: 70-85
- EIA-2: 90-95
- EIA-3: -

**Window period (week)**
- EIA-1: 15
- EIA-2: 9-10
- EIA-3: 7-8

EIA: enzyme immunoassay; PPV: positive predictive value

Recombinant Immunoblot assay (RIBA) 2.0 and 3.0:
SOD/targeted peptides

Carithers RL, et al. Semin Liver Dis 2000;20:159-71
Schematic Representation of the Methodology used to Measure HCV RNA

**PCR (polymerase chain reaction)**
- Add primers & enzymes
- Multiple copies of DNA made
- One detection probe per amplified copy

**TMA (transcription-mediated amplification)**
- Add primers & enzymes
- Multiple copies of RNA made
- One detection probe per amplified copy

**b-DNA (branched DNA)**
- Add probes & branched DNA
- Multiple probes per target
### Currently Available Molecular HCV RNA and Genotyping Tests

<table>
<thead>
<tr>
<th>HCV RNA Assay</th>
<th>Limit of detection (LOD)</th>
<th>Dynamic range of quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplicor HCV v2.0</td>
<td>50 IU/mL</td>
<td>-</td>
</tr>
<tr>
<td>Cobas Amplicor HCV v2.0</td>
<td>50 IU/mL</td>
<td>-</td>
</tr>
<tr>
<td>Cobas Amplipre/Cobas Amplicor HCV v2.0</td>
<td>10-20 IU/mL</td>
<td>-</td>
</tr>
<tr>
<td>Versant HCV RNA qualitative assay</td>
<td>10 IU/mL</td>
<td>-</td>
</tr>
<tr>
<td>Amplicor HCV Monitor v2.0</td>
<td>600 IU/mL</td>
<td>600-850,000 IU/mL</td>
</tr>
<tr>
<td>Cobas Amplicor HCV Monitor v2.0</td>
<td>600 IU/mL</td>
<td>600-700,000 IU/mL</td>
</tr>
<tr>
<td>Cobas Amplipre/Cobas Taqman HCV test</td>
<td>25 IU/mL</td>
<td>43-69,000,000 IU/mL</td>
</tr>
<tr>
<td>Cobas Taqman HCV v2.0 with high pure system</td>
<td>10 IU/mL</td>
<td>25-390,000,000 IU/mL</td>
</tr>
<tr>
<td>Versant HCV RNA 2.0 assay (bDNA)</td>
<td>200,000 genome equivalents/mL</td>
<td>200,000-120,000,000 genome equivalents/mL</td>
</tr>
<tr>
<td>Versant HCV RNA 3.0 assay (bDNA)</td>
<td>615 IU/mL</td>
<td>615-7,700,000 IU/mL</td>
</tr>
<tr>
<td>Abbott RealTime HCV assay</td>
<td>12 IU/mL</td>
<td>12-100,000,000 IU/mL</td>
</tr>
<tr>
<td>HCV NGI QuantaSure</td>
<td>2 IU/mL</td>
<td>2-2,000,000 IU/mL</td>
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### HCV Genotyping Assay

<table>
<thead>
<tr>
<th>HCV Genotyping Assay</th>
<th>Identifiable genotypes</th>
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<tbody>
<tr>
<td>InnO-LiPA HCV II</td>
<td>Genotype 1-6</td>
</tr>
<tr>
<td>Abbott RealTime HCV Genotype II</td>
<td>Genotype 1-6</td>
</tr>
<tr>
<td>Trugene HCV 5'NC Genotyping</td>
<td>Genotype 1-6</td>
</tr>
<tr>
<td>Trugene HCV NS5B Genotyping</td>
<td>Genotype 1-6</td>
</tr>
</tbody>
</table>
Flow Diagrams for the Diagnosis of HCV Infection

Anti-HCV assay → Non-reactive → Stop*

Reactive

HCV RNA → Detected → Current HCV infection → Link to care

Undetected → No current HCV infection → Additional testing

- Testing with another HCV antibody assay
- Repeat HCV RNA testing

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

Anti = antibodies; RNA = ribonucleic acid.
Genomic and Peptide Structures of HCV

HCV

Virology

Virus
50 nM, enveloped nucleocapsid, single-stranded (+) RNA

Family
Flaviviridae

Genotype
7 major, > 50 subtype

Mutation
High

Half-life
3 hours

Production
10^{12} virions/day

Natural immunity

Innate
Strong IFN and ISG response

Adaptive
T-cell, transient strain-specific neutralizing antibody?
HCV Infection and Host Innate Immune Responses

**Hepatitis C virus**

**Pathogen associated molecular patterns (PAMP)**
- Retinoid acid inducible gene 1 (RIG-1)
- Mitochondrial antiviral-signaling protein (MAV)
- Toll-like receptor 3 (TLR3)

**Endosome**
- Mitochondria
- TIR-domain adaptor protein inducing IFN β (TRIF)
- Interferon regulatory factor 3 (IRF3)
- Interferon regulatory factor 7 (IRF7)

**Signal transducer and activator of transcription (STAT)**
- STAT1
- STAT2
- STAT7
- IRF9

**Suppressor of cytokine signaling 3 (SOCS3)**
- Protein inhibitor of activated STAT 1 (PIAS1)

**Interferon sensitive response element (ISRE)**
- Interferon stimulated gene (ISG): protein kinase R (PKR), 2'₅' oligoadenylate synthetase (2'₅' OAS), Mx protein, IRF7, IL8 et c...
Blocking the Immune Responses by HCV NS3/4A, NS5A Proteins

Pathogen associated molecular patterns (PAMP)
- Viral nucleic acid
- Retinoid acid inducible gene 1 (RIG-1)
- Mitochondrial antiviral-signaling protein (MAV)

Endosome
- Toll like receptor 3 (TLR3)
- TIR-domain adaptor protein inducing IFN β (TRIF)
- Interferon regulatory factor 3 (IRF3)
- Interferon regulatory factor 7 (IRF7)

Mitochondria
- HCV NS3/4A protein
- Interferon regulatory factor 3 (IRF3)

IFN β
- IFNAR1
- Tyk2
- Jak1
- IRF9
- STAT2
- STAT1

IFN α
- IFNAR2
- Signal transducer and activator of transcription (STAT)
- Suppressor of cytokine signaling 3 (SOCS3)
- Protein inhibitor of activated STAT 1 (PIAS1)

HCV NS5A protein mutation (ISDR)

Interferon sensitive response element (ISRE)
- Interferon stimulated gene (ISG): protein kinase R (PKR), 2'-5' oligoadenylate synthetase (2'-5' OAS), Mx protein, IRF7, IL8 et c...

Hepatitis C virus

Signal transducer and activator of transcription (STAT)
Natural History of HCV Infection: Variability from Person to Person

Female sex, young age at infection

≥ 30 years

Rate of progression
(Fast)                                                                (Slow)

Normal liver → Acute infection → Chronic infection develops in 80% → Chronic hepatitis → Cirrhosis develops in 20% → Risk of carcinoma, 1-4% per year

≤ 20 years

Alcohol use, coinfection*

* Coinfection with HIV-1 or HBV

Extrahepatic Manifestation of HCV Infection

**Hematologic**
- Mixed cryoglobulinemia
- Aplastic anemia
- Thrombocytopenia
- Non-Hodgkin's b-cell lymphoma

**Dermatologic**
- Porphyria cutanea tarda
- Lichen planus
- Cutaneous necrotizing vasculitis

**Renal**
- Glomerulonephritis
- Nephrotic syndrome

**Endocrine**
- Anti-thyroid antibodies
- Diabetes mellitus

**Ocular**
- Corneal ulcer
- Uveitis

**Vascular**
- Necrotizing vasculitis
- Polyarteritis nodosa

**Neuromuscular**
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

**Autoimmune phenomena**
- CREST syndrome

**Salivary**
- Sialadenitis
Milestones of Therapy for Chronic Hepatitis C (Before 2010)

SVR$_{24}$ (%)

<table>
<thead>
<tr>
<th></th>
<th>1992-2000</th>
<th>2001-2010</th>
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<tbody>
<tr>
<td>IFN 6m</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>IFN 12m</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>IFN/RBV 6m</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>IFN/RBV 12m</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Peg-IFN 12m</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Peg-IFN/RBV 12m</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Response-guided therapy (RGT): 2004

IL28B genotypes: 2009
Chemical Structure and Linkage of Peg-IFN α-2a and Peg-IFN α-2b

PEG-IFN alfa-2a

\[ R_1 = CH_3(OCH_2CH_2)_n \]
where \( n = 420-510 \)

PEG-IFN alfa-2b

\[ R_2 = CH_3(OCH_2CH_2)_n \]
where \( n = 239-318 \)

R1 = CH3(OCH2CH2)n
where n = 420-510

PEGylation: attaching an inert polyethylene glycol (PEG) molecule to the interferon core protein

PEG moiety: branched (40kD) for alfa-2a; linear (12kD) for alfa-2b

PEG-IFN alfa-2a

PEG-IFN alfa-2b

Lys\textsuperscript{31,121, 131, 134}

His\textsuperscript{34} (> 50%),
remaining Lys, Cys, Ser

Lys\textsuperscript{31,121, 131, 134}

His\textsuperscript{34} (> 50%),
remaining Lys, Cys, Ser
Development of Peg-IFN (Major Advance for HCV treatment)

Peg-IFN showed an improved plasma half-life with sustained serum concentrations compared with c-IFN.

Chemical Structure and Pharmacokinetics of Ribavirin

Mechanisms (largely unknown)

1. Inhibition of host Inosine monophosphate dehydrogenase (IMPDH): rate limiting step of de novo GTP synthesis
2. Weak inhibitory effect on several viral polymerases
3. RNA mutagen: increased mutation rate puts he virus in jeopardy at the threshold of “error catastrophe”

<table>
<thead>
<tr>
<th>Ribavirin</th>
<th>Single Dose</th>
<th>Multiple Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>600 mg</td>
<td>600 mg bid</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>782</td>
<td>3680</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{tf}}$ (ng.hr/mL)</td>
<td>13400</td>
<td>228000</td>
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<tr>
<td>$T_{1/2}$ (hr)</td>
<td>43.6</td>
<td>298</td>
</tr>
<tr>
<td>Volume of distribution (L)</td>
<td></td>
<td>2825</td>
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<tr>
<td>Clearance (L/hr)</td>
<td>38.2</td>
<td></td>
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<tr>
<td>Bioavailability (%)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>(i) reversible phosphorylation pathway in nucleated cells</td>
<td>(ii) deribosylation and amide hydrolysis</td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney</td>
<td></td>
</tr>
</tbody>
</table>

Patterns of Virological Response after Treatment

Baseline

Treatment

Nonresponder

Partial responder

Breakthrough

Relapser

Sustained responder (cure)

Detection limit

HCV RNA Undetectable

HCV RNA

Time

6 months
Sustained Virologic Response with Peginterferon α-2a and Different Doses of Ribavirin for 24 or 48 Weeks


- Ribavirin: LD (800 mg/day); HD (1,000-1,200 mg/day)
- Viral load: low (≤ 800,000 IU/mL); high (> 800,000 IU/mL)
SVR with Peg-IFN α-2a and Different Doses of RBV for 24 or 48 Weeks: Cirrhosis or Bridging Fibrosis

Sustained Virologic Response (SVR) is Durable in CHC Patients with Peg-IFN α-2a + RBV

- Nine randomized controlled trial (n = 1,343), mean FU of 3.9 years (range 0.8-7.1 years)

The total number of patients in each group is shown at the base of the bar.
Serum sample from 0.9% patients contained HCV RNA (re-infection or relapse not clear)

Swain MG, et al. Gastroenterology 2010;139:1593-601
Initial Virologic Responses after Antiviral Therapy for HCV


c = rate of clearance; d = rate of infected-cell death.
Response-Guided Therapy for HCV-1/4 Patients Receiving Peginterferon plus Ribavirin (EASL)

Week 0  4  12  24  HCV RNA

- **Neg (RVR)**  
  - Pos < 2 log drop (NR)  
    - Stop Tx  
    - Pos (PR)
  - Pos > 2 log drop
  - Neg (EVR)

- **Neg (EVR)**
  - 24 weeks of therapy only if LVL* at baseline

- **Pos**
  - 48 weeks of therapy

- **Pos**
  - 72 weeks of therapy

* LVL (low viral load): < 400,000-800,000 IU/mL
NR: null response; PR: partial response; DVR: delayed viral response

EASL. J Hepatol 2014;60:392-420
Response-Guided Therapy for HCV-2/3 Patients Receiving Peginterferon plus Ribavirin (EASL)

Week 0 4 12 HCV RNA

Neg (RVR) Pos

Pos < 2 log drop or positive at week 24 → Stop Tx

Pos > 2 log drop but negative thereafter (DVR)

Neg (EVR)

12-16 weeks of therapy*

24 weeks of therapy

48 weeks of therapy

Risk factors (fibrosis, IR)

* Marginally less effective due to higher relapse rates, especially in G3 with high viral load

DVR: delayed viral response; IR: insulin resistance

EASL. J Hepatol 2014;60:392-420
Single Nucleotide Polymorphisms (SNPs) as Markers

Indirect Test

Direct Test

Marker SNPs

Disease Associated Variant

Linkage Disequilibrium
Interleukin-28B Gene Polymorphisms in HCV-1 Patients Receiving Peg-IFN/RBV

- Genome-wide association study more than 1,600 patients in IDEAL study
- **IL28B (IFN-λ-3) gene polymorphism**: chromosome 19, rs12979860

The SVR rates in East Asians is adopted from Liu CH et al.
IL28B Genetic Variation (Relationship with IL28B Amino Acid Substitution and Cellular Function Regulations)
Antiviral Targets: HCV NS3 Protease, NS5B Polymerase and NS5A Replication Complex Protein

- Structural and nonstructural proteins contribute to different processes in the viral life cycle.
- Nonstructural proteins play a key role in the replication and assembly of new virions.

Novel Therapeutic Targets for HCV Under Investigation

NA3/4A Protease inhibitors
- Telaprevir (Incivek)
- Boceprevir (Victrelis)
- RG7227 (Danoprevir)
- TMC435 (Simeprevir)
- MK-7009 (Vaniprevir)
- MK-5172 (Grazoprevir)
- BI201335 (Faldaprevir)
- BMS-650032 (Asunaprevir)
- ABT-450/r (Paritaprevir)
- GS-9256

NS4B inhibitors
- Clemizole

Host-targeted Antivirals
- Debio025 (Alisporivir)
- SCY-635
- Miravirsen (SPC3649)
- ITX-5061
- ANA773 (TLR-7)

NS5A inhibitors
- BMS790052 (Daclatasvir)
- GS-5885 (Ledipasvir)
- ABT-267 (Ombitasvir)
- MK-8742 (Elbasvir)
- PPI461
- PPI668

CNS5A Polymerase inhibitors
- BMS791325 (Beclabuvir)
- ANA598 (Setrobuvir)
- ABT-072
- ABT-333 (Dasabuvir)

Active site (nucleosides)
- RG-7128 (Mericitabine)
- GS-7977 (Sofosbuvir)
- IDX184

Non-nucleosides
- GS-9190 (Tegobuvir)
- BI207127 (Deleobuvir)
- TMC647055
- Filibuvir (PF-00868554)
- VX-222
- GS-9669
- BMS791325 (Beclabuvir)
- ANA598 (Setrobuvir)
- ABT-072
- ABT-333 (Dasabuvir)

NNI-site 1
- NNI-site 1
- NNI-site 1
- NNI-site 2
- NNI-site 1 & 2
- NNI-site 3
- NNI-site 4
New Standard of Care for HCV in 2011-2015


Standard Interferon

1991

Interferon + Ribavirin

Interferon + Telaprevir + P/R

GT1

2011

Boceprevir or Telaprevir + P/R

GT2/3

2013

Simeprevir or Sofosbuvir + P/R

2013

Sofosbuvir/Ribavirin

2014

Sofosbuvir/ledipasvir
Paritaprevir/r/ombitasvir/dasabuvir
Asunaprevir/daclatasvir

Novel IFN-free regimens (Phase III) under investigation

- Asunaprevir/daclatasvir/beclabuvir
- Grazoprevir/elbasvir
- Sofosbuvir/daclatasvir
- Sofosbuvir/simeprevir

P/R: peginterferon/ribavirin
r: ritonavir
GT: genotype
New Milestones of Therapy for Chronic Hepatitis C

Direct-acting antiviral agents (DAAs): 2011

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<tbody>
<tr>
<td>SVR12 or SVR24 (%)</td>
<td>6</td>
<td>16</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>6m IFN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN/RBV 6m</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN/RBV 12m</td>
<td></td>
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<tr>
<td>Peg-IFN 12m</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peg-IFN/RBV 12m</td>
<td></td>
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<td></td>
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<tr>
<td>1st generation DAA/Peg-IFN/RBV</td>
<td></td>
<td></td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Newer DAA/Peg-IFN/RBV</td>
<td>84</td>
<td></td>
<td></td>
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<tr>
<td>IFN-free DAA</td>
<td>95</td>
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SVR12 or SVR24 (%) for different therapy regimens from 1992-2000 to ~2013.
The Ideal All-Oral Regimens for HCV Infection

• **Super:** excellent sustained virologic response (SVR) rates
• **Safe:** few adverse events (AEs), few drug-drug interaction
• **Simple:** low pill burden, and no complex treatment regimens
• **Shorter:** at best within weeks
• **Save:** affordable to every patient

Impossible!
25 Years Since HCV Discovery: A Timeline for Major Milestones

1989: Discovery of hepatitis C virus

1991: First hepatitis C treatment approved

1992: US blood supply safe from hepatitis C virus

1996: Hepatitis C infections continue to dramatically decline

1998: CDC first recommends hepatitis C testing

2001: Increase in acute hepatitis C cases

2007: Deaths from hepatitis C surpass HIV in US

2009: USPSTF recommends hepatitis C testing for persons at high risk for infection and 1-time screening for everyone born 1945-1965

2010: Institute of Medicine report issued

2012: First National Testing Day; CDC recommends testing all people born 1945-1965 for hepatitis C

2013: Realizing the potential of an all-oral cure

2014: Elimination of Hepatitis C
The 25th Anniversary of the Discovery of HCV

- Early identify HCV-infected patients by screening program and accurate diagnostic tests.
- Provide easy accessible and affordable antiviral therapies to HCV-infected patients.
- Provide well surveillance programs in treated and untreated HCV-infected patients.
- Educate individuals about the universal precaution for HCV, who are uninfected or infected, treated or untreated.
Thank You for Your Attention