Long-Acting Treatments For Infections: Is Hepatitis Next?

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Johns Hopkins School of Medicine
Disclosures

• Merck, Excision Bio,
Learning Objectives

• Compare use of long-acting treatments for HCV and HBV
• List the challenges of making long-acting treatments
• Identify the lead compounds for HCV and HBV
New Tools Are Needed To Eliminate Hepatitis

Thomas NEJM 2019
Long-Acting Treatments For Hepatitis

- Strong precedence for contraception, mental health, HIV treatment, HIV prevention, and others
- Adherence and stigma overcome
- Easy to use in public health
- Side effects prolonged
- Pharmacology can be uneven (injections)
- “Drug tail” can promote resistance
Cabotegravir and Rilpivirine Injected Monthly is Noninferior to Pills for Treating HIV Infection

**Table 2. Efficacy Outcomes at Week 48.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Long-Acting Therapy (N = 308)</th>
<th>Oral Therapy (N = 308)</th>
<th>Difference (95% CI)</th>
<th>Adjusted Difference (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat exposed population</td>
<td></td>
<td></td>
<td>percentage points</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA level — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 copies/ml</td>
<td>285 (92.5)</td>
<td>294 (95.5)</td>
<td>−2.9 (−6.7 to 0.8)</td>
<td>−3.0 (−6.7 to 0.7)</td>
</tr>
<tr>
<td>≥50 copies/ml;‡</td>
<td>5 (1.6)</td>
<td>3 (1.0)</td>
<td>0.6 (−1.1 to 2.4)</td>
<td>0.6 (−1.2 to 2.5)</td>
</tr>
<tr>
<td>Level not below threshold — no. (%)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Discontinued treatment for lack of efficacy — no. (%)</td>
<td>3 (1.0)</td>
<td>2 (0.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Discontinued treatment for other reason — no. (%)</td>
<td>1 (0.3)</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No virologic data — no. (%)</td>
<td>18 (5.8)</td>
<td>11 (3.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Withdrawn from trial because of adverse event or death‡</td>
<td>11 (3.6)</td>
<td>5 (1.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Withdrawn from trial for other reasons</td>
<td>7 (2.3)</td>
<td>6 (1.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HIV-1 RNA level &lt;200 copies/ml — no. (%)</td>
<td>286 (92.9)</td>
<td>295 (95.8)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Swindells NEJM 2020
Cabotegravir Injections Prevent HIV Infection Better Than Pills

Hazard ratio, 0.34 (95% CI 0.18–0.62)
P<0.001

Weeks since Enrollment

Cumulative Incidence (per 100 person y)

No. at Risk
TDF–FTC
Cabotegravir

2281 2132 2081 2019 1913 1765 1624 1494 1295 1132 965 817 644 517 401 311 231 150 85 33 0

2280 2138 2091 2031 1920 1776 1633 1489 1315 1124 957 798 644 503 401 318 243 173 111 42 0

Landovitz NEJM 2021: HPTN 083
The Goals of Long-Acting Therapies For Hepatitis C and B Differ

**HCV, test and cure**
- Couple with point of care diagnostics
- Eliminates linkage
- Discounts retention
- Enables public health approach
  - Corrections
  - Mobile curative unit
  - Benefits all, even cirrhotic persons

**HBV, sustain care/prevent**
- Replace daily nucleoside/tide
- Pair with coming anti-RNA
- Use in pregnancy to prevent mother-infant transmission
  - In 2019 birth dose vaccine given for only 43% of deliveries
  - But, pre-natal visits occur

Spearman Lancet Gastro 2017; Thompson Lancet Global Health 2021
**Assets**

- Pan-genotypic medications
- 6-12 week duration curative
- High resistance barrier
- High real-world efficacy
- No hypersensitivity (lead in)
- Donations to MPP (GP)
- Patient interest

**Challenges**

- Pharmacology
  - First pass hepatic uptake
  - Solubility
- Potency
There Are Plans To Develop Long-Acting HCV Treatments – Longevity

- Unitaid-funded project, Liverpool, Andrew Owen PI
- Nanoformulate glecaprevir and pibrentasvir
- Unclear required and/or possible bioavailability
- Prior use: Peg-IFN, albuferon, RG-101
- ?others
Survey of Persons Living with HCV Supports Development of Long-Acting Approaches

- 43-question survey for 1457 individuals with or at risk of HCV at 28 sites in 9 countries
- High willingness, and for some a preference, for long-acting treatments vs pills
- Differences by sex, age, and site
Glecaprevir 300 mg/d
- HCV protease inhibitor
- Liver metabolized; renal safe
- Tmax 5 hrs
- Mol Wt 838 g/mol
- Water sol <0.1 to 0.3 mg/ml
- Charge 0; Polar surface 204 Å²

Pibrentasvir 120 mg/d
- HCV NS5A
- Liver metabolized; renal safe
- Tmax 5 hrs
- Mol Wt 1113 g/mol
- Water sol <0.1 mg/ml
- Charge 0; Polar surface 200 Å²

Glecaprevir, ABT 493, Pharmacokinetics
Pibrentasvir Pharmacokinetics
HCV RNA Suppression At Most Doses (GT 1)

Lawitz AA Chemo 2016
HCV RNA Suppression At Most Doses (GT 1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100 mg (n = 8)</th>
<th>200 mg (n = 8)</th>
<th>cirrhosis (n = 8)</th>
<th>300 mg (n = 8)</th>
<th>400 mg (n = 8)</th>
<th>700 mg (n = 8)</th>
<th>15 mg (n = 8)</th>
<th>40 mg (n = 8)</th>
<th>120 mg (n = 8)</th>
<th>cirrhosis (n = 8)</th>
<th>400 mg (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>4.1</td>
<td>4.2</td>
<td>3.9</td>
<td>3.8</td>
<td>4.0</td>
<td>4.3</td>
<td>3.4</td>
<td>4.1</td>
<td>4.5</td>
<td>3.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.47</td>
<td>0.64</td>
<td>0.45</td>
<td>1.21</td>
<td>0.66</td>
<td>0.27</td>
<td>0.77</td>
<td>0.45</td>
<td>0.27</td>
<td>0.17</td>
<td>0.49</td>
</tr>
<tr>
<td>Greatest change</td>
<td>4.5</td>
<td>4.9</td>
<td>4.5</td>
<td>4.8</td>
<td>4.7</td>
<td>4.7</td>
<td>4.3</td>
<td>4.6</td>
<td>4.9</td>
<td>4.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Least change</td>
<td>3.2</td>
<td>3.3</td>
<td>3.2</td>
<td>0.9</td>
<td>2.6</td>
<td>3.7</td>
<td>1.9</td>
<td>3.2</td>
<td>4.0</td>
<td>3.7</td>
<td>3.6</td>
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</tbody>
</table>
High Rate of SVR at Most Doses Except Genotype 3

A  Genotype 1

B  Genotype 2

D  Genotype 4, 5, 6

<table>
<thead>
<tr>
<th>Dose</th>
<th>Duration (wk)</th>
</tr>
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<tbody>
<tr>
<td>GLE 200 PIB 120</td>
<td>12</td>
</tr>
<tr>
<td>PIB 40 120</td>
<td>12</td>
</tr>
<tr>
<td>GLE 300 PIB 120</td>
<td>8</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>120</td>
</tr>
<tr>
<td>200 PIB 120</td>
<td>12</td>
</tr>
<tr>
<td>200 RBV 12</td>
<td>8</td>
</tr>
<tr>
<td>300 PIB 120</td>
<td>12</td>
</tr>
<tr>
<td>Genotype 4, 5, 6</td>
<td>120*</td>
</tr>
<tr>
<td>300*</td>
<td>12</td>
</tr>
</tbody>
</table>
Data Suggest Tolerance For Glecaprevir and Pibrentasvir Dosing/Duration For Non-3 Genotypes
Data Suggest Tolerance For Glecaprevir and Pibrentasvir Dosing/Duration For Non-3 Genotypes

*Modified ITT replicates what would be expected for one-shot cure*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total patients</th>
<th>Cohort, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3 fibrosis</td>
<td>181</td>
<td>4</td>
</tr>
<tr>
<td>OST</td>
<td>301</td>
<td>4</td>
</tr>
<tr>
<td>CKD stage 4-5</td>
<td>59</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>PPI use</td>
<td>180</td>
<td>3</td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>100</td>
<td>2</td>
</tr>
</tbody>
</table>

SVR12 (% Patients)
Assets and Challenges to Develop Long-Acting HBV Treatments

**Assets**
- Need: 257 million infected
- Overlap with HIV nucleoside/tide inhibitors
- Potency
- High resistance threshold
- No hypersensitivity
- MPP
- Fit with long-acting anti-RNA
- Need when birth dose vaccine not possible
- Need for CAB/RIL switch

**Challenges**
- Pharmacology
- Toxicity at site (TAF)
- ?Teratogenecity (ETV)
Tenofovir Prodrug As Long-Acting HBV Treatments

• Multiple TAF implants tried
  – Biodegradable, polymeric, refillable pumps
  – Desired levels of TFV-DP sustained in PBMC (40 fmol/10⁶ cells) in some
  – ? Hepatocyte concentrations
  – Limited efficacy to prevent SHIV
  – Local reactions sometimes severe

• Transdermal matrix

Tenofovir Injectable Protide Stable Nanocrystals

- TFV protides (NM1TFV) created using docosanol masking ester to make lipophilic
- Uptake in monocyte derived macrophages
- Sustained TFV concentrations (102.4 ng/g) in liver 56 days post injection
- Sustained TFV-DP concentrations (328 fmol/10^6 cells) 56 days
- Expected toxicity
- Anti-HBV efficacy in several humanized mice

Cobb Nature Communications 2021; Denise CROI 2020
Tenofovir Injectable Protide Stable Nanocrystals

Cobb Nature Communications 2021; Denise CROI 2020
Tenofovir Injectable Protide Stable Nanocrystals

Cobb Nature Communications 2021; Denise CROI 2020
Tenofovir Injectable Protide Stable Nanocrystals

Analysis:
- Viral load - HBV DNA
- HBsAg, Alb, blood and tissue drug concentration

TK-NOG males

Intrasplenic hepatocytes transplantation

HBV infection

Month 2 3 4 6 8 weeks

Post drug administration

NM1NTZ + NM1TFV 75 mg/kg i.m.

Weeks after drug administration

Weeks before and after drug administration

HBV DNA, IU/mL

Human albumin, mg/mL
A long-acting 3TC ProTide nanoformulation suppresses HBV replication in humanized mice

Weimin Wang, MD\textsuperscript{a}, Nathan Smith, PhD\textsuperscript{a}, Edward Makarov, BS\textsuperscript{a}, Yimin Sun, PhD\textsuperscript{a}, Catherine L. Gebhart, PhD\textsuperscript{b}, Murali Ganesan, PhD\textsuperscript{c,d}, Natalia A. Osna, PhD\textsuperscript{c,d}, Howard E. Gendelman, MD\textsuperscript{a,c}, Benson J. Edagwa, PhD\textsuperscript{a,*}, Larisa Y. Poluektova, PhD\textsuperscript{a,*}

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\textsuperscript{b}Molecular Diagnostics Laboratory, Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, United States
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\textsuperscript{d}Research Service, Veterans Affairs Nebraska-Western Iowa Health Care System, Omaha, NE, United States

Revised 25 February 2020
E-CFCP, a 4’ Modified NRTI, Durably Inhibits HBV In Mice And Cell Culture

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC$<em>{50}^{qPCR</em>{cell}}$ (nM)</th>
<th>CC$_{50}^{MTT}$ (μM)</th>
<th>S.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV</td>
<td>1.8</td>
<td>73</td>
<td>40,556</td>
</tr>
<tr>
<td>TAF</td>
<td>58</td>
<td>37</td>
<td>638</td>
</tr>
<tr>
<td>Z-CFCP</td>
<td>414</td>
<td>&gt;500</td>
<td>&gt;1,208</td>
</tr>
<tr>
<td>E-CFCP</td>
<td>1.8</td>
<td>169</td>
<td>93,889</td>
</tr>
</tbody>
</table>

Higashi-Kuwata J Hepatol 2021
E-CFCP, A 4’ Modified NRTI, Durably Inhibits HBV In Mice And Cell Culture

Higashi-Kuwata J Hepatol 2021
Entecavir as Long-Acting HBV Treatment

- ETV implants tried
- Hot melt extrudates coated tablets put in rodents
- >180 days of continuous release
- Low concentration
- High local toxicity
- More success with modifications (eg A Chattergee, mCMQ657 in dogs)
Long-Acting Treatments For Hepatitis - Summary

- Multiple promising applications for both hepatitis B and C
- Wanted by patients; useful for multiple settings
- Huge market of ~257 million with HBV and ~58 million with HCV
- Possibilities exist with adaptations of current drugs
- Coordinated multidisciplinary approaches needed
Partners

• Unitaid: Longevity, Centre of Excellence in long-acting therapeutics [https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/](https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/)
• US NIH/LEAP [https://www.longactinghiv.org](https://www.longactinghiv.org)
• MPP [https://medicinespatentpool.org/](https://medicinespatentpool.org/)
• CHAI [https://www.clintonhealthaccess.org/](https://www.clintonhealthaccess.org/)
• Treatment action group [https://www.treatmentactiongroup.org/](https://www.treatmentactiongroup.org/)
Hepatitis Extended Release Long Acting Injectable/Implantable Medication (HEP ELIM) Research Group

- LA/ER consortium – Ethel Weld, Charlie Flexner, Sue Swindells
- Liverpool – Andrew Owen, Steve Rannard, and Marco Siccardi
- Epidemiology – Shruti Mehta, Sunil Solomon, Ethel Weld
- Clinical – Mark Sulkowski, Dave Thomas
- DAIDS - Carl Dieffenbach and Peter Kim
  - CFAR - 5P30AI094189 (Chaisson)
- Clinton Foundation – Paul Domanico, Christian Ramers, Sean Regan
- Arnab Chatterjee Scripps
Challenges in Developing Long-Acting Treatments For Hepatitis

- Desired features opposite oral
  - Need to modify existing or use alternative formulation/approach
- Modeling targets based on evidence from oral paradigms
- Uncertainties from studies for approved drugs
  - ? Dose and duration effective vs necessary in liver tissue
- Absence of animal models
- Industry perceptions
- Funding commitments
## Implants vs Injectables

From Weld and Flexner, *Curr Opinion HIV AIDS* 2020

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swift/easy removal at the end of treatment or in setting of adverse</td>
<td>Specialized device w need for training/sterility/equipment/procedure for</td>
</tr>
<tr>
<td>effects</td>
<td>insertion &amp; removal</td>
</tr>
<tr>
<td>No oral lead-in required</td>
<td>Minor surgical procedure required to remove</td>
</tr>
<tr>
<td>No oral TDF/FTC needed to protect during subtherapeutic PK ‘tail’</td>
<td>Must be removed at the end of product lifespan</td>
</tr>
<tr>
<td>Lower dose/day</td>
<td>Impossible to discern from palpation how long the device has been in place</td>
</tr>
<tr>
<td>Can remain in place for years (require less interaction with</td>
<td>Can migrate from original insertion site to a place where palpation is</td>
</tr>
<tr>
<td>healthcare system)</td>
<td>difficult (esp. in beagles)</td>
</tr>
<tr>
<td>More consistent and predictable drug release kinetics</td>
<td>Regulated as both a drug and a device</td>
</tr>
<tr>
<td>PK properties may not depend on injection site</td>
<td>More complex uptake into generic marketplaces</td>
</tr>
<tr>
<td>Palpable under skin indicating its presence</td>
<td></td>
</tr>
<tr>
<td>Radio-opaque for visualization in case of unintended subcutaneous migration</td>
<td></td>
</tr>
<tr>
<td>Biodegradable versions also possible</td>
<td>Visibility (arm) &amp; possible stigma</td>
</tr>
<tr>
<td>Avoid high injection volumes</td>
<td></td>
</tr>
</tbody>
</table>
Extended Release HCV Treatment Options

Glecaprevir
- HCV protease inhibitor
- Liver metabolized; renal safe
- Tmax 5 hrs
- Mol Wt 838 g/mol
- Water sol <0.1 to 0.3 mg/ml
- Charge 0; Polar surface 204 Å²

Pibrentasvir
- HCV NS5A
- Liver metabolized; renal safe
- Tmax 5 hrs
- Mol Wt 1113 g/mol
- Water sol <0.1 mg/ml
- Charge 0; Polar surface 200 Å²

Extended Release HCV Treatment Options

Sofosbuvir
- HCV polymerase inhibitor
- Prodrug converted to tri-Phos within liver and susceptible to esterases
- Tmax 0.5-2 hrs
- Mol Wt 529 g/mol
- Water sol 105 mg/L
- Charge 0; Polar surface 153 A²

Daclatasvir
- HCV NS5A
- Liver metabolized; renal safe
- Tmax 2 hrs
- Mol Wt 739 g/mol
- Water sol >700 mg/ml
- Charge 0; Polar surface 175 A²

Glecaprevir and Pibrentasvir Selected

- Pangenotypic
- Already FDA approved
- Highly effective in 8 weeks
- "forgiveness" in real-world studies
- Safe and no hypersensitivity (need for test dose)
- In MPP
Short Duration, Low Dose Glecaprevir and Pibrentasvir Efficacious For Non-3 Genotypes

- **Genres**:
  - Genotype 1
    - GLE: 200, 200, 300
    - PIB: 120, 40, 120
    - Duration (wk): 12, 12, 8
    - Patients (%): 100, 100, 100
  - Genotype 2
    - GLE: 300, 200, 200
    - PIB: 120, 120, 120
    - RBV: 120
    - Duration (wk): 12, 12, 8
    - Patients (%): 100, 100, 100
  - Genotype 4, 5, 6
    - GLE: 300
    - PIB: 120
    - Duration (wk): 12
    - Patients (%): 100

Kwo J Hep 2013
Genotype 1 HCV

Glecaprevir

Pibrentasvir

Mean Change from Baseline (HCV RNA log₁₀ IU/mL)

Time Post First Dose (hours)

- 100 mg (n=8)
- 200 mg (n=8)
- 300 mg (n=8)
- 300 mg, cirrhosis (n=8)
- 15 mg (n=8)
- 40 mg (n=8)
- 120 mg, cirrhosis (n=8)
- 120 mg (n=8)
A

GT1
N = 40
GLE 200 mg
PIB 120 mg

GT1
N = 39
GLE 200 mg
PIB 40 mg

GT2
N = 25
GLE 300 mg
PIB 120 mg

GT2
N = 24
GLE 200 mg
PIB 120 mg

GT2
N = 25
GLE 200 mg
PIB 120 mg
RBV Weight-based

GT3
N = 30
GLE 300 mg
PIB 120 mg

GT3
N = 30
GLE 200 mg
PIB 120 mg
RBV Weight-based

GT3
N = 31
GLE 200 mg
PIB 120 mg
RBV Weight-based

GT3
N = 30
GLE 200 mg
PIB 40 mg

Day 0  12 wk  24 wk  36 wk
Open-label treatment

SVR12 assessment
A

Genotype 1

GLE 200
PIB 120

100
90
80
70
60
50
40
30
20
10
0

Patients (%)

GLE 200
GLE 300

B

Genotype 2

100
90
80
70
60
50
40
30
20
10
0

Patients (%)

GLE 300
GLE 200
GLE 200 RBV

D

Genotype 4, 5, 6

GLE 300
GLE 120

100
90
80
70
60
50
40
30
20
10
0

Patients (%)

GLE 300
GLE 120

Duration (wk)

GLE 12
GLE 12
GLE 8

GLE 12
GLE 12
GLE 12

GLE 12

SVR4
SVR12
SVR12, mITT
Table 2. Virologic response during and after treatment and reasons for non-response.∗

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prior Tx history</th>
<th>Dose GLE + PIB</th>
<th>Tx duration (weeks)</th>
<th>Sustained virologic response, n/N (%)</th>
<th>Reasons for non-response, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTW4</td>
<td>PTW12†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Virologic failure</td>
<td>Non-virologic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Breakthrough</td>
<td>Relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Missing SVR12 data</td>
<td>Early Tx discontinuation</td>
</tr>
<tr>
<td>1</td>
<td>TN or PR 200 + 120</td>
<td>12</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TN or PR 200 + 40</td>
<td>12</td>
<td>38/39 (97)</td>
<td>38/39 (97)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>TN or PR 300 + 120</td>
<td>8</td>
<td>34/34 (100)</td>
<td>33/34 (97)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TN or PR 200 + 120</td>
<td>12</td>
<td>24/25 (96)</td>
<td>24/25 (96)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TN or PR 200 + 120 + RBV</td>
<td>12</td>
<td>25/25 (100)</td>
<td>25/25 (100)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>TN or PR 300 + 120</td>
<td>8</td>
<td>53/54 (98)</td>
<td>53/54 (98)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TN or PR 300 + 120</td>
<td>12</td>
<td>28/30 (93)</td>
<td>28/30 (93)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TN or PR 200 + 120</td>
<td>12</td>
<td>28/30 (93)</td>
<td>28/30 (93)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TN or PR 200 + 120 + RBV</td>
<td>12</td>
<td>29/31 (94)</td>
<td>29/31 (94)</td>
<td>1 (3)</td>
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<td>TN or PR 200 + 40</td>
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High Pangenotypic Efficacy of Oral Glecaprevir (300mg) and Pibrentasvir (120mg)