A New Perspective On HCV Drug Resistance
Multiple Paths To Sustained Virologic Response:
Resistance Can Be Overcome

Slide set prepared by the
Forum for Collaborative HIV Research and
Hepatitis C Virus Drug Development Advisory Group
The Slide Deck

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Goals of the slide deck: Develop perspective on HCV viral resistance and what it means for future HCV therapy

The educational materials in this slide set:
1) Provide context for viral resistance in HCV
2) Address concerns around HCV resistance
3) Educate on prevention and how to overcome resistance to antiviral drugs

This educational material complements:
1) A primer of HCV viral lifecycle
2) A primer on how mutations are created and resistant variants are selected
Key points

1. HCV Is Curable
   a) Wild-type and resistant virus can be eliminated

2. Resistant Variants Occur Naturally
   a) Resistant variants to antiviral drugs exist before treatment
   b) Resistant variants can be selected/enriched during treatment
   c) Drug resistance may emerge during treatment with all (or any) antiviral drugs
   d) Resistance is a consequence of treatment failure, but is not always the cause

3. Maximize Response, Minimize Resistance
   Many factors contribute to treatment response: virus, drug and patient
   a) The **genetic barrier** is related to the number and type of mutations required to overcome the clinical activity of a regimen. Mutations that decrease viral fitness (defined in slide #30) increase the resistance barrier.
   b) The **pharmacologic barrier** is increased by higher potency and higher drug levels
   c) **Tolerability** of a regimen and **patient adherence** are critical for treatment success
HCV sequences are more genetically diverse than HBV or HIV.
Unlike HIV and HBV, HCV is curable

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Mutation Rates</td>
<td>Very High</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Virions Produced Daily</td>
<td>$10^{10}$</td>
<td>$10^{13}$</td>
<td>$10^{12}$</td>
</tr>
<tr>
<td>Viral Genetic Archiving</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Drug Targets</td>
<td>Multiple</td>
<td>One</td>
<td>Multiple</td>
</tr>
<tr>
<td>Cure With Current Therapy?</td>
<td>NO (Integrated viral DNA)</td>
<td>NO (cccDNA)</td>
<td>YES</td>
</tr>
<tr>
<td>Current Therapeutic Goal</td>
<td>Lifelong suppression</td>
<td>Lifelong suppression</td>
<td><strong>Cure</strong>: clearance from plasma and liver</td>
</tr>
</tbody>
</table>

Adapted from Soriano V. JAC. 2008; 62(1): 1-4
HBV, HIV and HCV have targeted drugs approved or in development.
HCV enzymes provide good targets for drug development

HCV Replicase

Structural

Protease

RNA Polymerase

HCV drug classification and development

Covalent

Slow reversible

- e.g. telaprevir, boceprevir*

Irreversible

- e.g. AVL-192†

NS3 Protease

- Non-covalent
  - Linear
    - ACH 1625
    - ABT 450/R
    - Asunaprevir (BMS 650032)
    - BI 201335
    - GS 9451
  - Macroyclic
    - Danoprevir (RG7227/ITMN 191)
    - GS 9256
    - MK 5172
    - TMC 435
    - Vaniprevir (MK 7009)

NS5A

- ABT 267
- AZD 7295
- GS 5585
- ACH 2928
- BMS 790052
- PPI 461

NS5B Polymerase

- Palm
  - ABT 333
  - ABT 072
  - GS 9190
  - Surobuvir (ANA 598)
- Thumb 1
  - BI 207127
  - BMS 791325
  - TMC 647055
- Thumb 2
  - BMS 791325
  - Filibuvir
  - GS 9669
  - VX 222

Active site

- GS 6620
- IDX 184
- INX 189
- PSI 7977
- PSI 938
- RG 7128
- TMC 649128

TLR-7

- ANA 773

Cyclophilin

- Debio 025
- SCY 635

* Approved 2011; † Preclinical

Compounds in Ph 1-3 trials (January 2012)
Examples of HCV NS5B polymerase inhibitors and their binding sites

**Active Site:**
- Nucleosides
  - IDX 184
  - PSI 7977
  - RG 7128

**Allosteric:**
- Thumb 1
  - BI 207127
  - TMC 647055
- Palm
  - ABT 072
  - ABT 333
  - ANA 598
- Allosteric GTP
  - ABT 072
  - ABT 333
  - ANA 598
- Allosteric:
  - Unclear
  - GS 9669
  - VX 222
- Allosteric:
  - Thumb 1
    - BI 207127
    - TMC 647055
  - Thumb 2
    - Thiophene
    - Filibuvir
    - GS 9669
    - VX 222
  - Allosteric GTP
    - ABT 072
    - ABT 333
    - ANA 598
Nucleotide analogs are chain-terminators

Nucleotide Chain-terminator (e.g., PSI-7977)

RNA chain cannot be elongated when analog is inserted

Mechanism of action, e.g., chain termination, does not rely on enzyme homology across HCV genotypes

Both pyrimidine and purine analogs can inhibit activity

Antiviral activity of nucleotides is conserved against PI-resistant or non-nuc polymerase inhibitor resistant virus

Mechanism of action and key attributes of cyclophilin inhibitor, alisporivir

Inhibition of Hepatitis C virus (HCV) replication

Key attributes of host-targeting antiviral (HTA), alisporivir

- Mechanism of action different from direct acting antivirals (DAA)
- High barrier for HCV resistance
- Compelling efficacy with pan-genotypic coverage
Mechanism of action of NS5A replication complex inhibitors

- Role of NS5A in HCV replication remains elusive
- Precise mechanism of action in HCV replication currently under investigation
- NS5A inhibitor, BMS-790052 and similar chemotypes:
  - Bind to HCV NS5A protein in cell culture\(^1\)
  - Interact with the NS5A N-terminus of Domain 1\(^2\)
  - Block both cis- and trans-acting functions of NS5A\(^3\)
  - Alter the subcellular localization of NS5A into functional replication complexes therefore suppressing HCV RNA replication\(^4\)

All antiviral drugs can select resistant variants

Amino acid changes conferring resistance to NS3 protease and NS5B polymerase inhibitors
Nucleotide changes result in codon changes that can confer resistance to a drug.

Example: Codon 155 of the HCV Protease

Consensus “wild type” amino acid: Arginine (R)

Resistant variant amino acid: Lysine (K)

AGG\textsubscript{155} → AAG\textsubscript{155}

G \rightarrow A

R155 \rightarrow R155K
Codon changes may result in amino acid changes, which can change the interaction with a drug.

- Decreased binding of a drug results in decreased inhibition of viral replication.
- Decreased binding to the natural ligand results in decreased viral replication.
Resistance often results in reduced viral fitness.

The A156T variant is less fit than WT. Steric hindrance prevents the substrate from efficiently binding to the mutant protease active site.
Resistance mutations associated with NS5B polymerase nucleoside and non-nucleoside inhibitors

**Nucleoside Inhibitors**
- R1626: S96T \(\textit{(in vitro)}\)
- R7128: S282T \(\textit{(in vitro)}\)

**Non-Nucleoside Inhibitors**
- Filibuvir: M423T (in patients)
- HCV796: C316Y/N, S365T/A (in patients)
- ABT333: S556G (in patients); C316Y, Y448C \(\textit{(in vitro)}\)

- Though \textit{in vitro} studies with \textbf{nucleoside analogs} have demonstrated the selection of resistant variants, they have not been observed in patients with HCV infection.

- Wide range in frequency of resistance mutations associated with \textbf{non-nucleoside analogs}. While many are only observed \textit{in vitro}, some are also associated with viral breakthrough in clinical trials.
Changes in drug susceptibility: Detection of resistance

- Sequence analysis and phenotype analysis are used in combination to identify/discover resistance pathways.

- **Sequence Analysis:** Detects specific amino acid substitutions relative to a pre-treatment or standard reference sequence that are known to decrease susceptibility to antiviral agents.
  - Can identify substitutions known to impact drug susceptibility
  - Can identify novel drug resistance pathways associated with treatment failure

- **Phenotypic Analysis:** Determines drug concentrations needed to inhibit viral replication.
  - Effective concentration (EC): drug concentration required to inhibit viral replication by 50% or 90% (EC$_{50}$ or EC$_{90}$)
  - Less susceptible (resistant) viruses will require *more* drug to be inhibited, thus an *increase* in EC$_{50}$ or EC$_{90}$
Resistant Variants Occur Naturally
Resistant variants are present before treatment

- HCV exists as a mixture of populations of genetically distinct, but closely related, virions in every patient\(^1\)
  - \(\sim 10^{12}\) viruses produced per day
  - \(\sim 1\) nucleotide mutation per virus produced
  - All possible single nucleotide-mutant viruses, and all combinations of double nucleotide-mutant viruses, are thought to preexist before treatment in most patients\(^2\)

- Most resistant variants are relatively unfit and are undetectable prior to therapy with current technology\(^3,4\)

Resistant variants can be selected during treatment.

Potent antiviral therapy eliminates sensitive variants.

Resistant variants are uncovered which can then expand.
Frequent monitoring of HCV RNA levels can detect treatment failure and resistance.

Patients have viral variants with different levels of resistance to a drug.
Say “NO” to CRAP therapy

Continued Replication under Antiviral Pressure

- Continued replication in the presence of drug will likely lead to further evolution of the viral population.

- In theory, further evolution can result in a more fit, drug-resistant viral population that may remain enriched in the patient, even in the absence of drug pressure.

- This should be prevented by discontinuing the direct acting antiviral if a patient has a confirmed increase in HCV RNA levels while adhering to therapy.
Potential fate of resistant variants after treatment

HCV RNA

- **Treatment**
  - **Return to pre-treatment state**
  - **Persistence of resistant virus**

**Sensitive virus**

**Resistant virus**

HCV DrAG ResisSS 2012 v.1 26 www.hivforum.org
Long-term follow-up of patients with resistant variants after failing treatment

- Population and clonal amino acid analyses of HCV from patients with protease inhibitor resistance indicate that drug-resistant patient viral populations may return to pre-treatment levels over time in many patients.

Patient viral populations may return to pre-treatment state over time

- For protease inhibitors (telaprevir or boceprevir), 59-89% of patients no longer had detectable resistant variants after a median follow-up time of 25-29 months.

- Understanding the clinical significance of treatment-acquired resistance requires studies in which patients who experienced virologic failure while on a direct acting antiviral (DAA), are re-treated with a DAA regimen.
Many factors contribute to response
Virologic barriers to resistance

Genetic barrier

• Number and type of nucleotide changes required for a virus to acquire clinical resistance to an antiviral regimen\(^1\)

Viral fitness

• Relative capacity of a viral variant to replicate in a given environment

• Resistance mutations frequently compromise viral function and thus reduce viral fitness compared to wild-type in a drug-free environment

Multiple nucleotide changes maybe required to create a single amino acid change.

Example: Codon 155 of the HCV Protease

<table>
<thead>
<tr>
<th>Subtype 1a</th>
<th>Subtype 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGG → AAG</td>
<td>AGG → AAG</td>
</tr>
<tr>
<td>(R155) (R155K)</td>
<td>(R155) (R155K)</td>
</tr>
<tr>
<td>1 step</td>
<td>2 steps</td>
</tr>
</tbody>
</table>

HCV DrAG ResisSS 2012 v.1
Clinical implications of genetic barrier to resistance – acquisition of protease inhibitor resistant variant V36M+R155K

Subtype 1a
V36M+R155K variant observed clinically\(^1,2\)

Subtype 1b
V36M+R155K variant not observed clinically

### Resistant profiles in non-SVR patients

<table>
<thead>
<tr>
<th>Variant</th>
<th>% of sequenced patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subtype 1a</td>
</tr>
<tr>
<td>WT</td>
<td>16%</td>
</tr>
<tr>
<td>V36M</td>
<td>10%</td>
</tr>
<tr>
<td>R155K</td>
<td>20%</td>
</tr>
<tr>
<td>V36M+R155K</td>
<td>46%</td>
</tr>
<tr>
<td>V36A</td>
<td>3%</td>
</tr>
<tr>
<td>T54A</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>A156S/T</td>
<td>3%</td>
</tr>
</tbody>
</table>

Note: Information from a subset of patients in trials. Not a complete list of treatment-emergent substitutions observed in clinical trials. See drug prescribing information for a complete list.

Sullivan, J. *et al.* EASL, Berlin - March 31, 2011 (oral presentation)
Combination drug regimens increase the genetic barrier to resistance

Eliminate variants with addition of Peg-IFNα/RBV or DAA(s) with non-overlapping resistance
Lack of cross-resistance between Peg-IFNα/RBV &/or a combination of antiviral agents may provide an opportunity for elimination of resistant variants

<table>
<thead>
<tr>
<th>Target</th>
<th>Variant</th>
<th>NS3 Covalent: Slow Reversible</th>
<th>NS3 Non-covalent: Linear and Macrocyclic</th>
<th>NS5A inhibitor</th>
<th>NS5B nucleoside</th>
<th>NS5B Palm</th>
<th>NS5B Thumb 1</th>
<th>NS5B Thumb 2</th>
<th>Peg-IFN</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3 Protease</td>
<td>V36M</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td></td>
<td>T54A</td>
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<tr>
<td></td>
<td>R155K</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
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<td>S</td>
<td>S</td>
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</tr>
<tr>
<td></td>
<td>A156T</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td></td>
<td>D168V</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS5A</td>
<td>L31V</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Y93H</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>NS5B</td>
<td>S282T</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>C316Y</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td></td>
<td>M414T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>R422K</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>M423T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>P495S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Note this is not a comprehensive list of known HCV direct acting antivirals (DAA) resistance pathways. 4 fold shift represents arbitrary cutoffs for illustrative purposes only.

S = Susceptible
(< 4 fold shift in HCV replicon EC50)

R = Resistant
(>4 fold increase in EC50)
Terms used to guide treatment response in HCV infection

- **HCV RNA undetectable**: HCV RNA level below the limit of detection of a particular assay (not necessarily to be interpreted as HCV RNA “negative” or having cleared HCV for patients on treatment)

- **RVR (Rapid virologic response)**: Undetectable HCV RNA at week 4 of therapy
- **eRVR (Extended RVR)**: Undetectable HCV RNA at weeks 4 and 12 of therapy

- **EVR (Early virologic response)**: >2log_{10} decline in HCV RNA at week 12 of therapy (also known as partial EVR, pEVR)
- **cEVR (Complete EVR)**: Undetectable HCV RNA at week 12 of therapy

- **SVR (Sustained virologic response)**: Undetectable HCV RNA 24 weeks after treatment cessation

- **Null responder**: < 2log_{10} IU/mL decline in HCV RNA at week 12 of therapy

- **Failure of HCV therapy**: Persistence of HCV RNA in serum after therapy

Shiffman M.L. *Curr Gastro Reports*, 2006; 8:46-52
Resistant variants can be eliminated with a combination drug regimen

3 patients with naturally occurring protease inhibitor-resistant (V36M) variants attained SVR with protease inhibitor + Peg-IFNα/RBV

![Graph showing HCV RNA levels over weeks with SVR indicated]
Patients with protease inhibitor-resistant variants can respond to Peg-IFNa/RBV

Unpublished data, example from telaprevir PROVE2 study
Patients with naturally occurring polymerase inhibitor-resistant variants can respond to protease inhibitor + Peg-IFNα/RBV

<table>
<thead>
<tr>
<th>Target</th>
<th>Variant</th>
<th>NS3 Covalent: Slow Reversible</th>
<th>NS3 Non-covalent: Linear and Macroyclic</th>
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<th>NS5B nucleoside</th>
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<th>NS5B Thumb 1</th>
<th>NS5B Thumb 2</th>
<th>Peg-IFN</th>
<th>RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS5B</td>
<td>R422K</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>M423T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Unpublished data, examples from telaprevir PROVE1 study

Below sequencing assay LOD

HCV RNA (IU/mL)

Weeks

HCV RNA LOD (10 IU/mL)
Pharmacological barriers to resistance

Higher potency
- Create/use drugs with stronger binding affinity

Higher drug levels
- Create/use drugs with longer half-life
- Increase target organ exposure
- Take recommended dosage at recommended dosing intervals
- Follow recommended food intake requirements

Improved tolerability and adherence
- Create/use drugs with minimal drug/drug interactions
- Create drugs with favorable safety profiles and convenient dosing schedules
- Develop better side effect management protocols

Combination drug regimens
- Develop potent regimen of direct-acting antiviral drugs with or without Peg-IFNa/RBV
Resistance is not an all or none phenomenon

- Clinical resistance occurs if drug levels are not sufficient to inhibit viral replication
- Highly resistant viruses need very high drug levels (may not be achievable) to inhibit their replication

![Graph showing mean plasma levels of drug over time](image-url)
Importance of drug levels over time

Drug trough levels must be sufficient to suppress viral replication
Resistance emerges as a result of treatment failure

Baseline contains WT + resistant variants in treatment naïve individuals

- Activity of Peg-IFNα/RBV inadequate to suppress NS3 inhibitor-resistant variants
- Activity of Peg-IFNα/RBV suppresses NS3 inhibitor-resistant variants

Kwo PY., et al  Hepatology, 2008;48:1027A
Contribution of Peg-IFNα/RBV to SVR

1. Baseline contains WT + resistant variants in treatment naïve individuals
2. Protease Inhibitor + Peg-IFNα + RBV
   - SVR ~ 70%
3. Protease Inhibitor + Peg-IFNα + RBV
   - SVR ~ 46%
4. Peg-IFNα + RBV
   - SVR ~ 36%

Peg-IFNα/RBV (PR) treatment experienced patients can be re-treated

<table>
<thead>
<tr>
<th>Prior PR response</th>
<th>Retreatment SVR rate (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR</td>
</tr>
<tr>
<td>Relapse</td>
<td>22%</td>
</tr>
<tr>
<td>Partial</td>
<td>15%</td>
</tr>
<tr>
<td>Null</td>
<td>5%</td>
</tr>
</tbody>
</table>

New regimen: Protease Inhibitor + Peg-IFNα+RBV

Definitions

**Prior relaper**: Achieved undetectable HCV RNA at end of treatment, but failed to achieve SVR

**Prior partial responder**: Achieved ≥2 log drop in HCV RNA at week 12 of prior therapy, but never became undetectable while on treatment

**Prior null responder**: Achieved <2log drop in HCV RNA at week 12 of prior therapy

See prescribing information of approved therapies for treatment recommendations and available data supporting re-treatment of specific patient populations
IL28B genotype: Is there a role in the era of direct acting antivirals (DAAs)?

- Certain single nucleotide polymorphisms (SNPs) upstream of \textit{IL28B} gene are associated with the rate of SVR in patients treated with Peg-IFNα/ RBV:
  - SNP rs12979860: favorable allele=C, unfavorable allele=T
  - SNP rs8099917: favorable allele=T, unfavorable allele=G
- IL28B genotype can have an impact on the efficacy of a Peg-IFNα/RBV/DAA regimen
- IL28B genotype has also recently been shown to affect the activity of an interferon-free IFN-free, combination DAA regimen, although its impact is likely dependent on the anti-HCV potency and durability of the regimen
IL28B genotype effect on SVR in genotype-1 treatment-naïve patients

Certain single nucleotide polymorphisms (SNPs) upstream of *IL28B* gene are associated with SVR in patients treated with Peg-IFNα/RBV (PR)\(^1-3\):

- SNP rs12979860: favorable allele=C, unfavorable allele=T

<table>
<thead>
<tr>
<th>IL28B SNP rs12979860</th>
<th>PR (Ideal)</th>
<th>Telaprevir(^5) (ADVANCE)</th>
<th>Boceprevir(^6) (SPRINT-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT(^4) Population</td>
<td>Adherent(^3) Population</td>
<td>TVR/PR</td>
<td>PR control</td>
</tr>
<tr>
<td>CC</td>
<td>69%</td>
<td>~79%</td>
<td>90%</td>
</tr>
<tr>
<td>CT</td>
<td>33%</td>
<td>~38%</td>
<td>71%</td>
</tr>
<tr>
<td>TT</td>
<td>27%</td>
<td>~26%</td>
<td>73%</td>
</tr>
</tbody>
</table>

* Includes BOC/ RGT and BOC/ PR48 arms, mITT

1 Tanaka Y., *et al.* *Nature Genetics*, 2009; 41:1105-1109
6 VICTRELIS™ [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2011

Footnotes: 1) Data from ADVANCE and SPRINT-2 based only on subjects who consented to IL28B genotype analysis; 2) Results are confounded by variable treatment durations in active and control arms
IL28B Genotype Can Influence Activity of an IFN-free Regimen: Proportion of GT1 patients with HCV RNA Not Detected at Treatment week 12 by IL28B Genotype and Subtype (per protocol analysis)

<table>
<thead>
<tr>
<th></th>
<th>GT-1a</th>
<th>GT-1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI201335 + BI207127TID + RBV</td>
<td>22/25</td>
<td>39/61</td>
</tr>
<tr>
<td>BI201335 + BI207127BID + RBV</td>
<td>6/7</td>
<td>10/22</td>
</tr>
<tr>
<td>BI201335 + BI207127TID, no RBV</td>
<td>3/3</td>
<td>2/9</td>
</tr>
</tbody>
</table>

* *1L28B SNP rs12979860

BI 201335: Protease Inhibitor
BI 207127: Polymerase Inhibitor

Zeuzem et al, 2011 AASLD Annual Meeting Boston, USA. Late-breaker#15
• There is an urgent need for safe and effective treatment regimens that do not include Peg-IFNa and/or RBV.

• In a Peg-IFNa/RBV/DAA regimen, Peg-IFNa/RBV enhance DAA antiviral durability by suppressing DAA-resistant variants.

• Numerous clinical trials investigating the efficacy of combination DAA regimens to replace Peg-IFNa and/or RBV have been conducted or are in progress.

• Challenge: *Anti-HCV potency without durability ≠ SVR*

• Lessons learned from trials conducted to date:
  - Two potent, low resistance barrier DAAs are most likely not adequate to achieve SVR for a majority of patients.
  - Virologic breakthrough with a combination DAA regimen can occur early (few days) or late (2-3 months); only SVR proves efficacy.
  - HCV genotype/subtype can have a major impact.
  - Inclusion of RBV may have a role in combination DAA therapy.
Maximize Response, Minimize Resistance
A balance of multiple factors contribute to SVR

**Virus**
- High genetic barrier
- Low viral fitness of resistant variants
- IFN-responsive

**Treatment Regimen**
- Good tolerability
- Small pill burden
- Short duration
- Better potency
- Better PK

**Patient**
- IL28B “C/C”
- Young age
- Low BMI
- Adherent

**Virus**
- Drug resistance
- High viral load
- Genotype 1

**Treatment Regimen**
- Poor tolerability
- Adverse events
- Drug interactions

**Patient**
- IL28B “T/T or C/T”
- HIV coinfection
- Substance abuse
- Insulin resistance
- Elderly
- High BMI
- Poor adherence
Regimen characteristics that increase likelihood of achieving SVR

- Combination regimens
- Overcome virologic resistance
- Adherence-friendly regimen
- Shorter regimen
- Minimal drug-drug interactions
- Good tolerability
- Potent viral suppression
- Combination regimens
Patient factors can provide obstacles to achieving SVR

Modifiable Factors:
- Non-adherence
- Unmanaged Depression
- Fatty Liver
- Insulin resistance

Unmodifiable Factors:
- Genetics (IL28B TT/CT)
- African American
- Male
- Age > 50yrs
Adherence shifts the balance for SVR

Doctors and patients can maximize response:
- Right dose of drug
- At the right time
- Follow dietary recommendations
- Actively manage side effects
Future drug regimens could improve SVR rates

Industry, academia, regulators and community can work together to improve the quality of drugs available for HCV infected patients

**Improved Regimen**
- Improved tolerability
- More convenient dosing
- Smaller pill burden
- Shorter duration

SVR
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Scott Seiwert
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Mark Sulkowski
Tracy Swan
Theresa Turcotte
David Wyles
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Selected Bibliography contd.

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Ralston R. et al. Long-term Follow-up of Patients Treated with Boceprevir in Combination with PEG-Intron/Ribavirin (P/R): Durability of Responses and Rates of Reversion of Resistance Mutations. *International HIV and Hepatitis Drug Resistance Workshop, 2010*


Zeuzem S. et al. Long-Term Follow-up of Patients with Chronic Hepatitis C Treated with Telaprevir in Combination with Peginterferon Alfa-2a and Ribavirin: Interim Analysis from the EXTEND Study. *AASLD 2010*
Please send comments to:

Nina Mani, FCHR
nmani@hivforum.org
Resistant variants can be eliminated with a combination drug regimen

<table>
<thead>
<tr>
<th>Target</th>
<th>Variant</th>
<th>NS3 Covalent: Slow Reversible</th>
<th>NS3 Non-covalent: Linear and Macrocyclic</th>
<th>NS5A inhibitor</th>
<th>NS5B nucleoside</th>
<th>NS5B Palm</th>
<th>NS5B Thumb 1</th>
<th>NS5B Thumb 2</th>
<th>Peg-IFN</th>
<th>RBV</th>
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</thead>
<tbody>
<tr>
<td>NS3</td>
<td>V36M</td>
<td>R</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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</tr>
</tbody>
</table>

3 patients with naturally occurring protease inhibitor-resistant (V36M) variants attained SVR with protease inhibitor + Peg-IFNα/RBV

![Graph showing HCV RNA levels over weeks with SVR marker]
Patients with protease inhibitor-resistant variants can respond to Peg-IFNa/RBV

Patient with selected NS3 R155K variant achieved SVR with Peg-IFNa/RBV

- **S** Patient with selected NS3 R155K variant achieved SVR with Peg-IFNa/RBV

Initiation of Peg-IFNa/RBV regimen

Unpublished data, example from telaprevir PROVE2 study

**Note:** The table and diagram illustrate the response of patients with protease inhibitor-resistant variants to Peg-IFNa/RBV treatment. The **R** in the NS3 column indicates the presence of protease inhibitor-resistant variant R155K. The SVR marker indicates patients who achieved a sustained virologic response.
Patients with naturally occurring polymerase inhibitor-resistant variants can respond to protease inhibitor + Peg-IFNα/RBV

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<tbody>
<tr>
<td>NS5B</td>
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<td>R</td>
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</tbody>
</table>

Unpublished data, examples from telaprevir PROVE1 study

**Below sequencing assay LOD**

**Graph**: HCV RNA (IU/mL) vs. Weeks

- **HCV RNA LOD (10 IU/mL)**

**Legend**:
- R422K
- M423A
- M423I
- M423V
- Below sequencing assay LOD