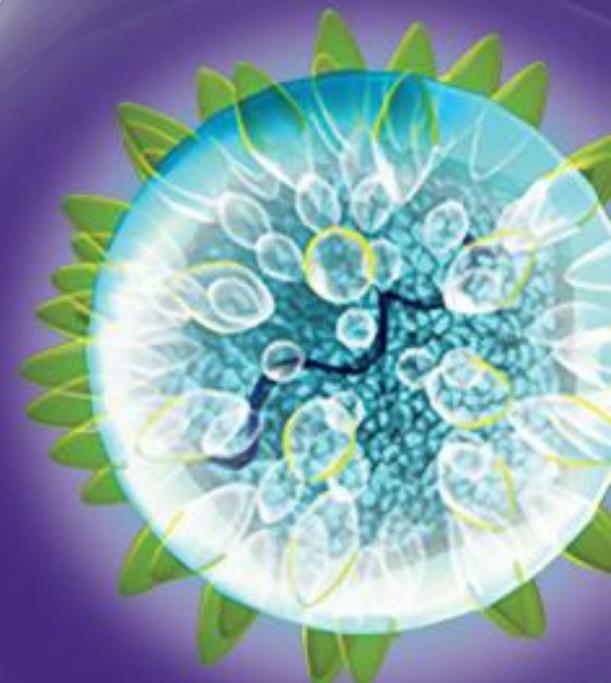


# Resistance in the Era of HCV Protease Inhibitors

*Antiviral drug resistance and the battle for a  
cure below the limit of detection*

Ann Kwong, PhD



CDC Symposium

“Identification, Screening and Surveillance of HCV Infections in  
the Era of Improved Therapy for Hepatitis C”

December 1, 2011

Atlanta, GA



# Agenda

- Overview on HCV resistance
- Case study: Telaprevir/Peg IFN alfa/RBV (INCIVEK™) clinical virology

# HCV Resistance: Key Points

## 1. HCV is curable

- a) Wild-type and resistant virus can be eliminated
- b) The presence of resistant virus does not preclude successful treatment

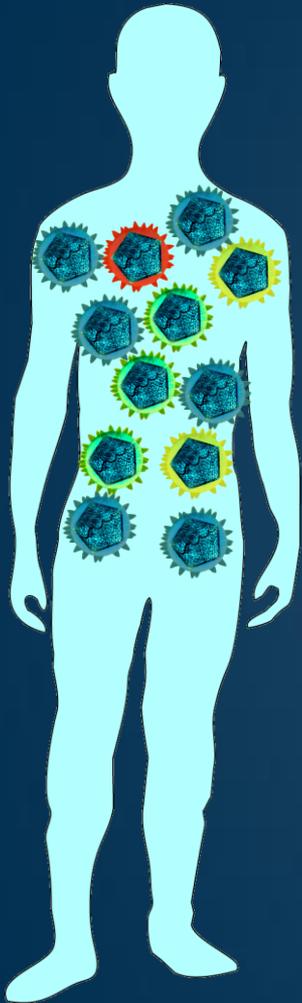
## 2. Resistance is natural

- a) Resistant variants to antiviral drugs exist before treatment
- b) Resistant variants can be selected during treatment
- c) Resistance is a marker for treatment failure, but not always the cause

## 3. Maximize response, minimize resistance

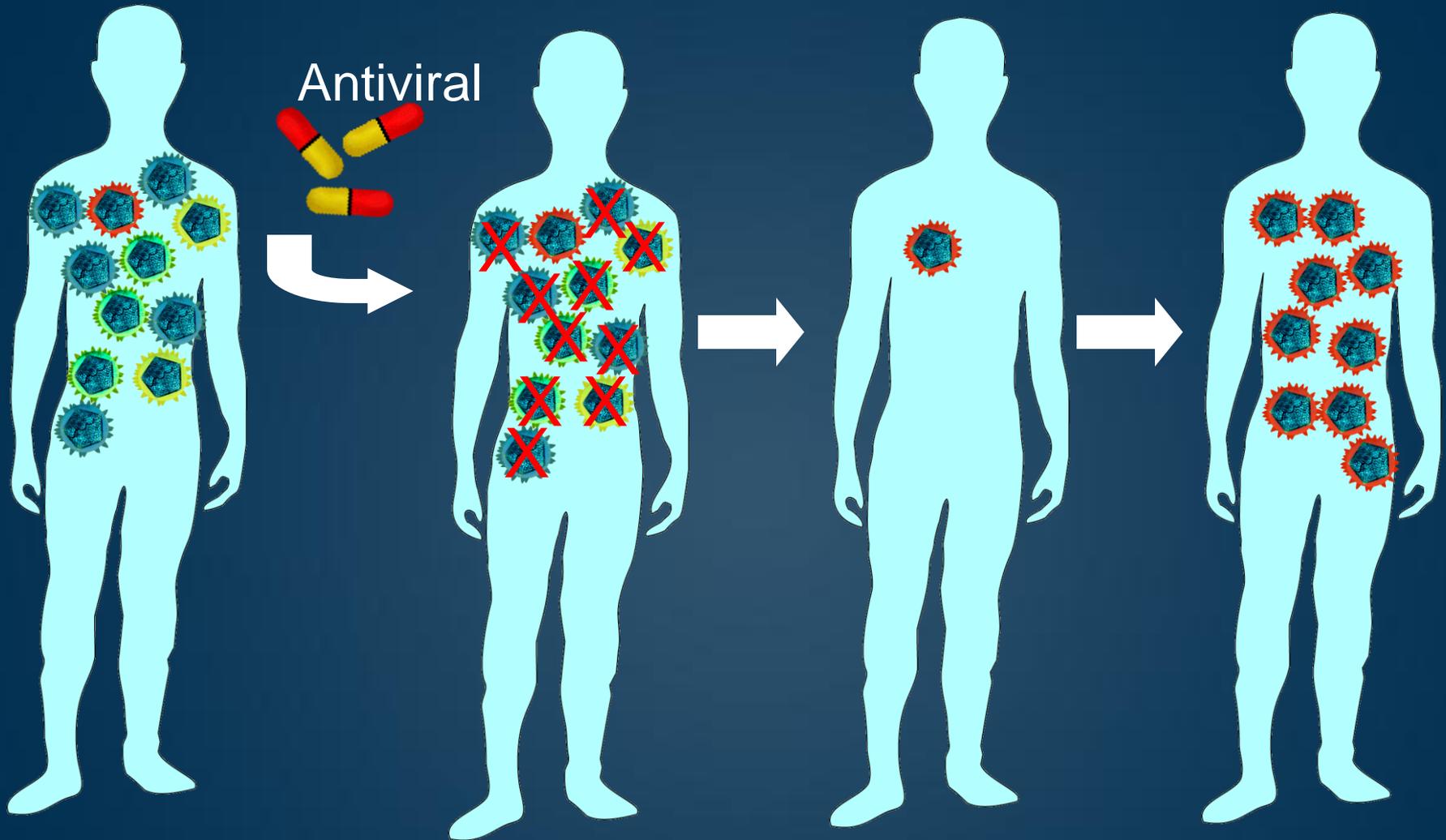
- a) Many factors contribute to response: virus, drug and patient
- b) No cross-resistance between different mechanisms of action

# Resistant variants are present before treatment



- Plasma contains ~ 1,000,000 HCV per mL
- In most patients, naturally occurring resistant variants are below the limit of detection for sequencing (~1,000 HCV per mL)
- Most resistant variants are very unfit and are not detected prior to therapy
- Patients with detectable resistant variants prior to therapy are rare (<2% each)<sup>1,2</sup>

# Resistant variants are selected during treatment

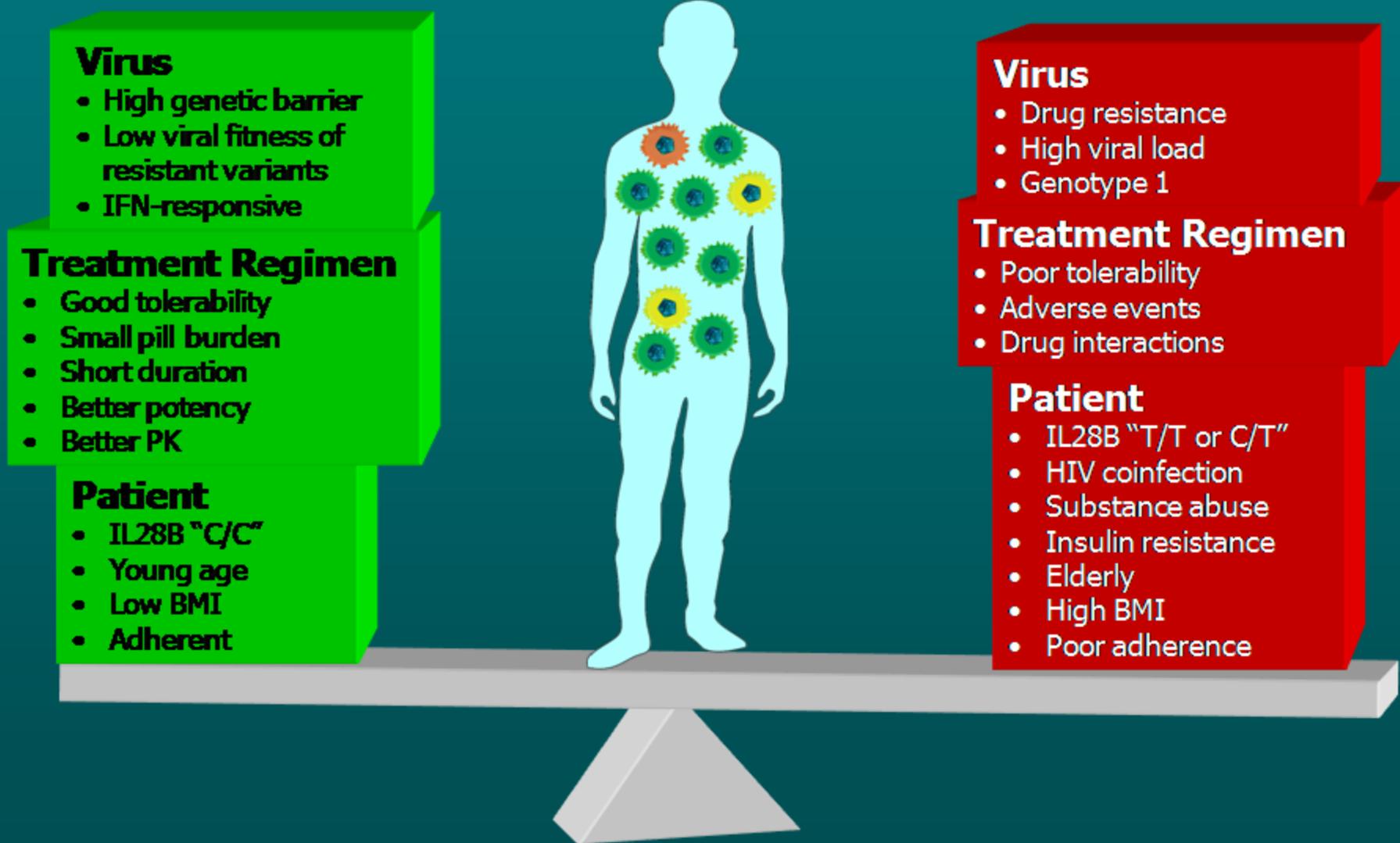


Potent antiviral therapy eliminates sensitive variants

Resistant variants are uncovered which can then expand

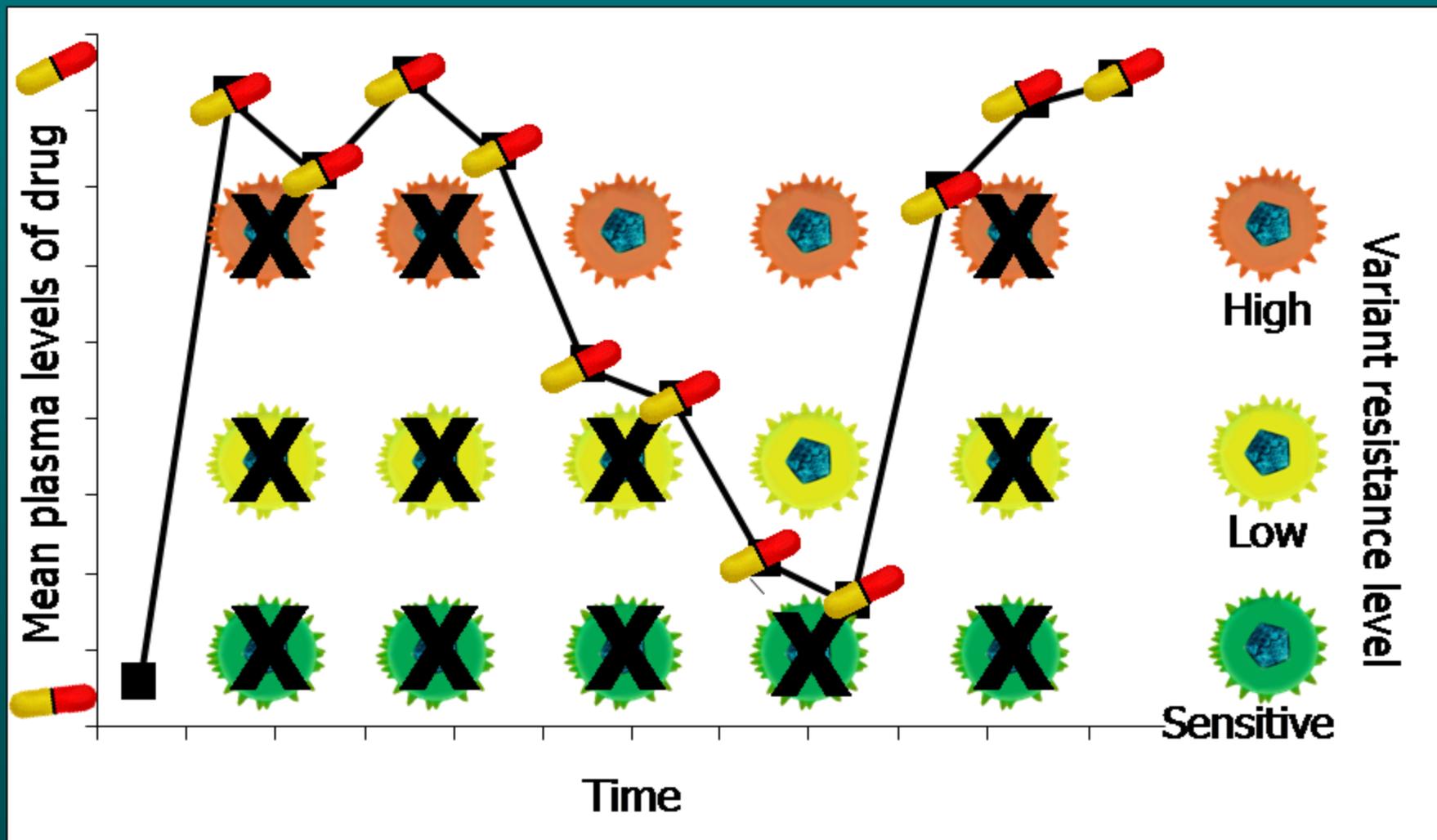


# A balance of multiple factors contribute to SVR



# Importance of drug levels over time

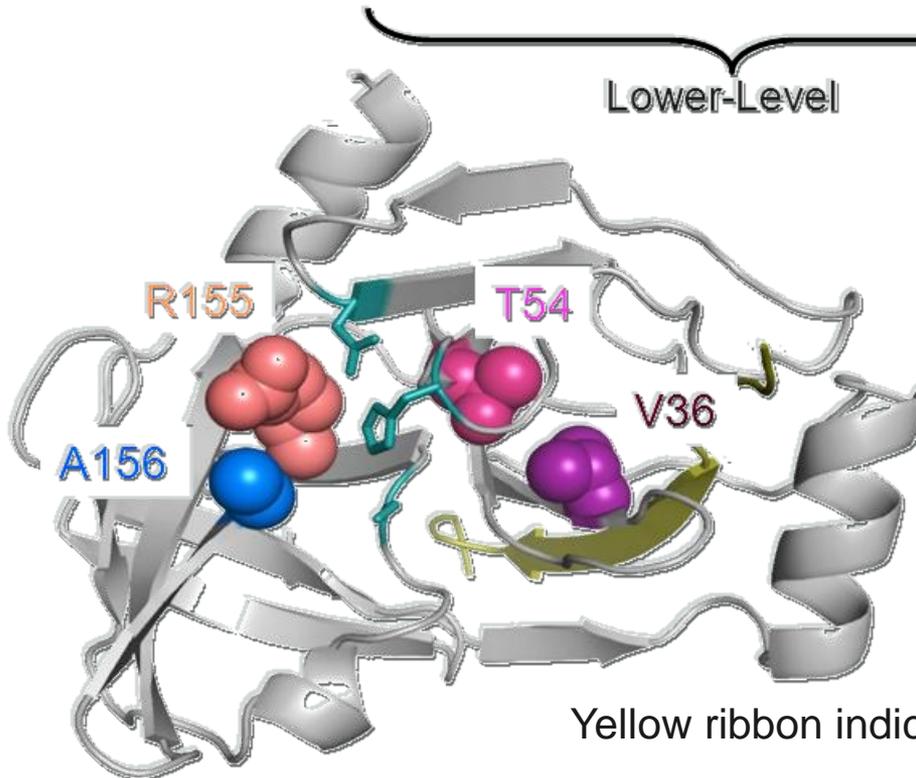
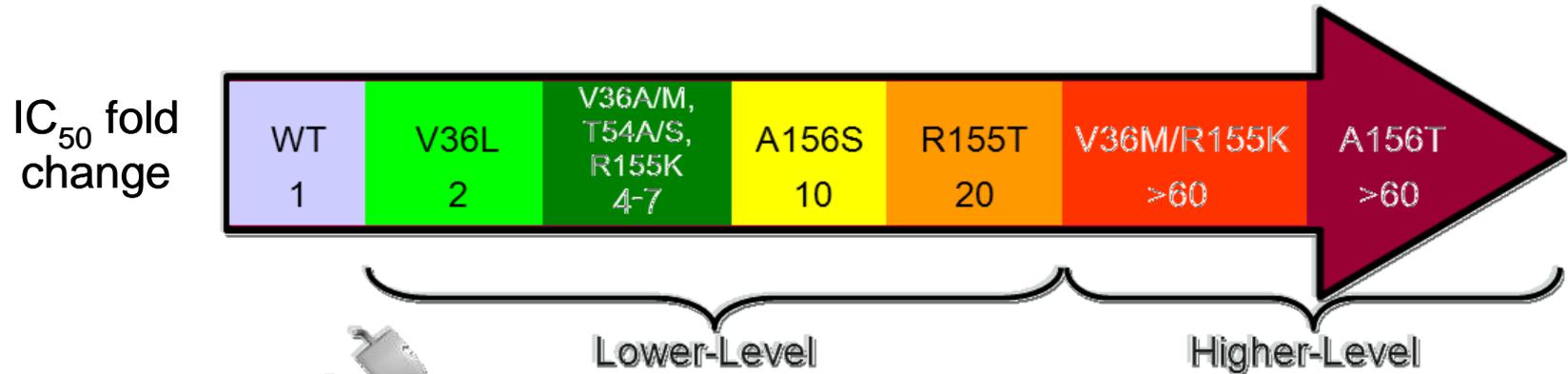
- Clinical resistance occurs if drug levels are too low to inhibit viral replication AND if resistant variants are fit and replicate



# Agenda

- Overview on HCV resistance
- Case study: Telaprevir/Peg IFN alfa/RBV (INCIVEK™) clinical virology

# Amino Acid Substitutions Less Sensitive to Telaprevir Observed in Clinical Studies

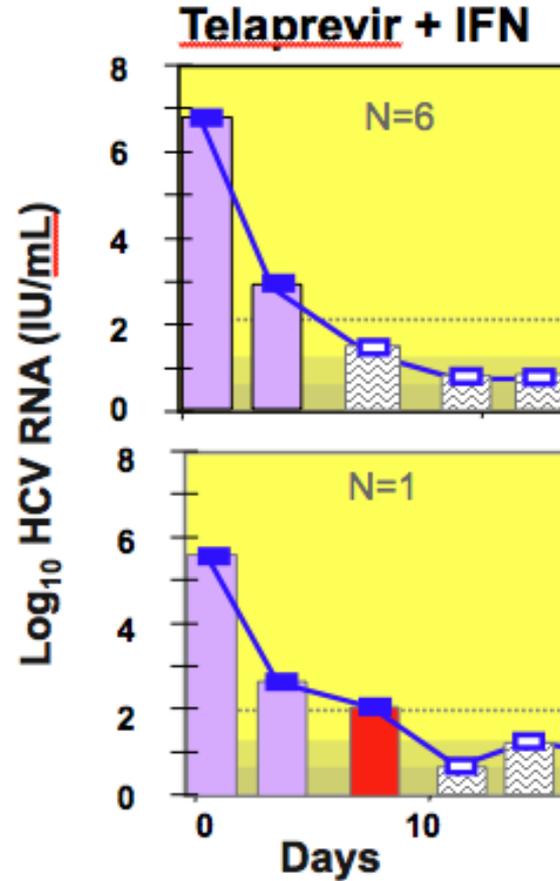
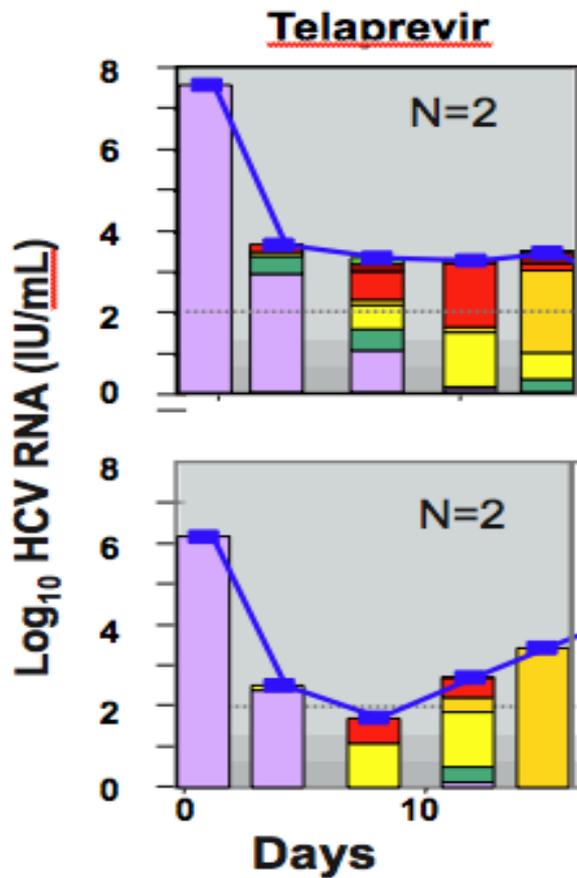


Location of Resistance Substitutions in the HCV NS3/4A Protease

Yellow ribbon indicates NS4A cofactor

TVR suppresses WT and low-level resistant variants

IFN suppresses WT and high-level resistant variants

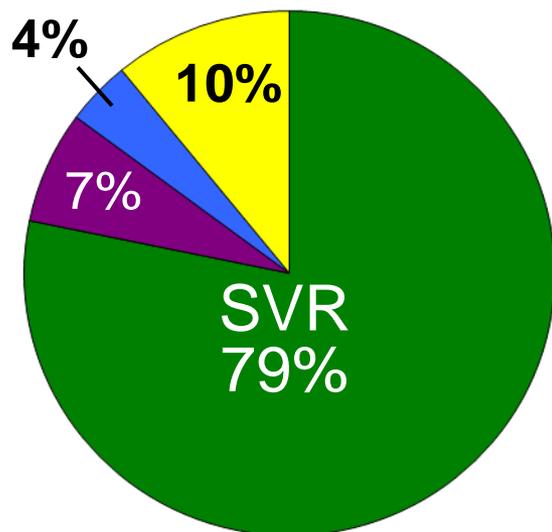


■ HCV RNA (> 100 IU/ml)  
□ HCV RNA (< 100 IU/ml)  
 < Sequencing Assay LOD

■ WT  
■ V36A/M  
■ T54A  
■ R155K/T  
■ 36/155  
■ A156V/T  
■ 36/156

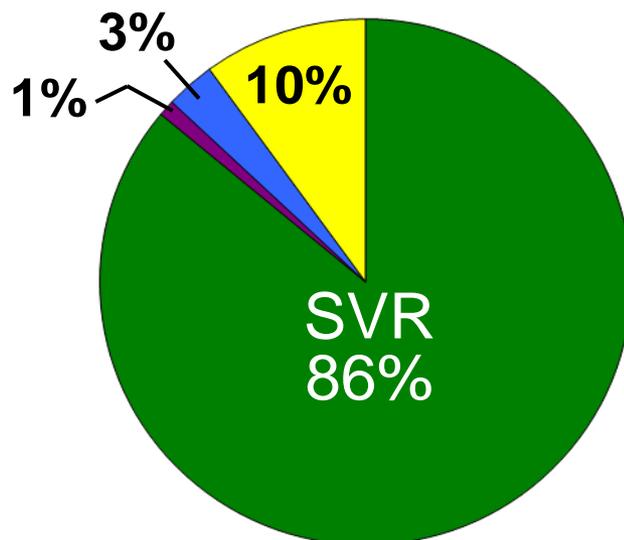
# INCIVEK ph3 treatment outcomes: naïve and relapsers have similar outcomes, prior null and partial responders fare worse

**ADVANCE (T12PR)  
Treatment-Naïve**



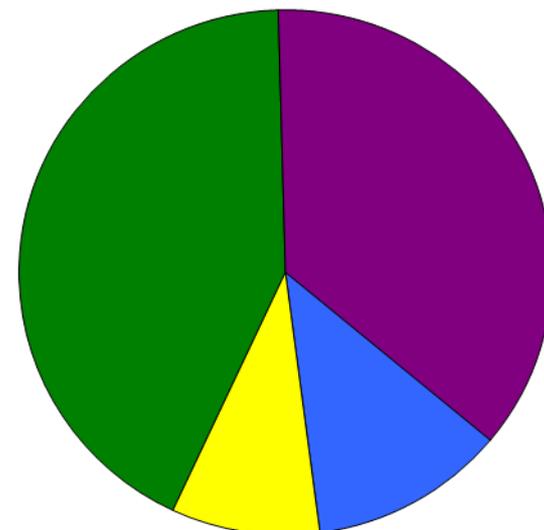
**N=363**

**REALIZE (All T12PR48)  
Prior PR Relapsers**



**N=286**

**REALIZE (All T12PR48)  
Prior PR Nonresponders**



**N=244**

■ **SVR**    
 ■ **Other**    
 ■ **Relapse**    
 ■ **Breakthrough**  
 (BT, on-Treatment virologic failure)

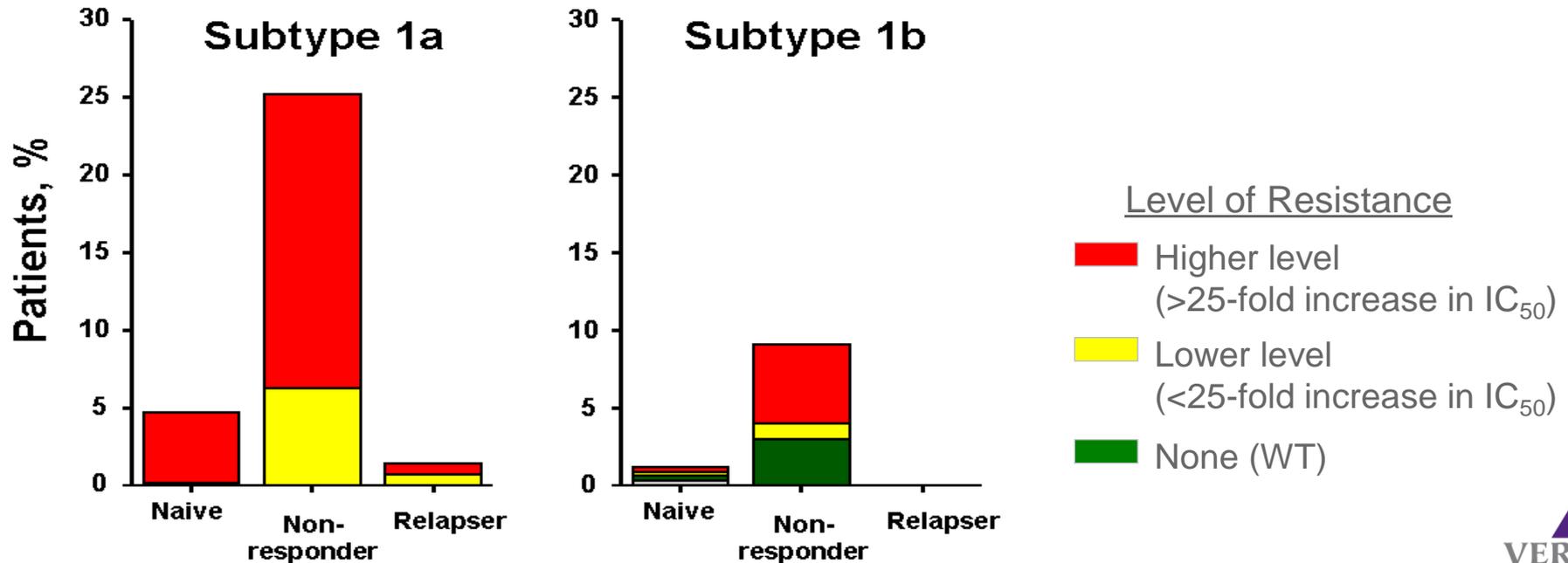
On-treatment failure includes subjects who met a protocol-defined virologic stopping rule or who had detectable HCV RNA at the time of their last dose of INCIVEK and subjects who had viral breakthrough on Peg-IFN/RBV.

“Other” includes patients with missing SVR assessment and patients with detectable HCV RNA at last study dose but who did not have vBT



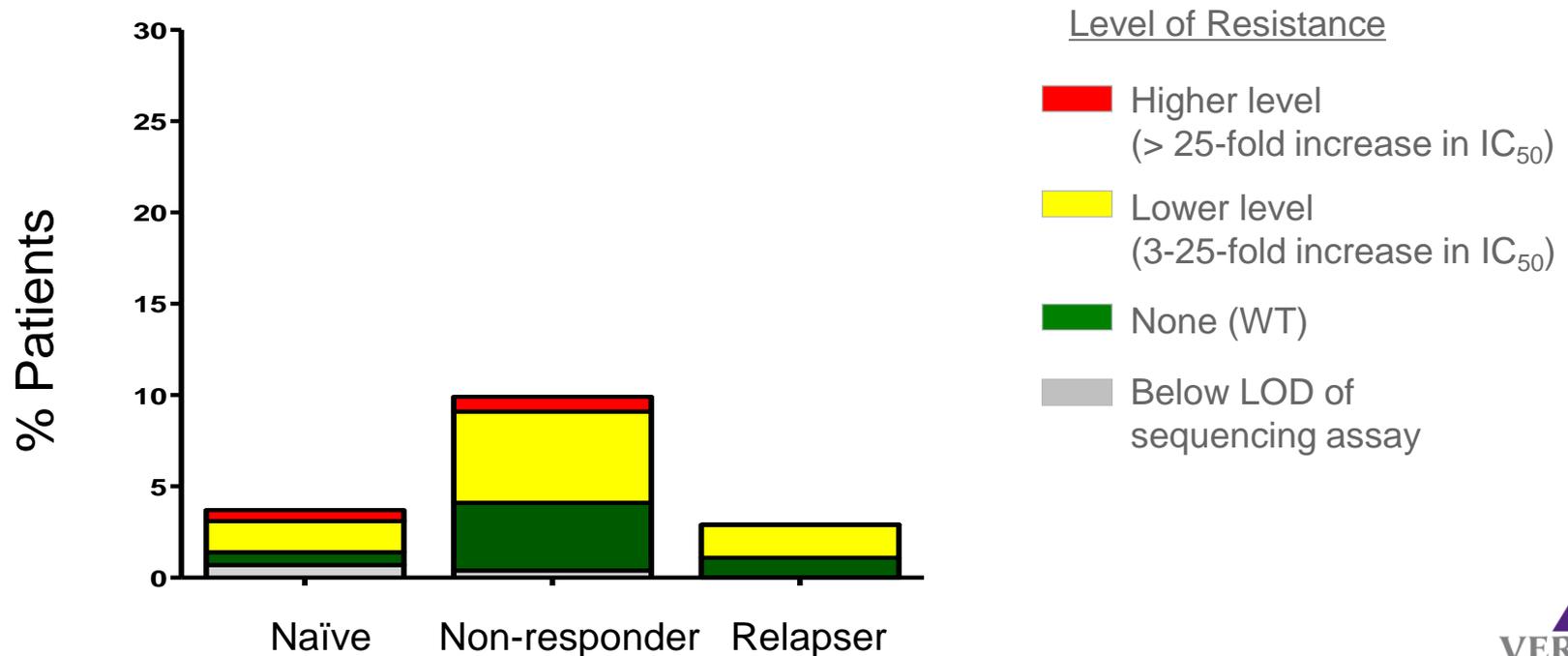
# Characterization of variants associated with viral break through (BT) on telaprevir (wks 1-12) in ph3 studies

- Viral BT is associated with higher-level resistant variants which cannot be suppressed by clinically achievable levels of TVR
- T/PR suppresses WT and lower-level resistant variants
- Virologic failure is likely due to an insufficient PR response

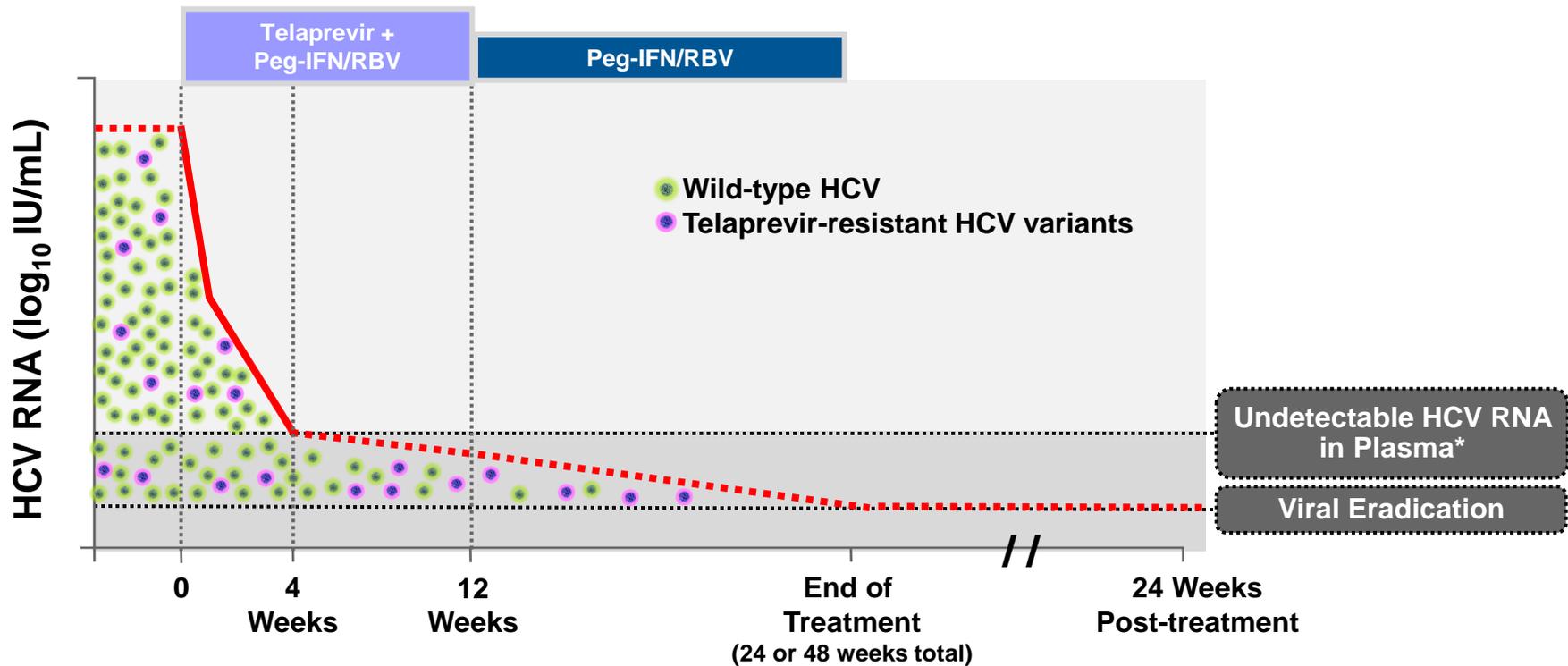


# Characterization of variants associated with viral relapse after completion of INCIVEK in ph3 studies

- Relapse was predominantly associated with either WT or lower level resistant variants
- This suggests that relapsers had an inadequate level of exposure to TVR



# Model for the role of TVR and PR in the INCIVEK regimen

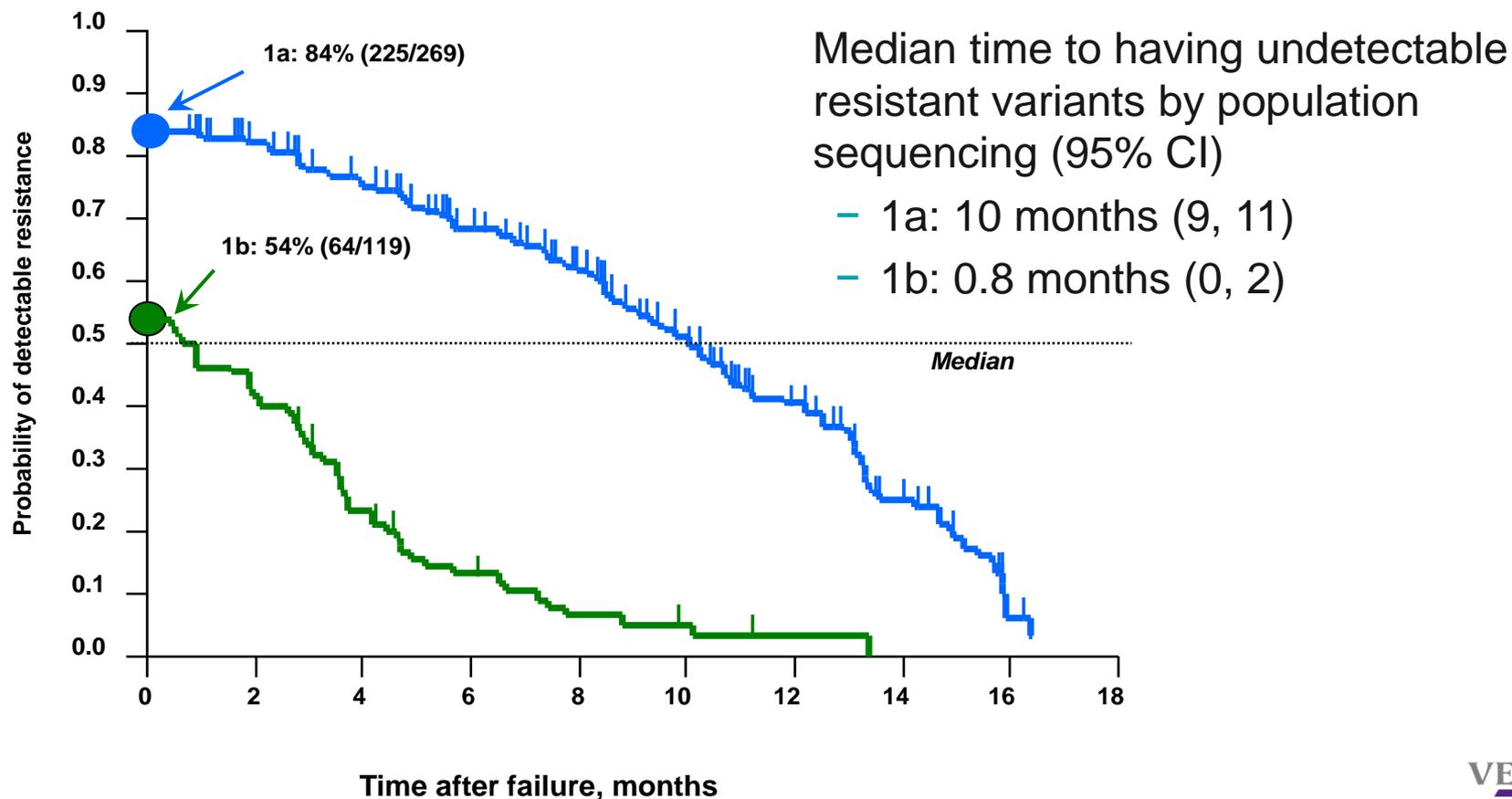


- Telaprevir + Peg-IFN/RBV clears most wild-type and lower-level resistant HCV variants in the first 12 weeks
- Continued Peg-IFN/RBV is necessary to clear the remaining virus



# What happens to patients who fail INCIVEK therapy?

- There is a return to baseline as telaprevir-resistant variants diminish over time
- BUT, it shouldn't matter how much resistant virus you have as long as you can inhibit the variant.



# Summary

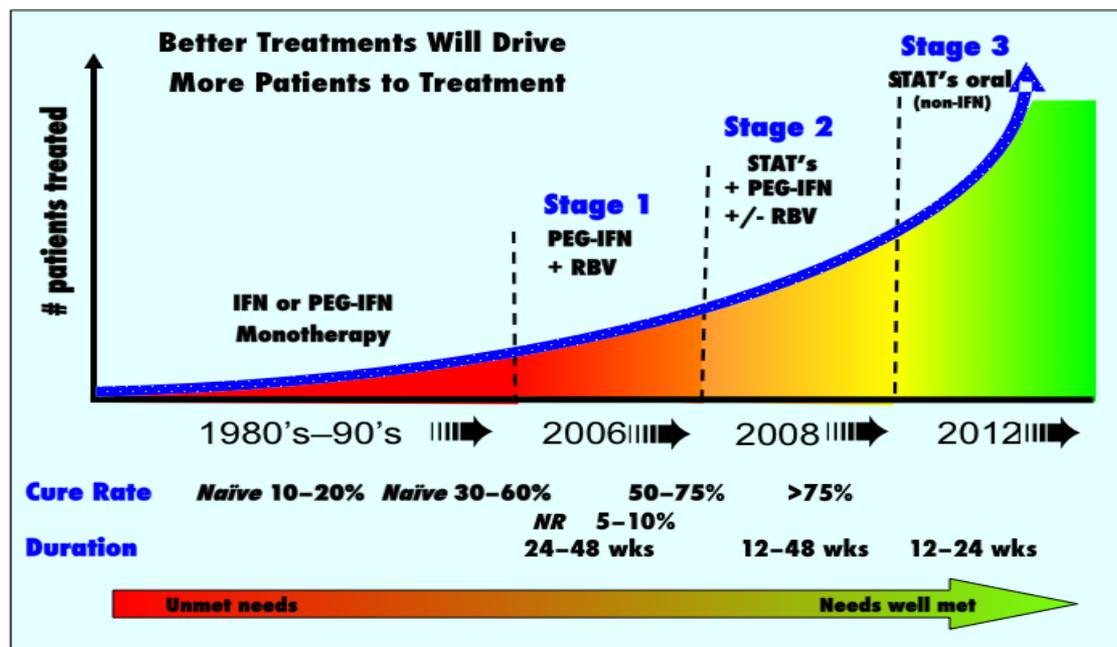
- HCV resistance overview
  - Unlike HIV or HBV, HCV can be cured
  - Resistant variants pre-exist and can be selected during treatment
  - Resistance is a marker for treatment failure, but not always the cause
  - Multiple factors contribute to response: virus, drug and patient
  - Maximize response, minimize resistance

# Summary

- HCV resistance overview
  - Unlike HIV or HBV, HCV can be cured
  - Resistant variants pre-exist and can be selected during treatment
  - Resistance is a marker for treatment failure, but not always the cause
  - Multiple factors contribute to response: virus, drug and patient
  - Maximize response, minimize resistance
- Telaprevir clinical virology
  - TVR-resistant variants pre-exist in all patients prior to treatment
  - Both WT and TVR-resistant virus are eradicated with INCIVEK
  - Viral BT is likely due to a poor Peg/RBV response to inhibit higher level resistant variants
  - TVR-resistant variants decline over time after treatment and are sensitive to other antiviral drugs
  - Telaprevir-resistant variants have provided insight into the battle for a cure which takes place below the LOD



# Looking ahead



- The approval of telaprevir represents a major paradigm shift with a significant increase in SVR and decrease in duration
- Need to improve efficacy and **tolerability** and decrease AEs: all oral treatment regimens are progressing quickly to address this issue
- Need better treatment for patients with cirrhosis, who failed therapy with telaprevir and boceprevir; have HIV or HBV coinfections, are IFN intolerant/contraindicated, have bleeding disorders, have non-genotype 1 HCV, are on opiate substitutes, etc
- **Need to improve diagnosis, access to care and treatment rates**

# Acknowledgments

- The patients and investigators in the telaprevir clinical studies
- Slides prepared by Tara Kieffer and the Vertex Clinical Virology
- Slides prepared by the Forum for Collaborative HIV Research and the Hepatitis C Virus Drug Development Advisory Group (HCV DRAG)