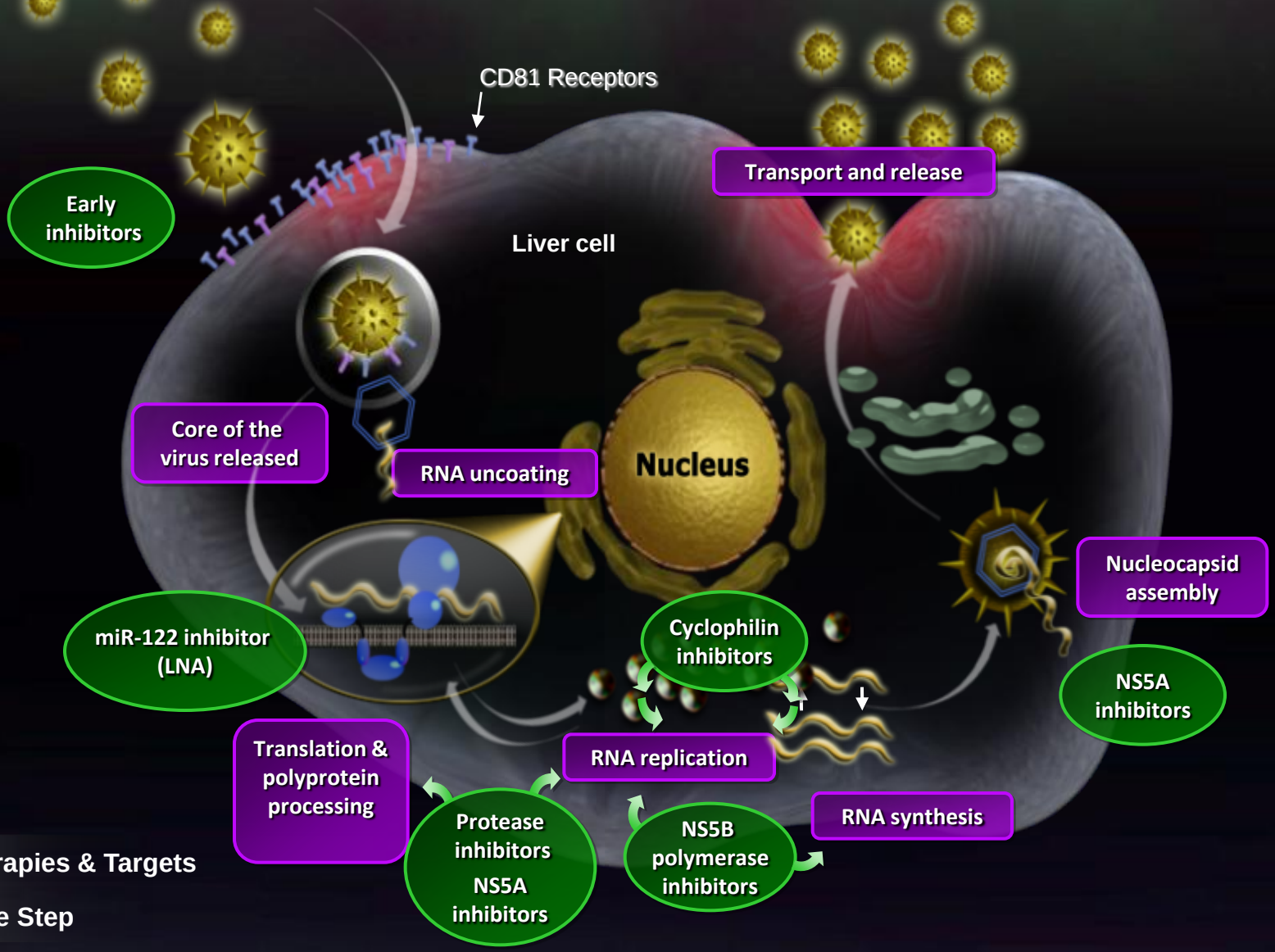
Journées Scientifiques en Infectiologie - Jeudi 29 novembre 2012, Paris

Workshop sur la prise en charge des patients infectés VIH-VHC
en vue de la rédaction d'une position d'experts

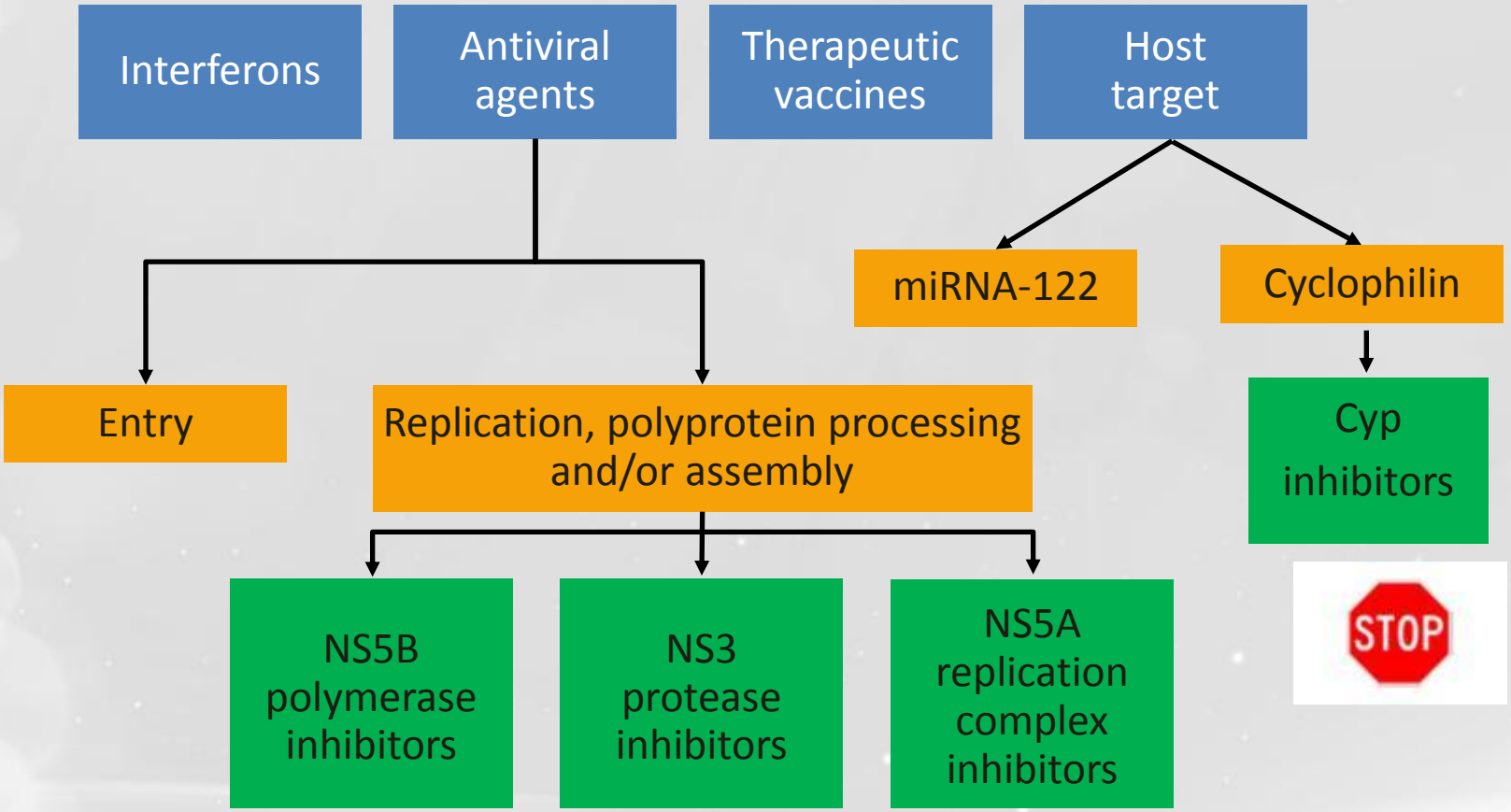
Nouvelles Molécules anti-VHC en développement

Philippe HALFON ***MD, PharmD, PhD***
Marseille

Drug targets in the HCV lifecycle



Investigational Agents for HCV



Investigational HCV Regimens in Phase III Clinical Trials

•Regimens With 1 DAA + PegIFN alfa/RBV

- Faldaprevir* (BI 201335, PI)
- Daclatasvir* (BMS-790052, NS5A)
- Sofosbuvir* (GS-7977, NI)
- Simeprevir* (TMC435, PI)
- Alisporivir* (CYP) On Hold
- Vaniprevir† (MK-7009, PI)

•Alternative Dosing

- TVR BID* (approved PI)

•Regimens With 2 DAAs + PegIFN alfa/RBV

- Daclatasvir + asunaprevir*

•New Interferons

- PegIFN lambda-1a + RBV
- PegIFN lambda-1a + daclatasvir + RBV**
- PegIFN lambda-1a + Asupranavir + RBV**

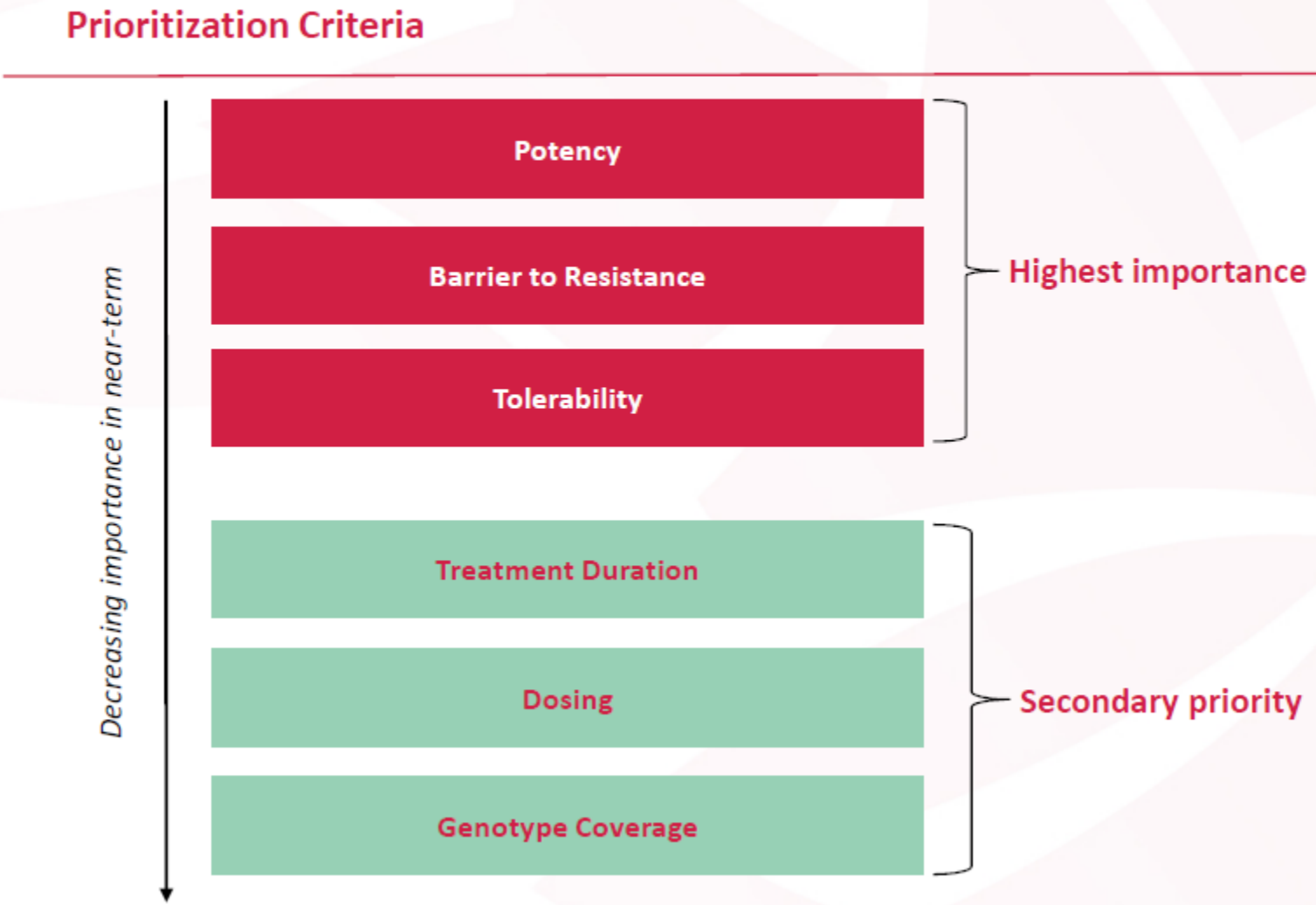
•IFN-Free Regimens

- Sofosbuvir + RBV
- Sofosbuvir + GS-5885 (FDC) ± RBV
- Daclatasvir + asunaprevir
- ABT-450/RTV + ABT-267 ± ABT-333 ± RBV
- Faldaprevir+BI207127+RBV

*Studied with pegIFN-α2a. †Studied with both pegIFN-α2a and pegIFN-α2b.** Phase 2a

ClinicalTrials.gov

Differentiating Attributes of Future Therapy Beyond Cure



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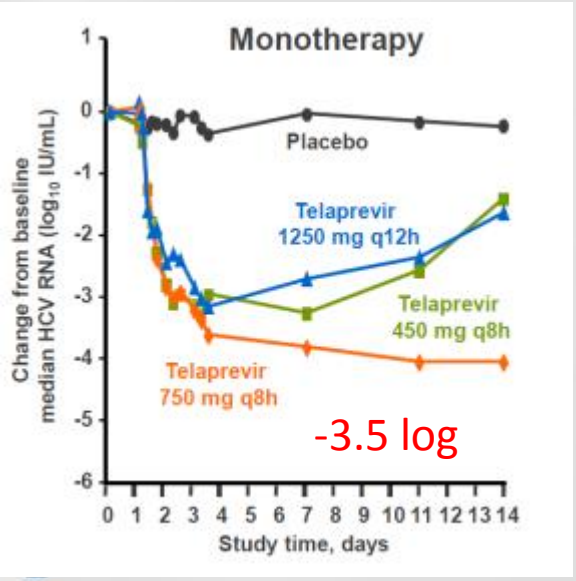
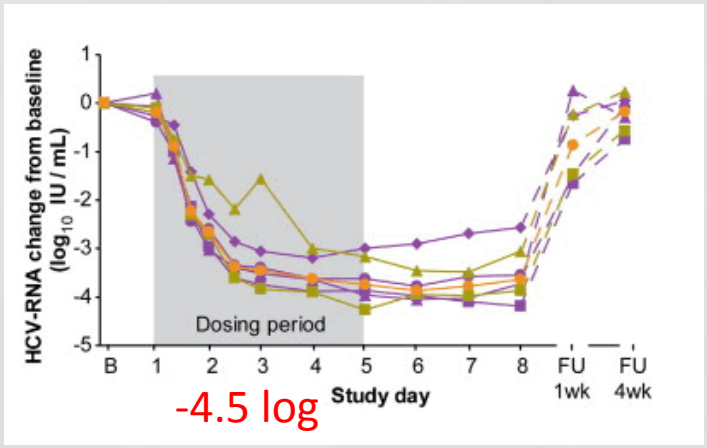
Potency

In Vivo Viral load decline DAA comparison after 3 days

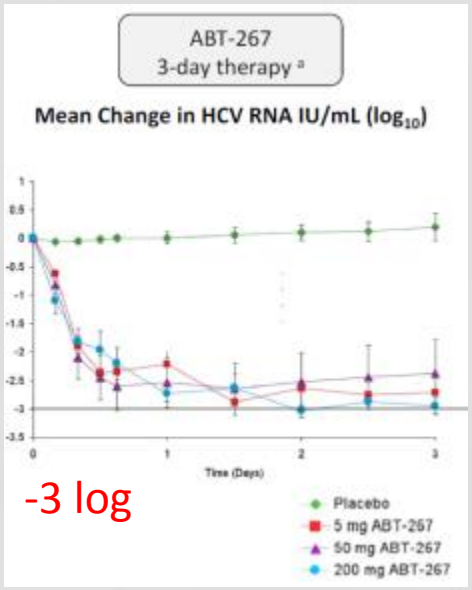
PI 1° : Telaprevir



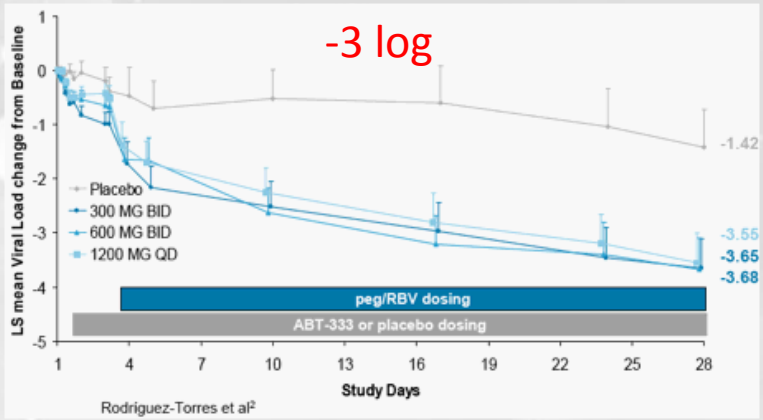
PI 2° : TMC 435 : Simeprevir

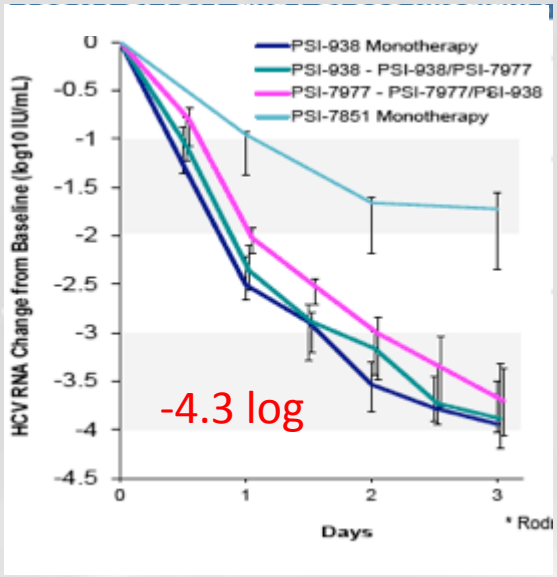


NS5 A I : ABT-267



NNI : ABT-333





GS 7977

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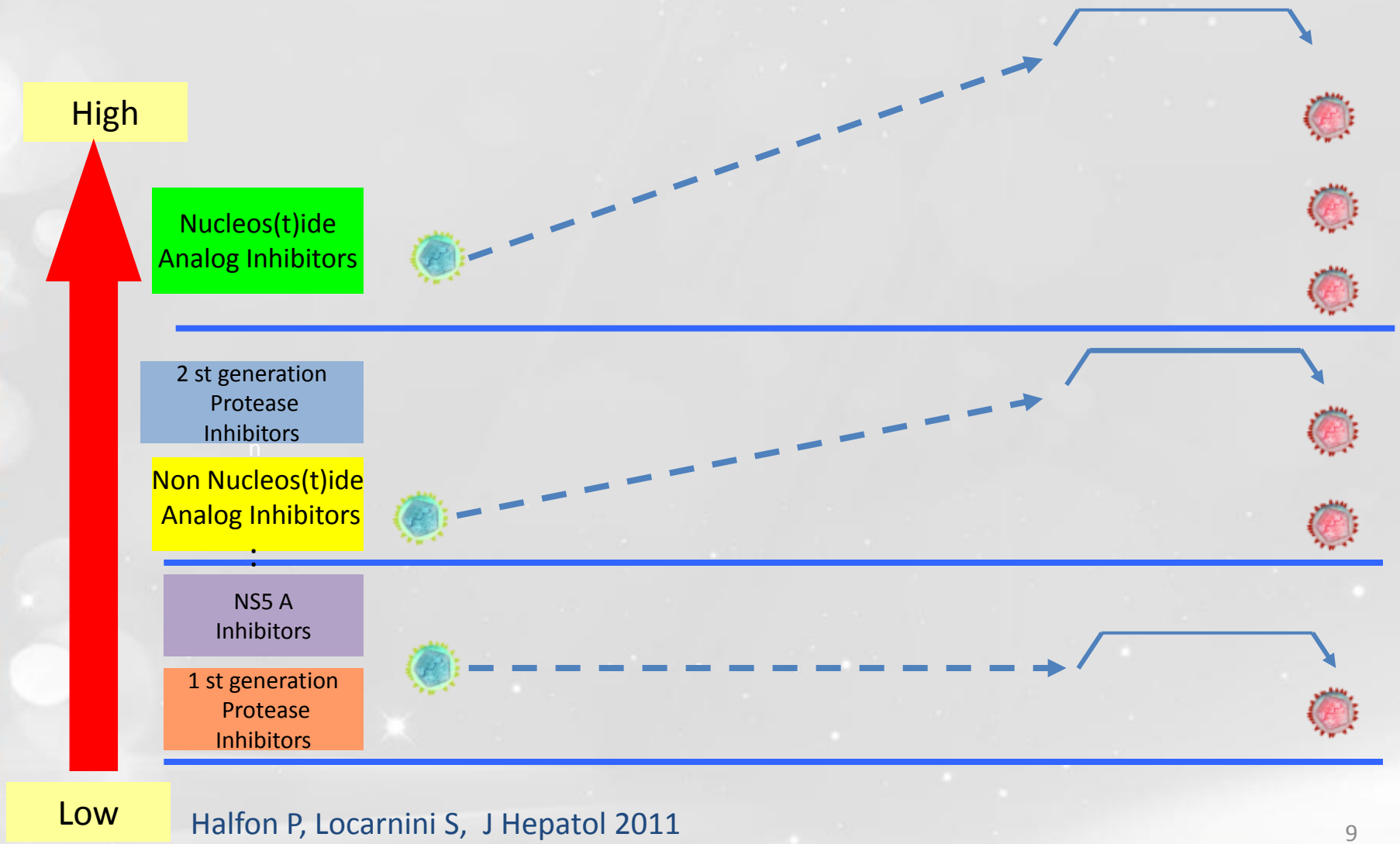
Resistance

Genetic Barrier for HCV Direct Antiviral Agents



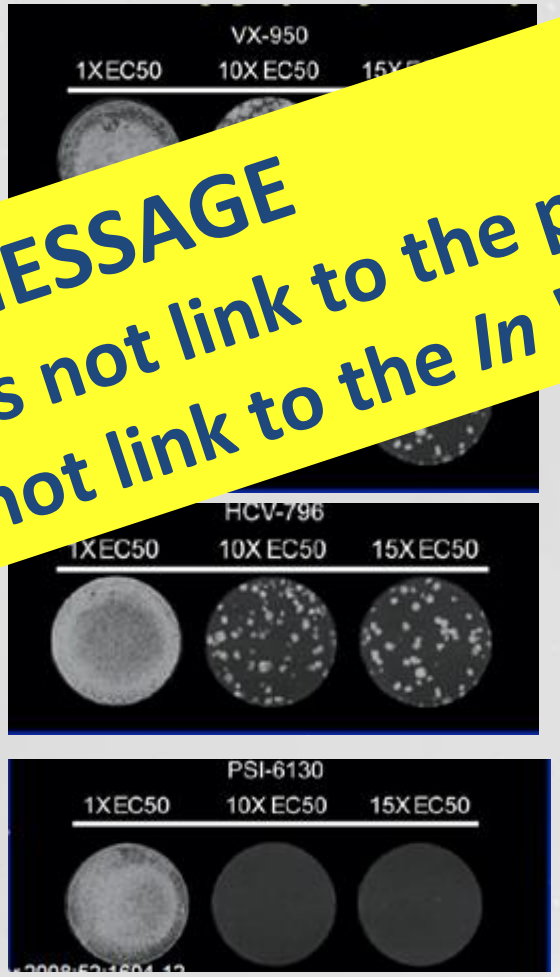
Halfon P, Locarnini S, J Hepatol 2011

In Vitro Resistance to DAA
14 days monotherapy (Replicon)

Protease Inhibitors

NS5 A Inhibitors

Nucleoside Inhibitors



Poten… …M

0.01-0.1

10-1000

10-100

KEY MESSAGE

The genetic barrier is not link to the potency

The *In vitro* Potency is not link to the *In Vivo* activity

Adapted from McCown et al. AAC 2008

Barrier to resistance depend on number and probability of nucleotide exchanges

Main first generation NS3 Protease-Inhibitor Resistance site (R155K)

One nucleotide exchange for subtype 1a versus two nucleotide exchanges for subtype 1b

NS3 protease sequence

```
            155
HCV-1a   GIFRAAV
HCV-1b   GIFRAAV

HCV-1a     AGG → AAG      (R155K)

HCV-1b     CGG → AAG      (R155K)
```

Kieffer et al., Hepatology 2007
Sarrazin et al., Gastroenterology 2010

NS3, NS5A and non-nuc resistance mutations typically require transitions while nuc resistance site requires transversion (S282T)

NS5B polymerase in favor of transitions (A ↔ G and C ↔ T) over tranversions (A/G ↔ C/T and C/T ↔ A/G

NS3 protease sequence

```
            155
HCV-1a   GIFRAAV
HCV-1b   GIFRAAV

          Transition

HCV-1a     AGG → AAG      (R155K)

         Tranversion

HCV-1b     CGG → AAG      (R155K)
```

Powdrill et al., PNAS 2011

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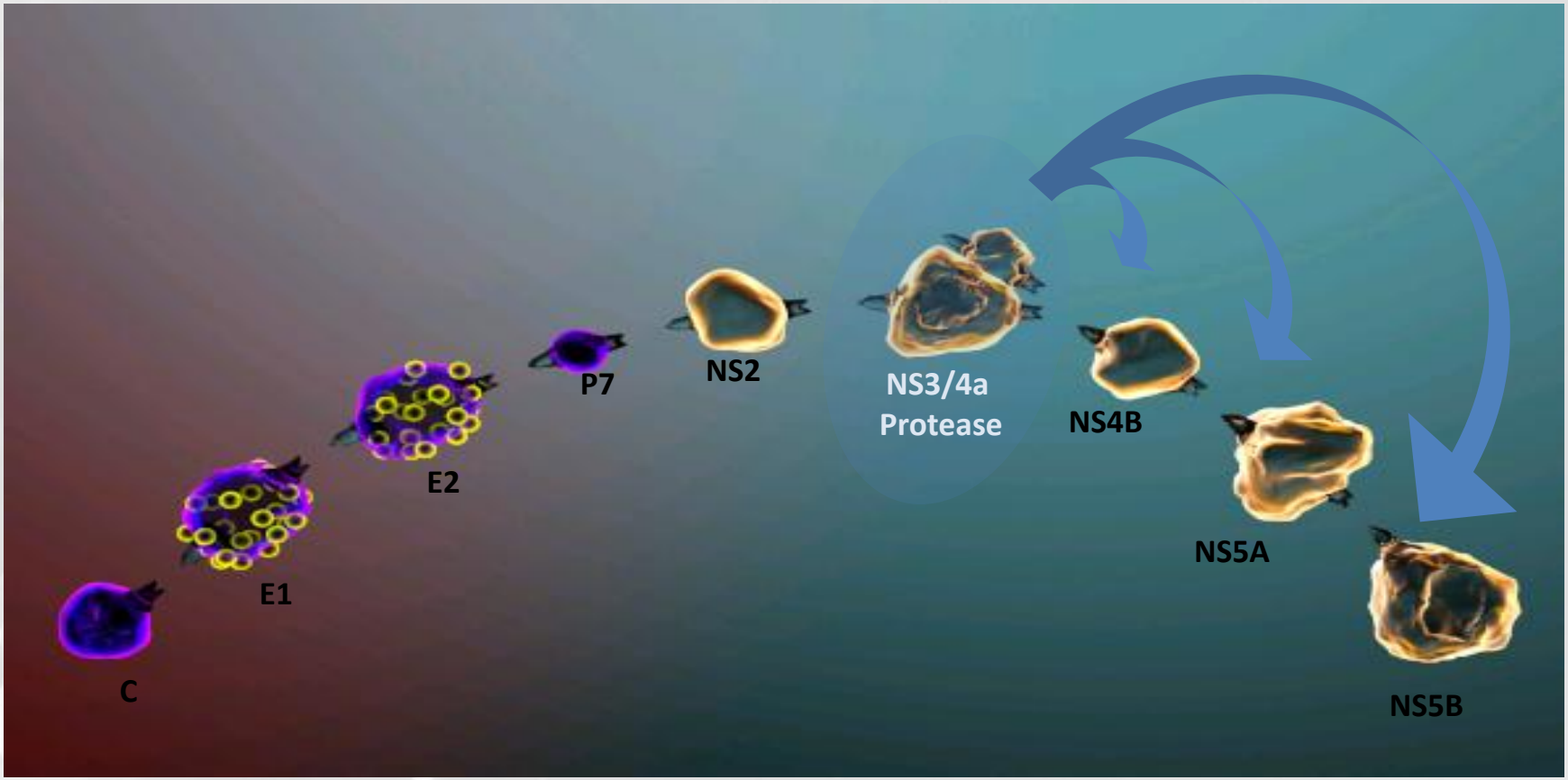
Mechanism of Action

NS3/4a Cleaves Nonstructural

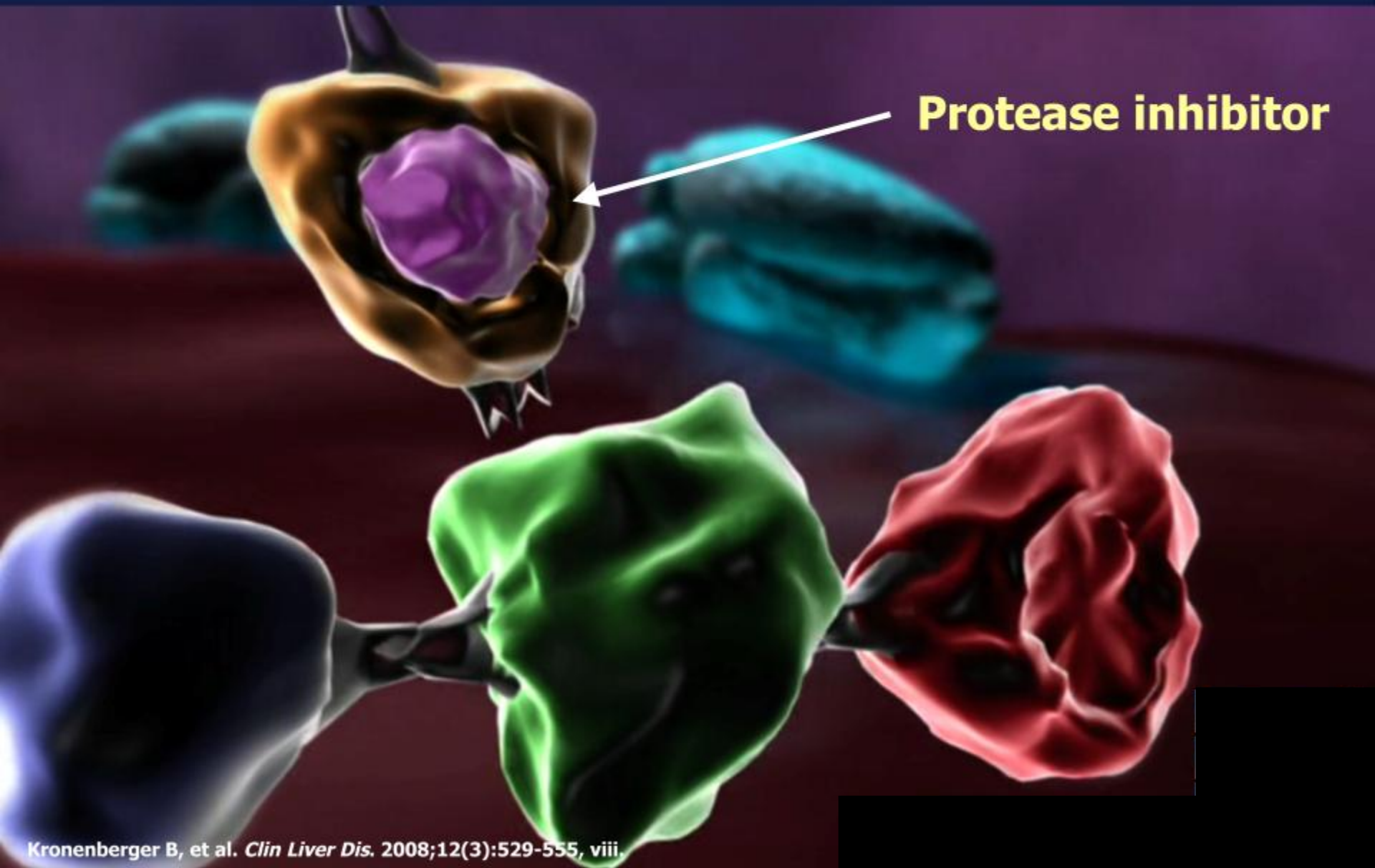
Proteins from the Polypeptide Chain[1,2]

Viral Replication Initiated



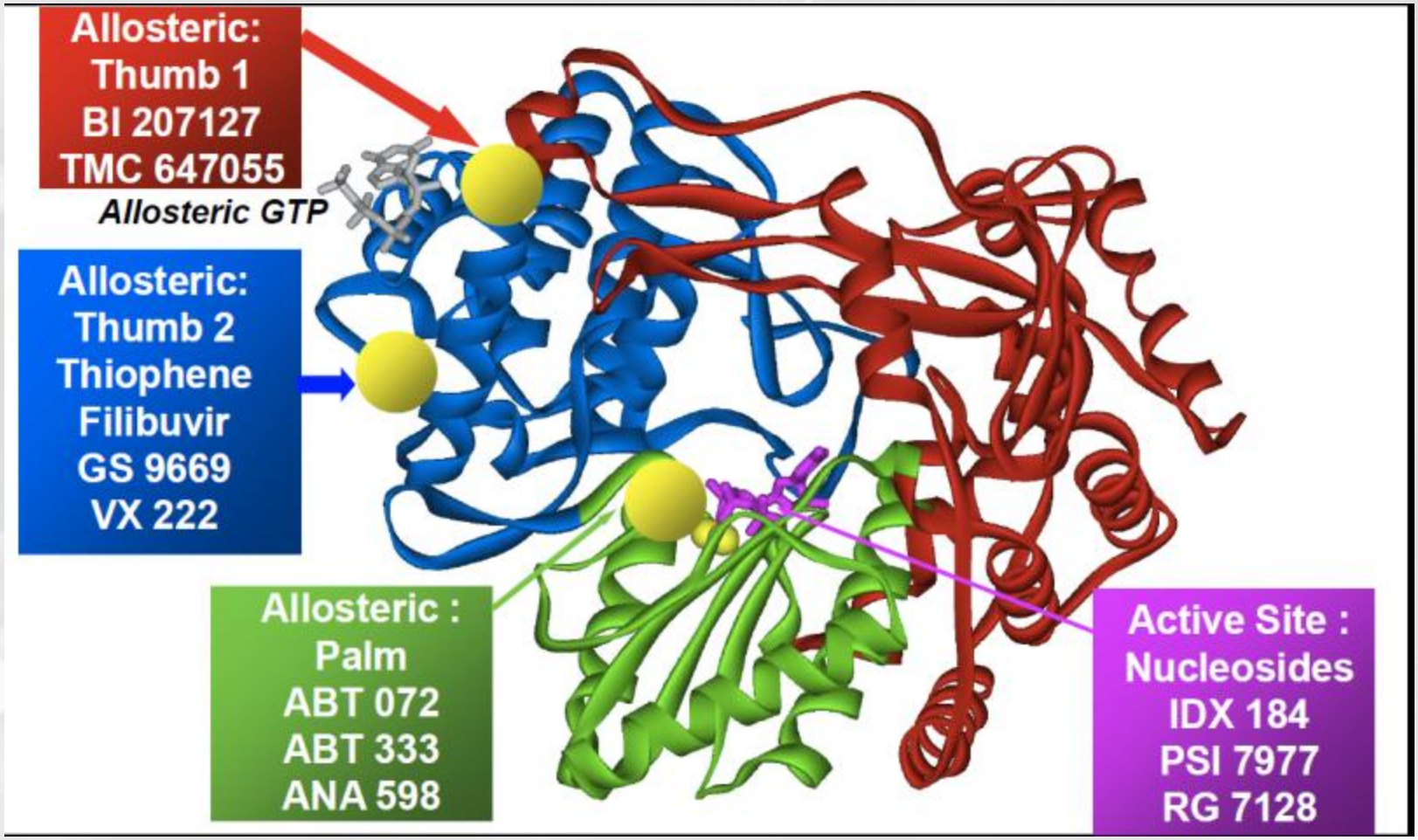
1. Lindenbach BD, et al. *Nature*. 2005;436:933. 2. Lindenbach BD, et al. *Science*. 2005;309:623.

Switching Off the Protease Prevents Cleavage of the Polyprotein Chain, Halting Replication



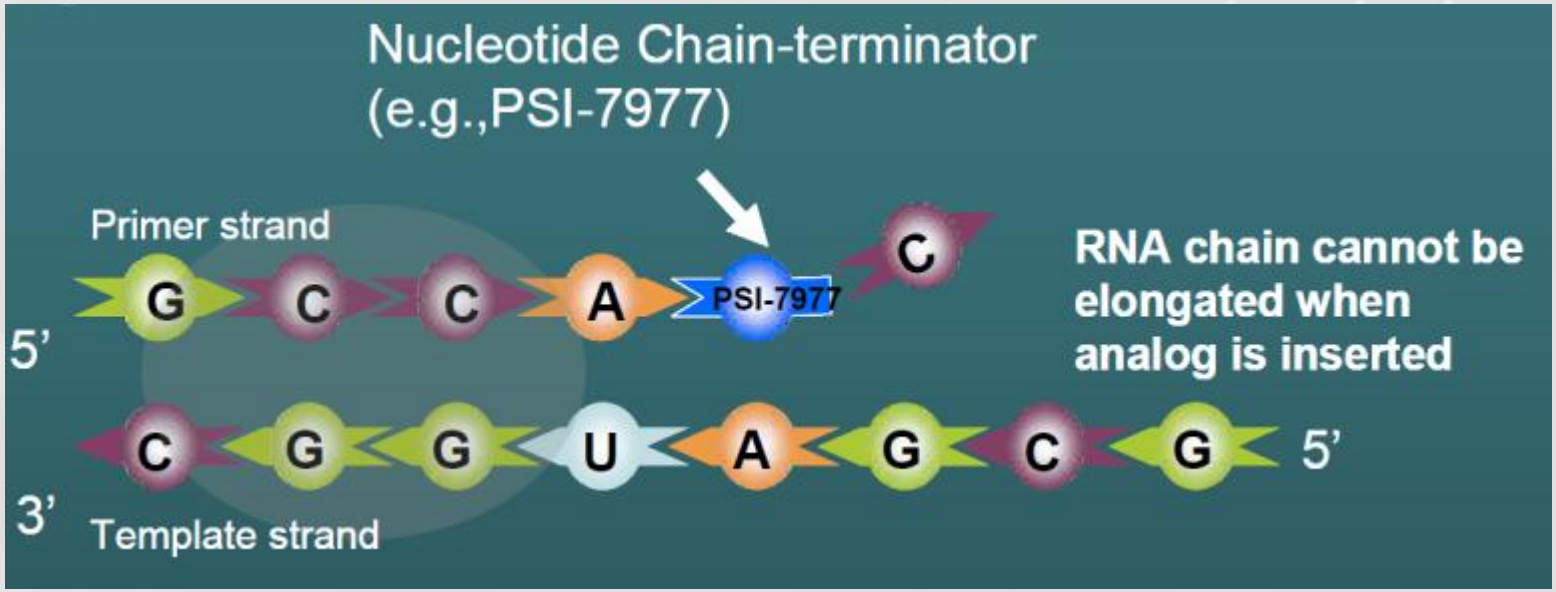
Kronenberger B, et al. *Clin Liver Dis.* 2008;12(3):529-555, viii.

Examples of HCV NS5B polymerase inhibitors and their binding site

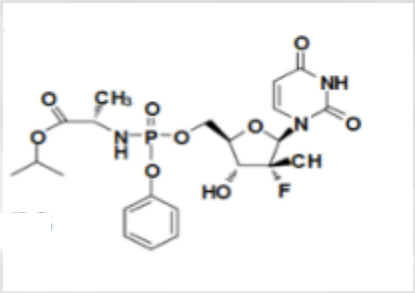


Electron-Proton, Neutron, Atomic…
GS 7977= Sofosbuvir

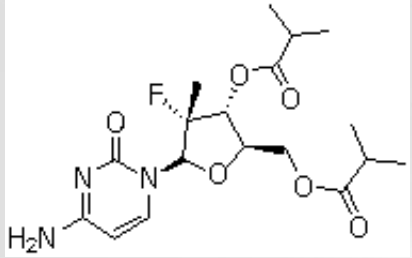
Nucleotide /Nucleoside analogs



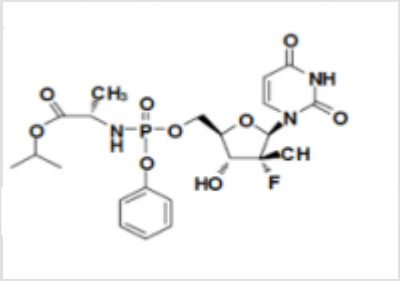
Sofosbuvir :
Nucleotide

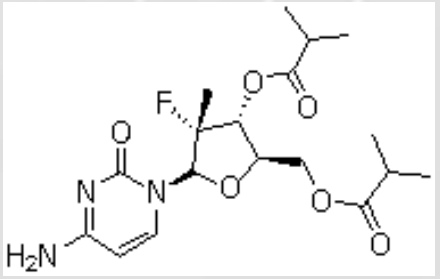


Mericitabine :
Nucleoside



Nucleotide /Nucleoside analogs comparison





	Sofosbuvir	Mericitabine
Type	Nucleotide	Nucleoside
Efficacy/ *in Vitro*	Moderate	Moderate
Genetic barrier	High	High to medium
Pangenotype activity	yes	Yes : 1a<1b
IL28 CC influence	No	yes
Toxicity and AEs	Not yet reported	few
DDIs	low	low

Comparison of DAA Profiles

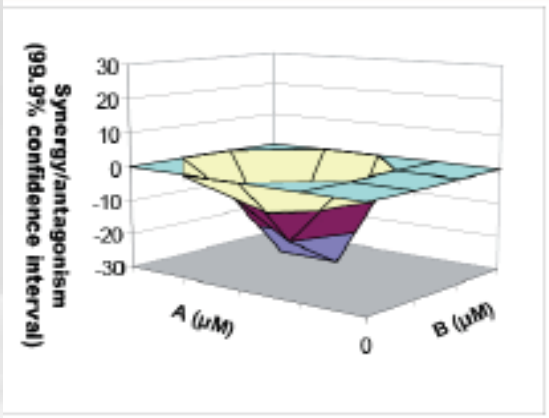
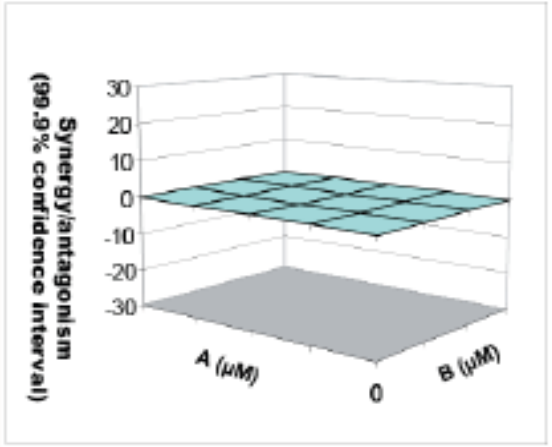
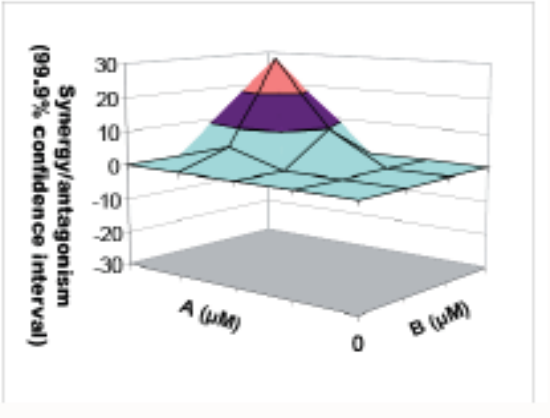
Characteristic	DAA				
	PI, 1st Generation	PI, 2nd Generation	NS5A Inhibitors	NS5B Nucleot/side Inhibitors	NS5B Non Nucleoside Inhibitors
Efficacy	🟡	🟢	🟢	🟢	🟡
Resistance Profile	🔴	🟡	🟡	🟢	🔴
Pangenotypic Efficacy	🔴	🟡	🟡	🟢	🔴
Adverse Events	🔴	🟢	🟢	🟢	🟡
Drug–Drug Interactions	🔴	🟢	🟡	🟡	🟡

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

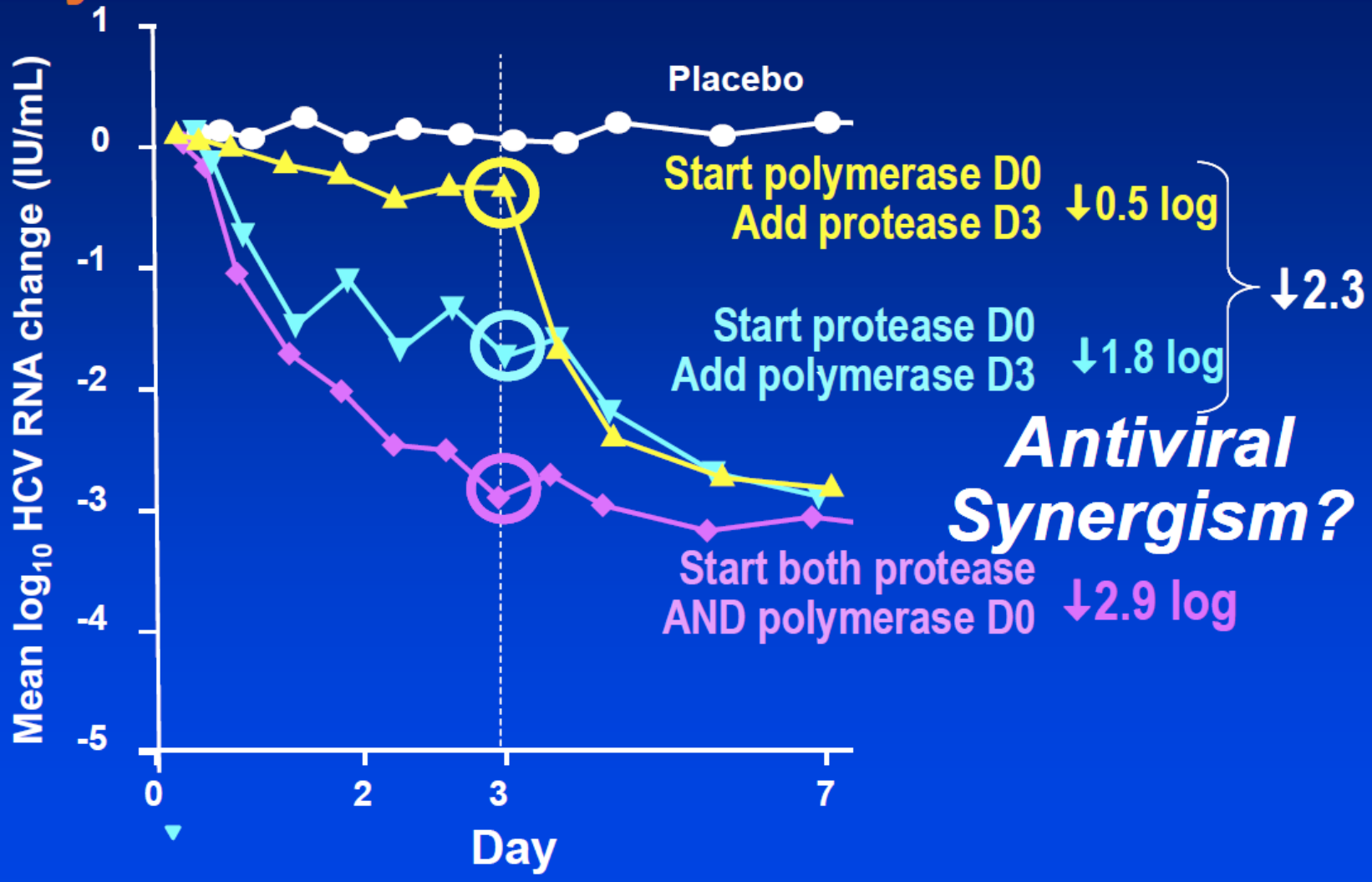
Adapted from: Farnik H, et al. Antivir Ther. 2012;17:771-783.

Evaluation of synergy of drug-drug combinations

Bliss independence model

Antagonistic	Additive	Synergistic
		
Least Desirable	Most Common	Most Desirable

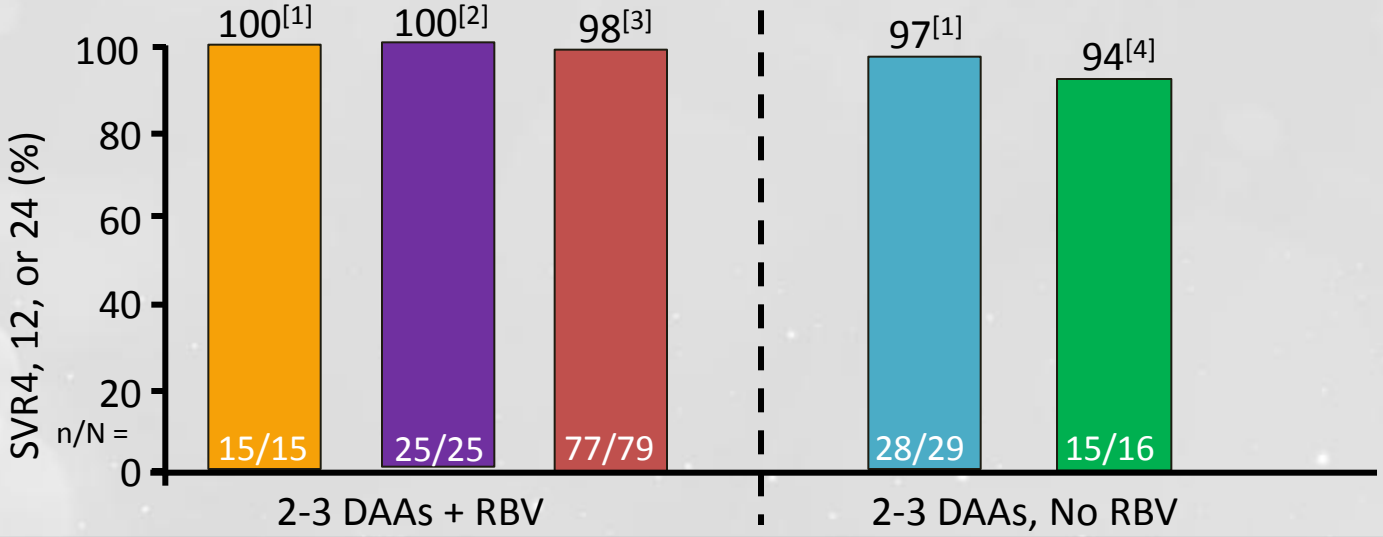
Will combining protease inhibitor with polymerase inhibitor better than either alone?



Potent IFN-Free DAA Regimens in Treatment-Naive Genotype 1

- Sofosbuvir (Nuc) + Daclatasvir (NS5A) + RBV x 24 wks
- Sofosbuvir (Nuc) + GS-5885 (NS5A) + RBV x 12 wks
- ABT-450/r (PI) + ABT-333 (NNI) + ABT-267 (NS5A) + RBV x 12 wks
- Sofosbuvir (Nuc) + Daclatasvir (NS5A) x 24 wks
- Daclatasvir (NS5A) + asunaprevir (PI) + BMS 791325 (NNI) x 12 wks

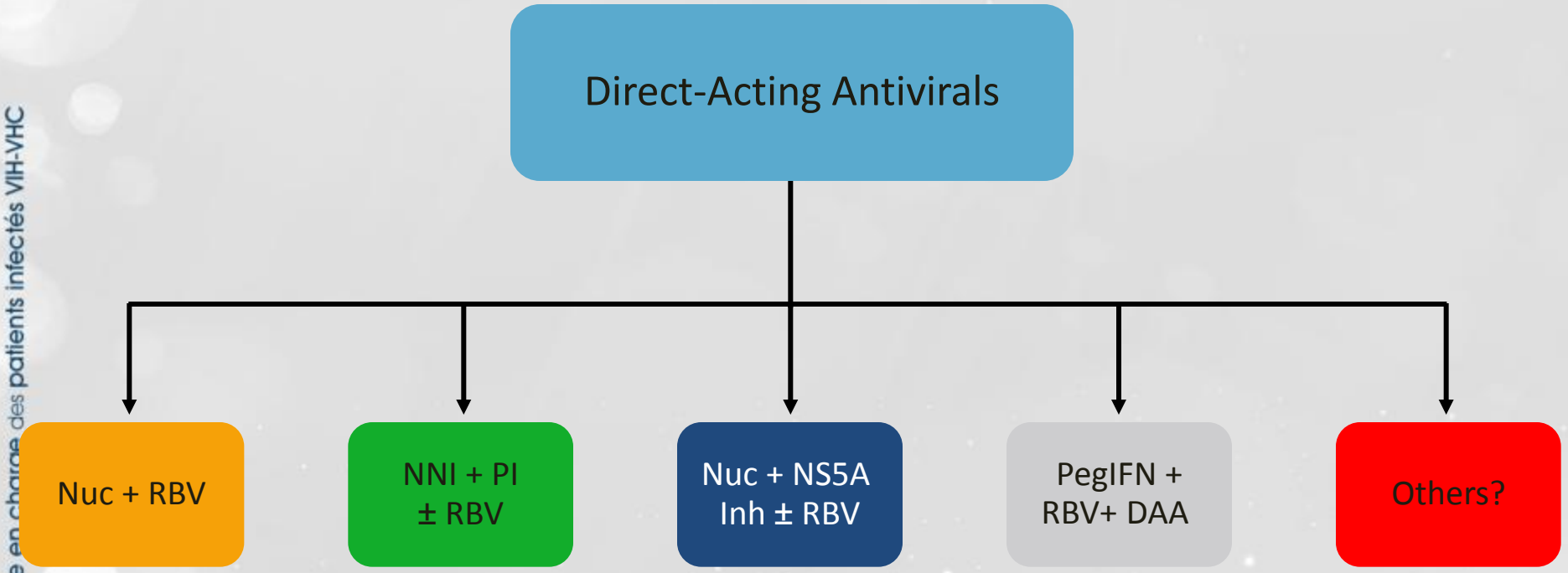
Ribavirin-Free Regimen



- **Major caveats: few number of patients, No/few patients with cirrhosis**

1. Sulkowski M, et al. AASLD 2012. Abstract LB-2. 2. Gane E, et al. AASLD 2012. Abstract 229.3. Kowdley KV, et al. AASLD 2012. Abstract LB-1. 4. Everson G, et al. AASLD 2012. Abstract LB-3.

Toward a Future of Personalized Medicine for HCV Therapy



Ongoing Clinical trail in HIV-HCV co-infected patients

	Faldaprevir 12/24 wks	+	PR 24/48 wks	→	G1 Naïves or RR
	Simeprevir 12wks	+	PR 24/48 wks	→	G1 Naïfs and NR
	Daclatasvir 24 wks	+	PR 24/48 wks	→	G1 Naïves
ANRS	Asunaprevir	+ Daclatasvir	+ PR 24/48 sem	→	G1 NR
	Sofosbuvir 12/24 wks	+	R 12/24 wks	→	G2/3 Naïves or NR

- Multiples DDI with anti-HIV compounds : patient selection and switch HIV-therapy

Avantages des nouvelles thérapies

- Efficacité Importante (80-100% SVR) en synergie
- Une prise par jour
- Durée de traitement raccourci (12-24 s)
- Simplification des Protocoles—Pas de RGT
- Peu d'effets secondaires
- IFN-Free
- RBV-Free?

Inconvenients des nouvelles thérapies

- Peu d'études et études portant sur un faible nombre de patients
- Potentiel de toxicité reste à evaluer
  - Molécules de multiple classes (nucs, nonnucs, PI, alisporivir) pouvant avoir une toxicité additionnelle
- Efficacité et tolérance chez les cirrhotiques peu evaluée
- Peu de données—DDIs, dans des populations particulières (OLTx, HIV, ESRD)
- Enregistrement, disponibilité et remboursement de ces molécules non connues
- Coût de ces traitements non établi, Quid PED

"All the News That's Fit to Print"

The New York Times

Late Edition

Today: Hot. Really hot. Global warming hot. Highs: 98, Lows: 97. Tomorrow: 80% Chance of hurricane; 90% Chance of flood. Yesterday Tropical Storm Florence ravaged Brooklyn and Manhattan. Weather Map on page D18.

VOL. CLIV NO 53,011 MONDAY, MAY 15, 2023 12 DOLLARS

HCV ELIMINATED FROM PLANET

Deadly bloodborne virus cured. Joins list of unintimidating diseases; polio, consumption, scurvy, cabin fever.

By Rómulo A. Tenés

Voltaire, in his Dictionnaire Philosophique said:

"What? A rigorous test is requested to affirm that the surface of a sphere is equal to that of the quadruple of the surface of the circle round its central point..." and yet does it not have to be rigorous, for example, in certifying the whole of Picasso's false work between 1891 and 1897 which was undoubtedly made by his father, José Ruiz Blasco? Or the centenary canvas, 1903 "Dama en Eden Concert" as a true one?

Well, dear investors in art, that is how it is. In insulting arbitrariness, contrary to the most elemental common sense, and to the exclusive benefit of unscrupulous art merchants, science is not used in certifying Picasso's work.

A grotesque example of this is Josep Palau i Fabre, "biographer", whose only merit resides in idolising Picasso to his own benefit. A clumsy hearing aid to his ear, he pretends to listen, expecting the paintings to speak. He is deaf. Fine.

Cure Attributed to Stem Cell Research

But, surprise! Concepción, Claude, and Paloma Ruiz-Picasso defend the esoteric, clumsy, and grotesquely irrational system of certifying the work of their father. To their own benefit, and with catastrophic results: thousands of false works, and the subsequent loss of credit.

Would an investor in art allow such an individual to enter his company entrusted with its management, or as an instructor for his children?

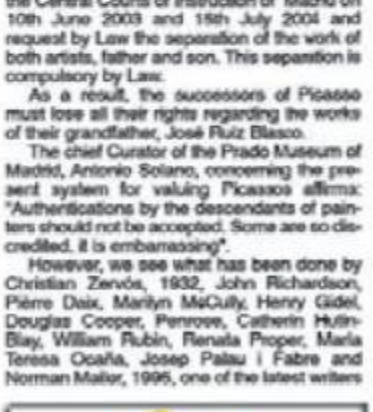
Why then does he accept him in his investments in art? why does he not demand modern, rigorous, scientific certificates?

"Dama en Eden Concert", timidly remained silent in the face of the grotesque system of certifying its virginity.

Photo: Béatrice HATALA

"Dama en Eden Concert", oil on canvas, 80x59 cm. Picasso 1903. Signed in the top right-hand corner, with scientific certificates issued by Doctor Marianne Tauber from the Swiss Institute for Art Research, Phd. in Chemical Engineering, Francesc Servera, from Lausanne and Barcelona University; and by Historian and friend of Picasso, Pierre de Champris. Pierre Daix says in his Dictionary that "We owe Champris the best study on Picasso's pictorial sources, written about in his book *Ombre et soleil, Paris 1960*. Analysed by X-Ray, appearing on the sub-layer, is the father of the artist reading. Picasso marked the frame with the numbers "323" and "323".

José Ruiz Blasco. 1895. Oil on canvas, attribu-



Hepatologists Party Like it's 1999.

This report contains 256 pages and certi- narchy, which is verified in a Calligraphy Report dated 27th December 2002 by the expert calligraphers Ms. Rosa Torrents Boley and Ms. Silvia Tarrago Goarré, from Barcelona, Spain.

files that Picasso had taken over by deceitful means all the works whose author was undoubtedly his father, José Ruiz Blasco in the period between 1892 and 1897. Specifically, the "J" of José Ruiz had been falsified to the "P" of Pablo, and was unlawfully and deceivingly assumed by Pablo Ruiz Picasso; this lie was made worse with the fraudulent Picasso donation in 1970 to Barcelona City Council: a donation which contained all the works of José Ruiz between 1892-1897.

What did Concepción Ruiz Walter, Claude, and Paloma Ruiz Gilot know?

This circumstance, would not worry us if it were not for the fact that the researcher was compelled to register the irregularities before the Central Courts of Instruction of Madrid on 10th June 2003 and 15th July 2004 and request by Law the separation of the work of both artists, father and son. This separation is compulsory by Law.

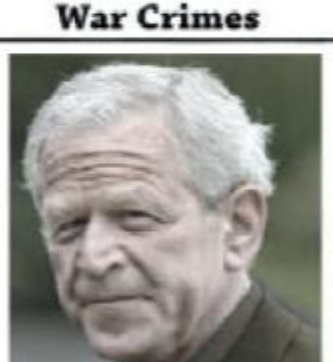
As a result, the successors of Picasso must lose all their rights regarding the works of their grandfather, José Ruiz Blasco.

The chief Curator of the Prado Museum of Madrid, Antonio Solano, concerning the present system for valuing Picassos affirms: "Authentications by the descendants of painters should not be accepted. Some are so discredited, it is embarrassing".

However, we see what has been done by Christian Zervós, 1932, John Richardson, Pierre Daix, Marilyn McCully, Henry Gidel, Douglas Cooper, Penrose, Catherin Hutin-Blay, William Rubin, Renata Proper, Maria Teresa Ocaña, Josep Palau i Fabre and Norman Mailer, 1995, one of the latest writers

narchy, which is verified in a Calligraphy Report dated 27th December 2002 by the expert calligraphers Ms. Rosa Torrents Boley and Ms. Silvia Tarrago Goarré, from Barcelona, Spain.

Former President Bush indicted for War Crimes



Rómulo-Antonio Tenés, Spain, a researcher and artist, is the author of the book **Fraud Picasso.** He takes to Court Goya's New Caprices Exhibition for proved fraud at the National Library of Spain, La Vanguardia, 11.8.81-. He achieved the removal of a false painting attributed to Darío de Regoyos from the Prado Museum news flash by REUTER and EFE World Press Agencys 20.09.1989. He participated in the Homage to Picasso 1981 at Skira Art Gallery along with Henry Moore, Chillida, Tapies, Miró, Rafael Alberti, Canogar, Oleiza, Saura, and other famous artists. In La Vanguardia, dated 8-03-1983, he published a study on Picasso's plagiarisme of the horse in the Guernica, which was painted by Ricardo Marín, Nuevo Mundo

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en vue de la rédaction d'une position d'experts

Journées Scientifiques en Infectiologie
Jeudi 29 novembre 2012, Paris

Société de Pathologie Infectieuse de Langue Française

SFLS Société Française de Lutte contre le SIDA

AFEF Association Française pour l'Etude du Foie

SNFMI Société Nationale Française de Médecine Interne