Focus su epatite C e terapie di nuova generazione

"Inquadramento farmacologico dell'HCV"

Marcella Bado

U.O.C. Farmacia

IRCCS San Martino - IST

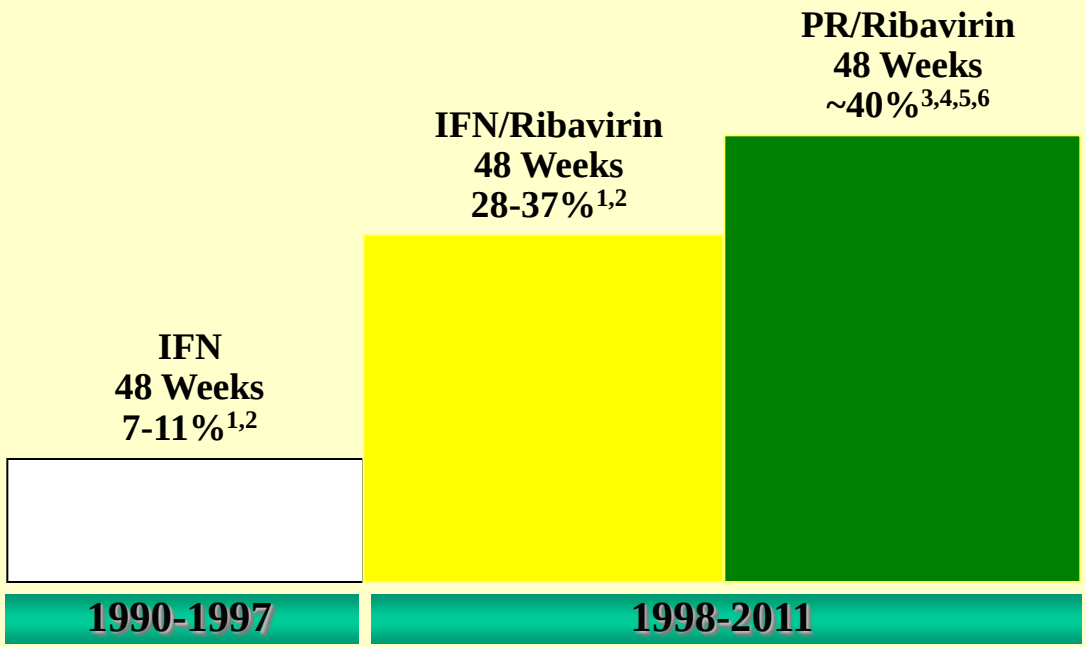
Genova, 8 aprile 2014

Starhotel President

SIFO

Società Italiana di Farmacia Ospedaliera
e dei Servizi Farmaceutici delle Aziende Sanitarie

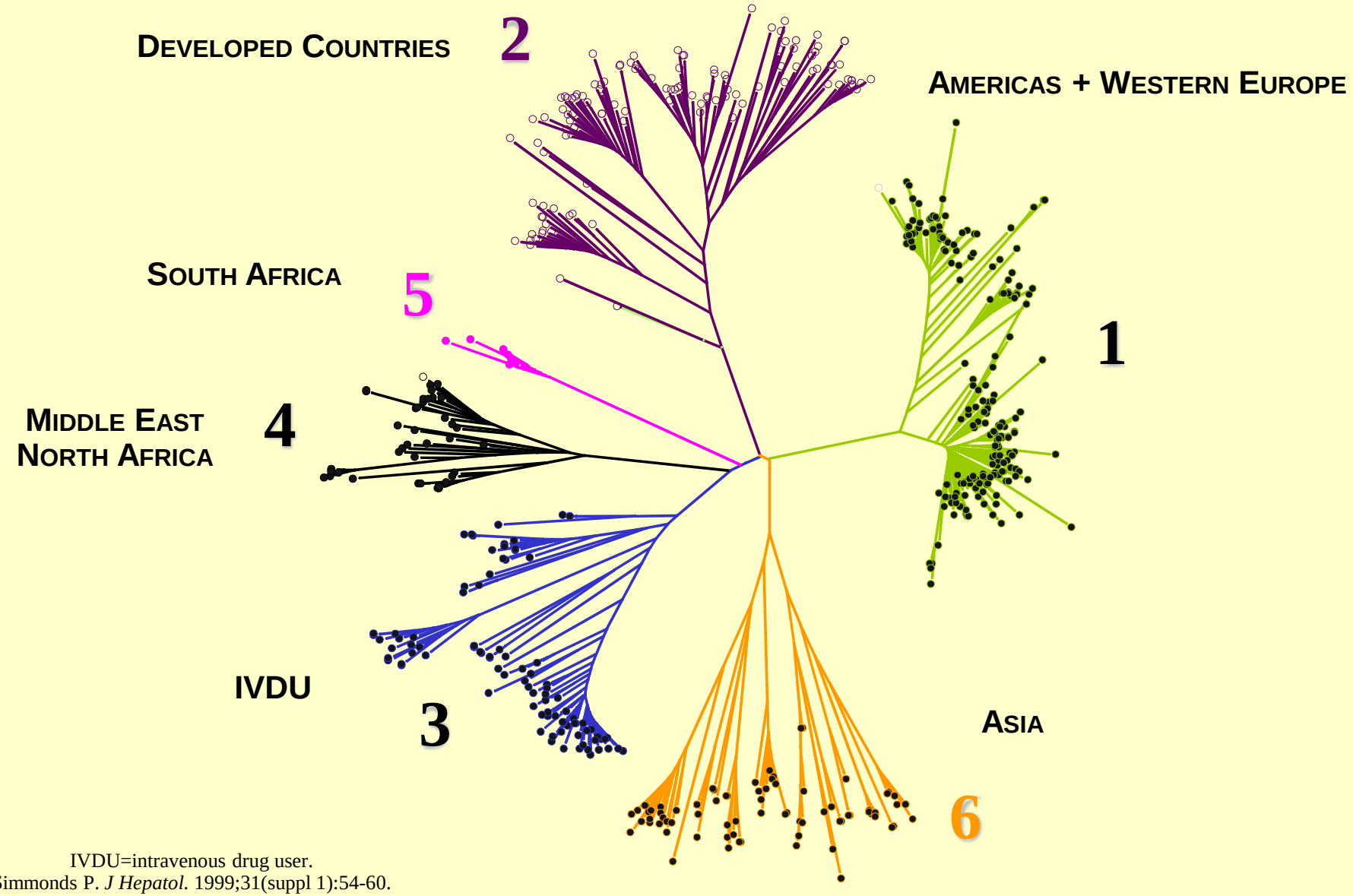
Trattamento HCV (Genotipo 1)



[1]McHutchison, NEJM (339) 1998; [2]Poynard, Lancet (352) 1998; [3]Manns, Lancet (358), 2001; [4]Lindsay, Hepatology (34) 2001; [5]Fried, NEJM (347), 2002; [6]McHutchison, NEJM (361) 2009; [7]Kwo, Lancet (376) 2010; [8]Poordad, NEJM (364) 2011; [9]Bacon, NEJM (364) 2011.

HCV=hepatitis C virus; IFN=interferon; PR=peginterferon α-2b + ribavirin; DAA/PR48=direct-acting antiviral/PR.

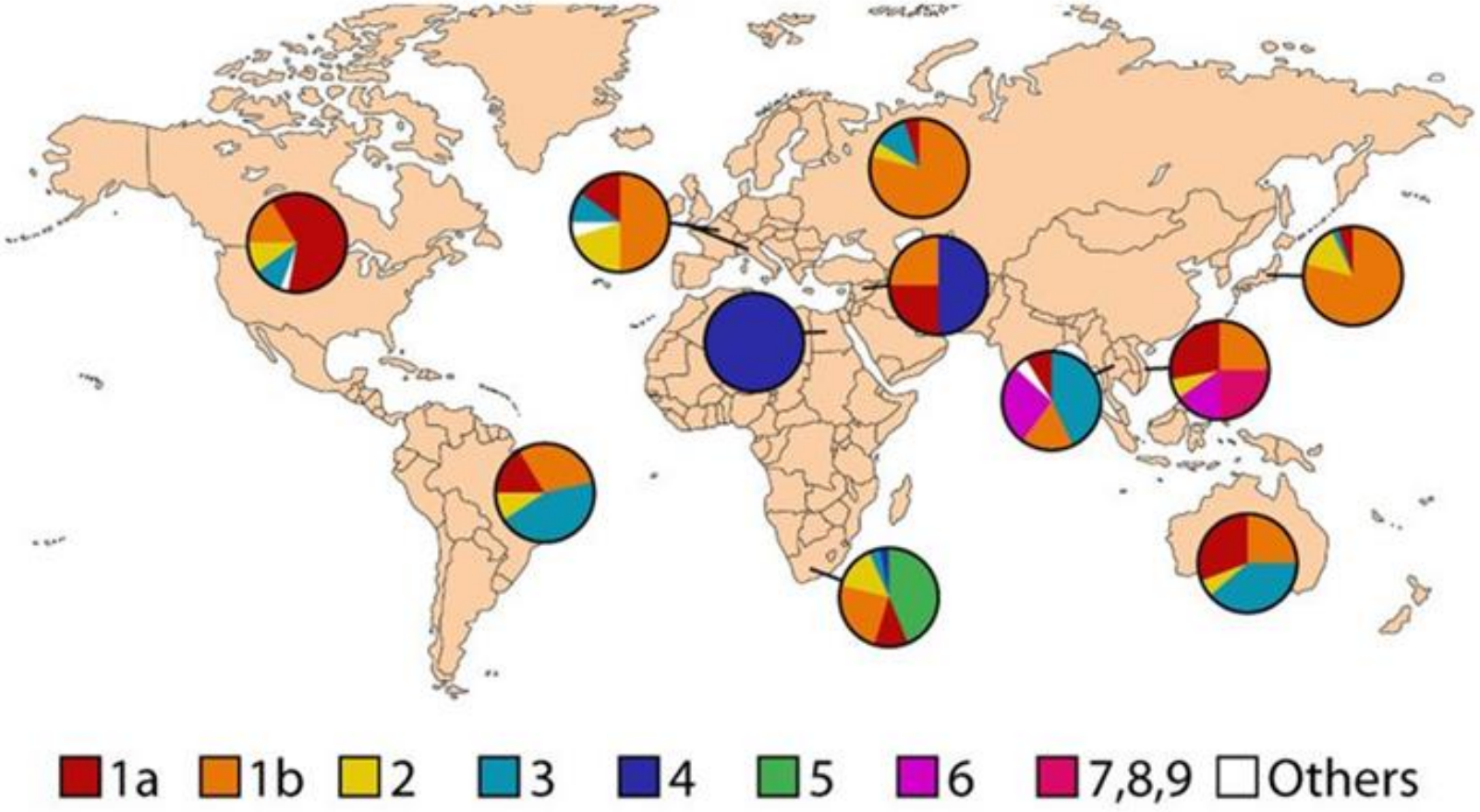
Genotipi HCV



IVDU=intravenous drug user.

Simmonds P. *J Hepatol.* 1999;31(suppl 1):54-60.

Distribution of hepatitis C genotypes

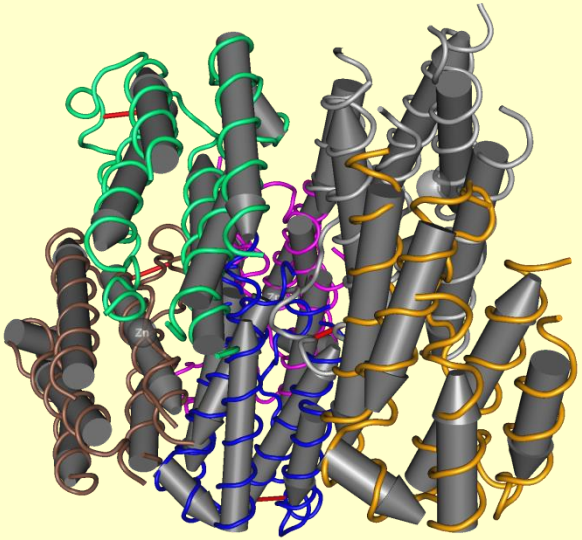


Epidemiology of Infectious Diseases. Available at: http://ocw.jhsph.edu.

Interferone

- Insieme di proteine inducibili implicate in
  - Risposta antivirale
  - Regolazione crescita e differenziamento cellulare
  - Risposta immunitaria innata

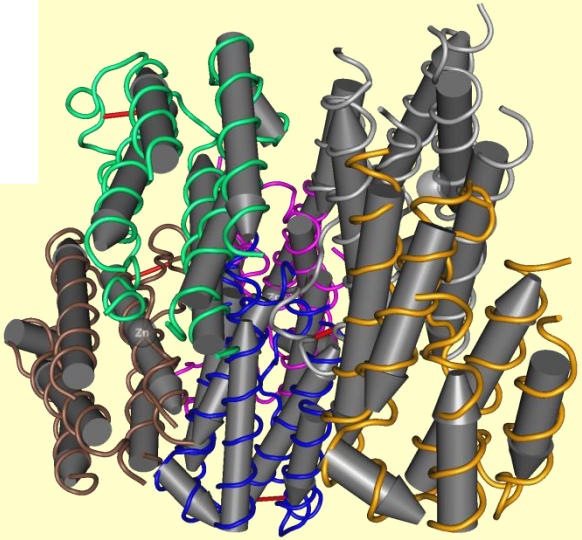
- SISTEMA INTERFERON
  - Tipo I
    - Alfa, Beta, Epsilon, Kappa, Omega
  - Tipo II
    - Gamma
  - Tipo III
    - Lambda



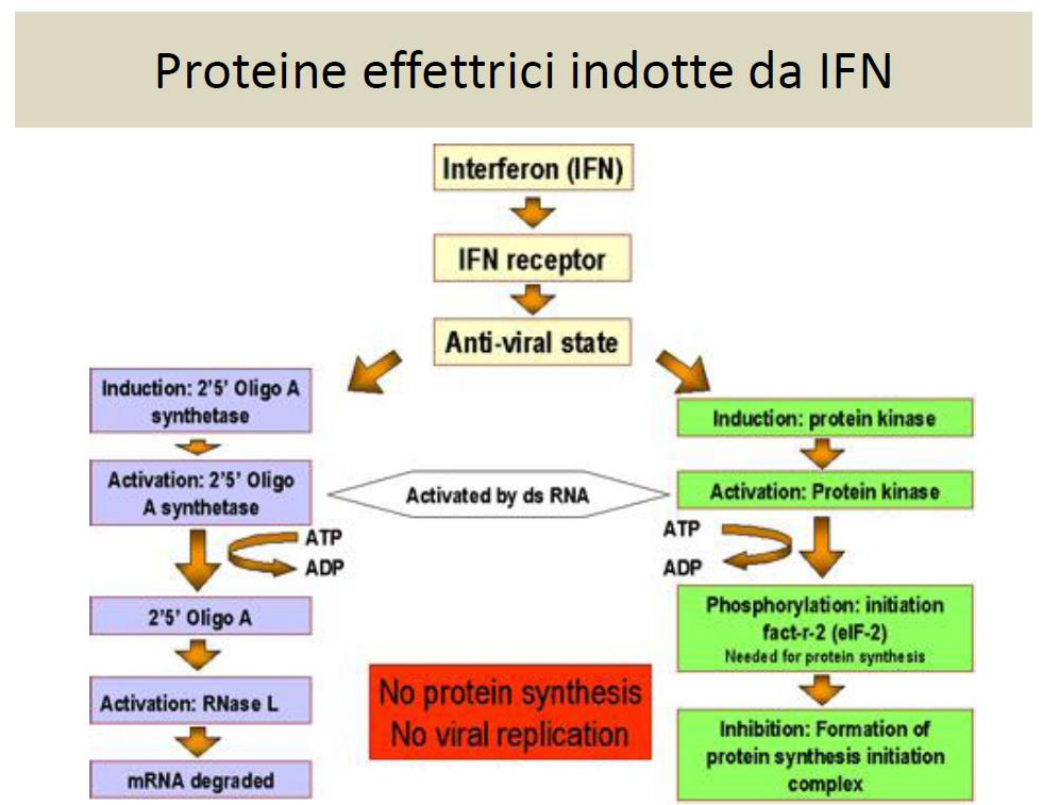
Interferone

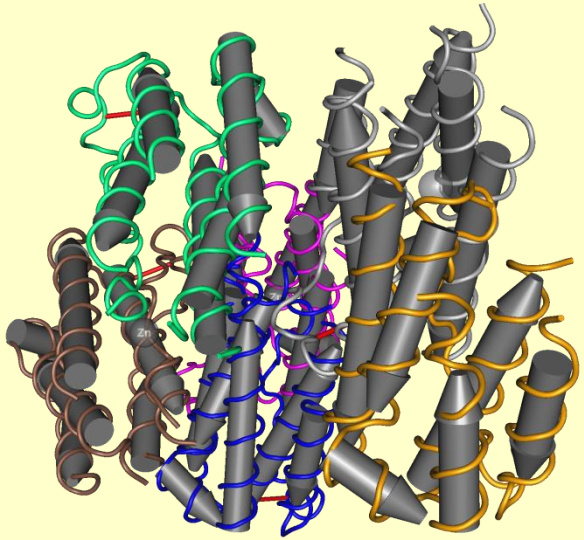
Proteine effettrici indotte da IFN (alfa/beta)

- 2’-5’ oligoA sintetasi
  - 2’-5’ oligoA in presenza di dsRNA attiva RNasi L che degrada RNA virale
  - 2’-5’ oligoA in presenza di dsRNA attiva apoptosi
- Protein-chinasi dsRNA-dipendente (PKR)
  - Inattiva eIF-2 impedendo traduzione
  - Attiva NFkB che induce apoptosi e attiva IFN-beta
- Proteine Mx
  - Inibizione replica virus influenzale
- ADAR-1
  - Converte adenosina in inosina alterando RNA
- P56 (IFIT1)
  - Inattiva eIF-2 impedendo traduzione



Interferone

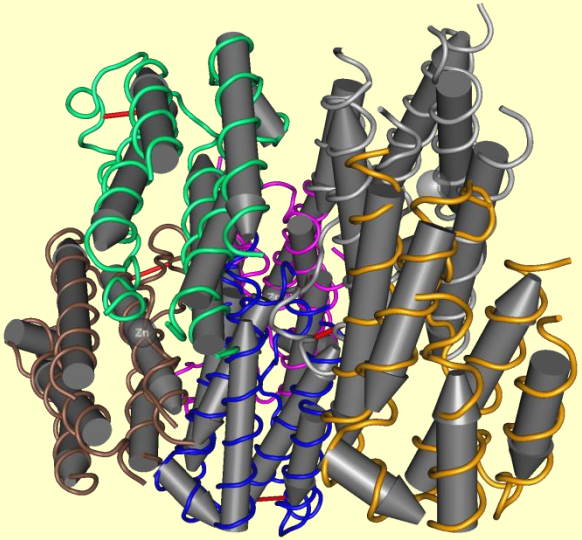




Interferone

Interferon – Problemi nell'uso clinico

- Effetti indesiderati
  - Febbre
  - Cefalea
  - Dolori muscolari
  - Vomito e diarrea
  - Malessere diffuso
  - Affaticabilità
  - Depressione
- Tossicità
  - Rene
  - Fegato
  - Midollo osseo
  - Muscolo cardiaco
- Risposta anticorpale anti-IFN
  - Alcuni anticorpi sembrano neutralizzare l'effetto dell'IFN
  - Fenomeno descritto soprattutto in pazienti con Sclerosi Multipla
- Costi

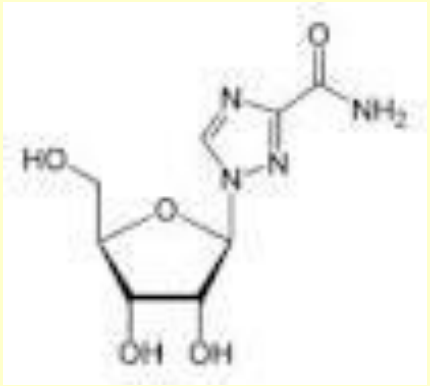


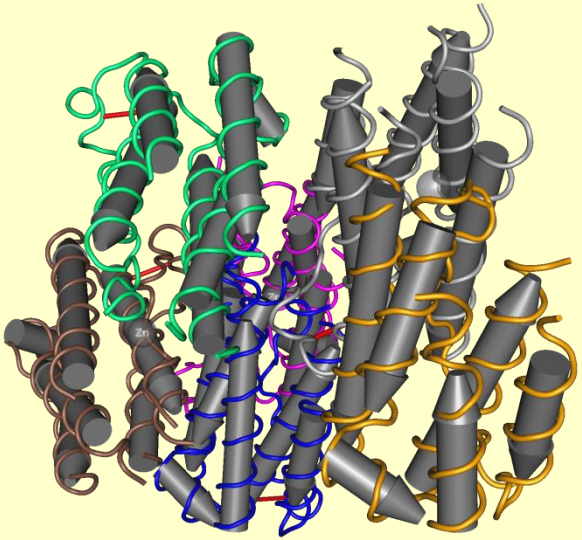
Ribavirina+Interferone

La ribavirina è un **analogo nucleosidico sintetico che *in vitro* esplica un'attività contro alcuni virus a RNA e DNA.**

Il **meccanismo** con cui ribavirina in associazione con peginterferone alfa-2b o interferone alfa-2b esercita i suoi effetti contro l'HCV **è sconosciuto**.

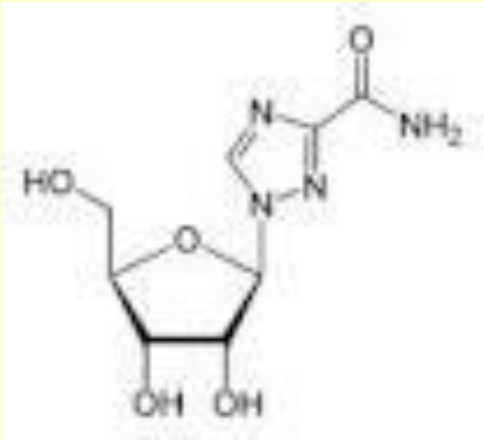
Ribavirina in monoterapia non ha alcun effetto nell'eliminare il virus dell'epatite (HCV-RNA) o nel migliorare l'istologia epatica dopo 6 o 12 mesi di terapia e 6 mesi di follow up.

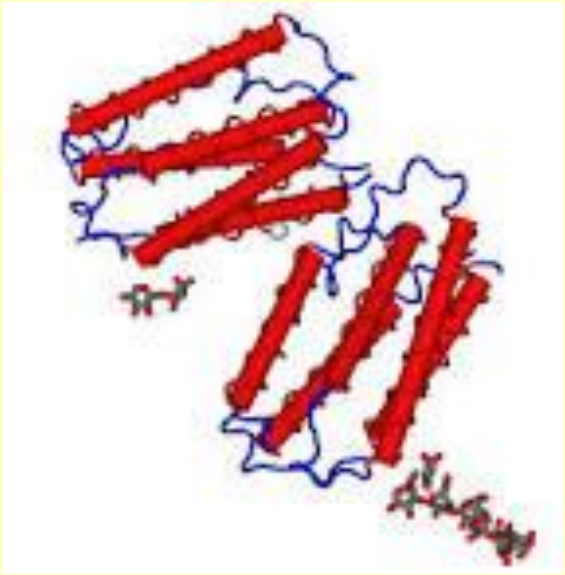




EPAR ribavirina agg. 2014

Ribavirina+Peg-interferone

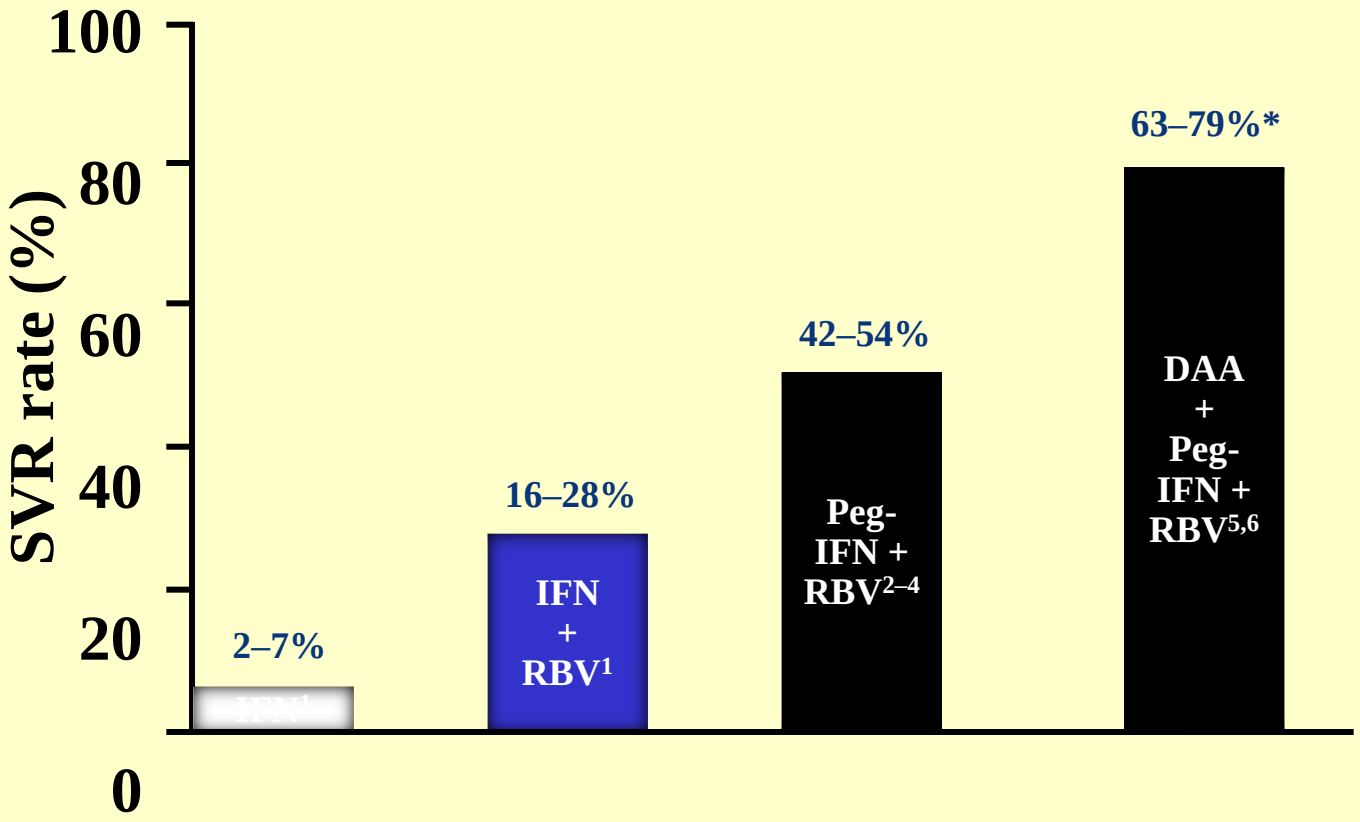




EPAR Pegasys e Pegintron agg. anno 2013

HCV
DAA - direct-acting antiviral agents

SVR in genotype 1 HCV in 2011: **boceprevir and telaprevir**



*Treatment-naïve patients

1. McHutchison JG, et al. N Engl J Med 1998;339:1485–92; 2. Fried M, et al. N Engl J Med 2002;347:975–82
3. Manns MP, et al. Lancet 2001;358:958–65; 4. Hadziyannis SJ, et al. Ann Intern Med 2004;140:346–55
5. Telaprevir EU SmPC; 6.Boceprevir EU SmPC

HCV
DAA - direct-acting antiviral agents

Molecules	Class	Genotype	Company	FDA	EMA	AIFA
telaprevir	NS3/4 A PI	1	Janssen Cilag	SI	SI	SI
boceprevir	NS3/4 A PI	1	MSD	SI	SI	SI
Sofosbuvir	NPI	Pangenotypic	Gilead Sciences	SI	SI	(CNN) Comm. PR
Simeprevir	NS3/4 A PI	1	Johnson & Johnson	SI	SI	(CNN) Comm. PR

Adapated from Raymond Schinazi Liver International 2014

HCV
DAA - direct-acting antiviral agents

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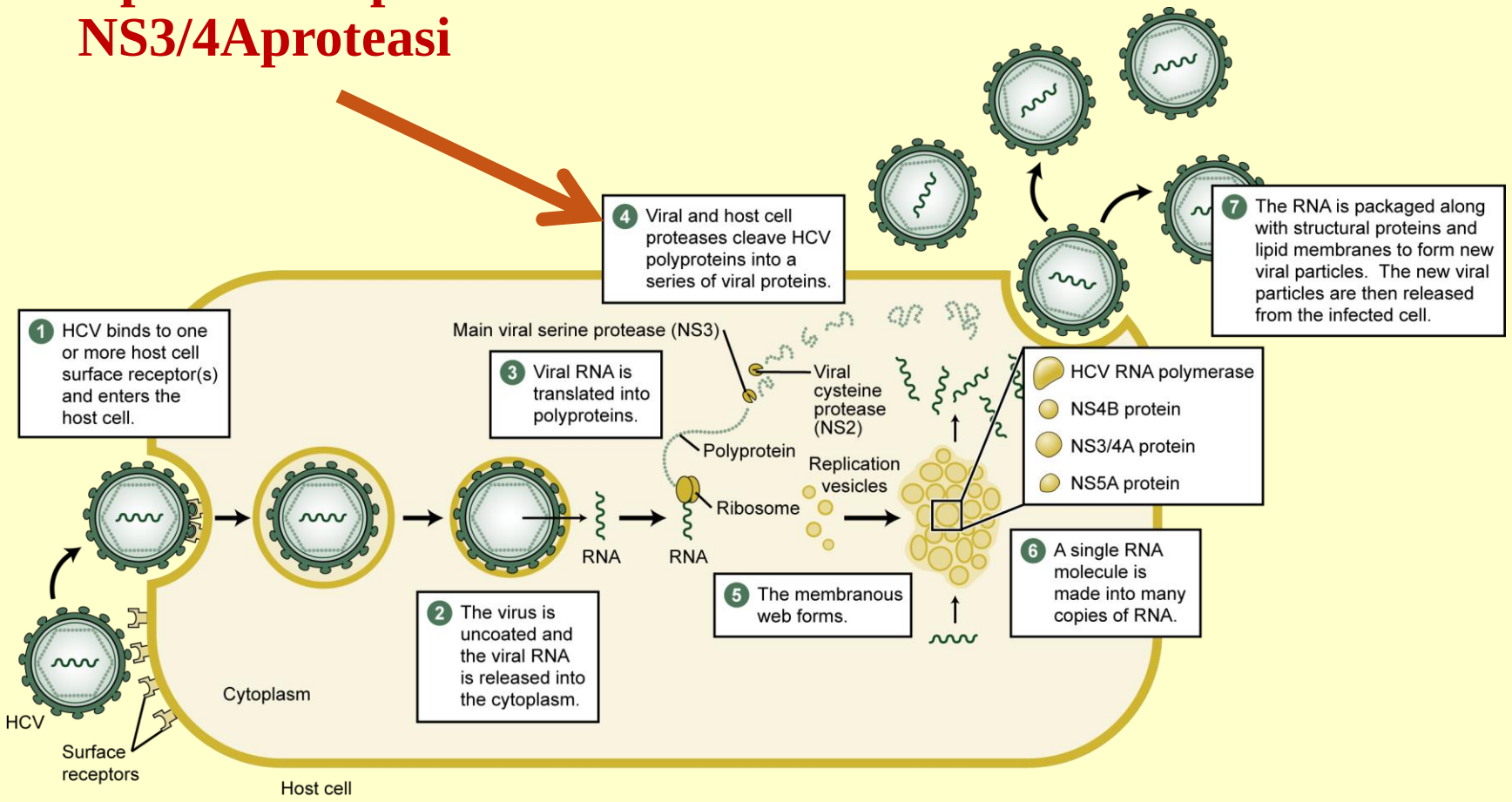
Adapated from Raymond Schinazi Liver International 2014

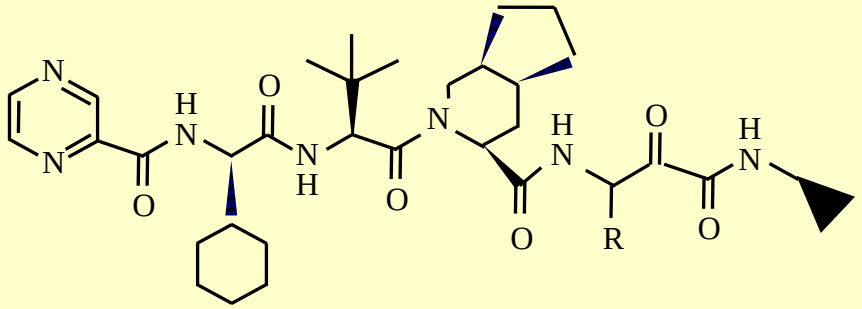
HCV life cycle

boceprevir/telaprevir
NS3/4Aproteasi



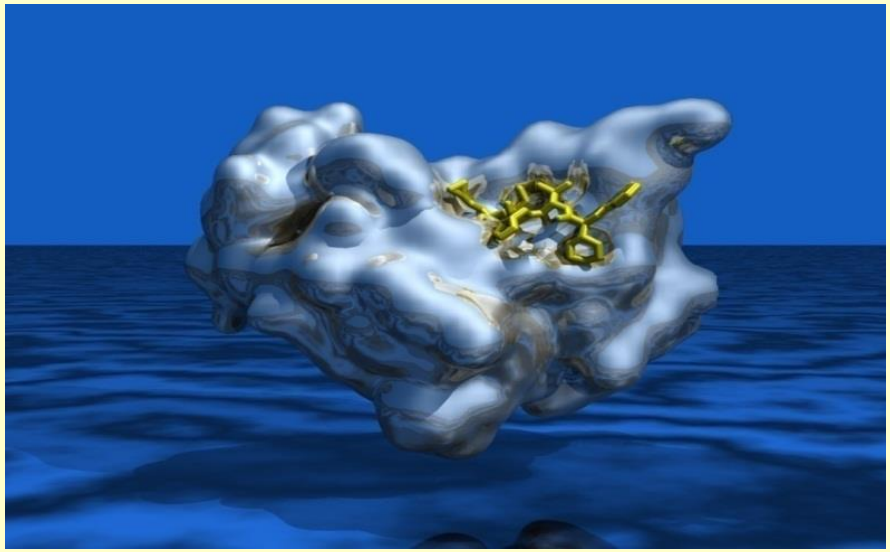
Adattato da Mandell et al, 2010; Moradpour et al, 2007.

TELAPREVIR



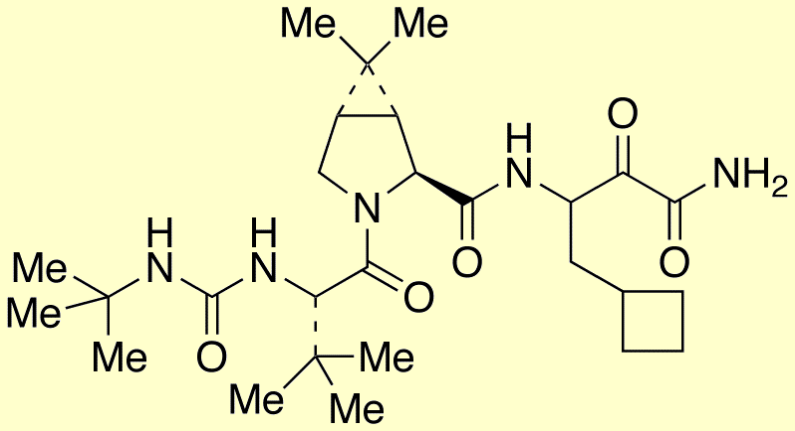
Telaprevir is a reversible, covalent, tight- and slow-binding **inhibitor of the HCV NS3-4A protease**

Telaprevir is a potent, selective**, peptidomimetic inhibitor of the hepatitis C virus (HCV) NS3-4A serine protease**



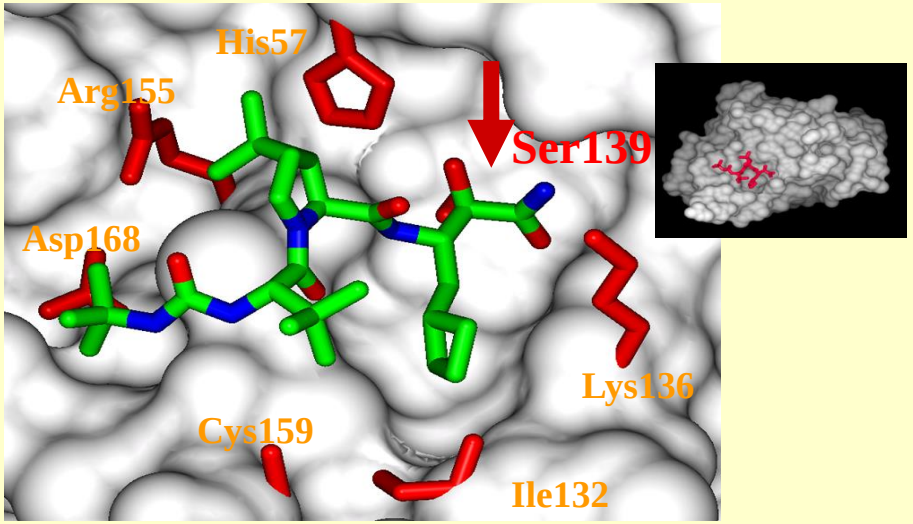
EPAR telapravir

BOCEPREVIR



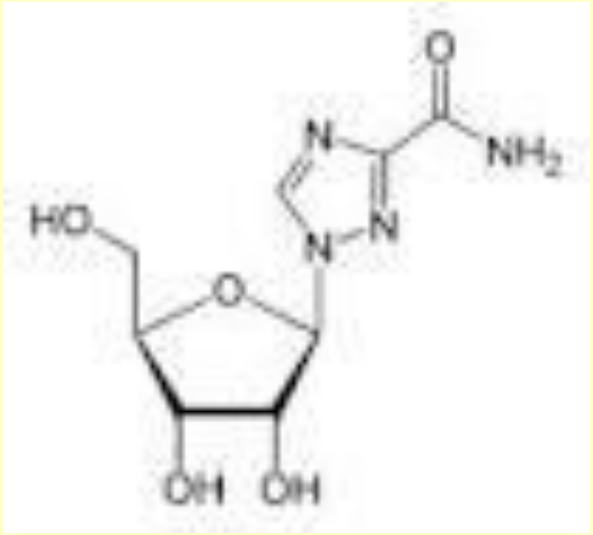
Boceprevir is an **inhibitor of the HCV NS3 protease.**

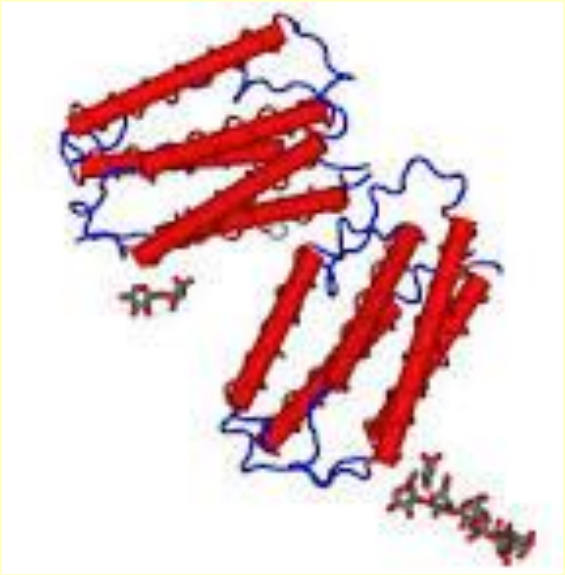
Boceprevir covalently, yet reversibly**, binds to the NS3 protease active site serine (Ser139) through a (alpha)-ketoamide functional group** to inhibit viral replication in HCV-infected host cells.



Kwo PY et al Lancet 2010; 376: 705; Schiff E et al J Hepatol 2008; 48: S46.

TRIPLICE TERAPIA
RIBAVIRINA+PEGIN+DAA



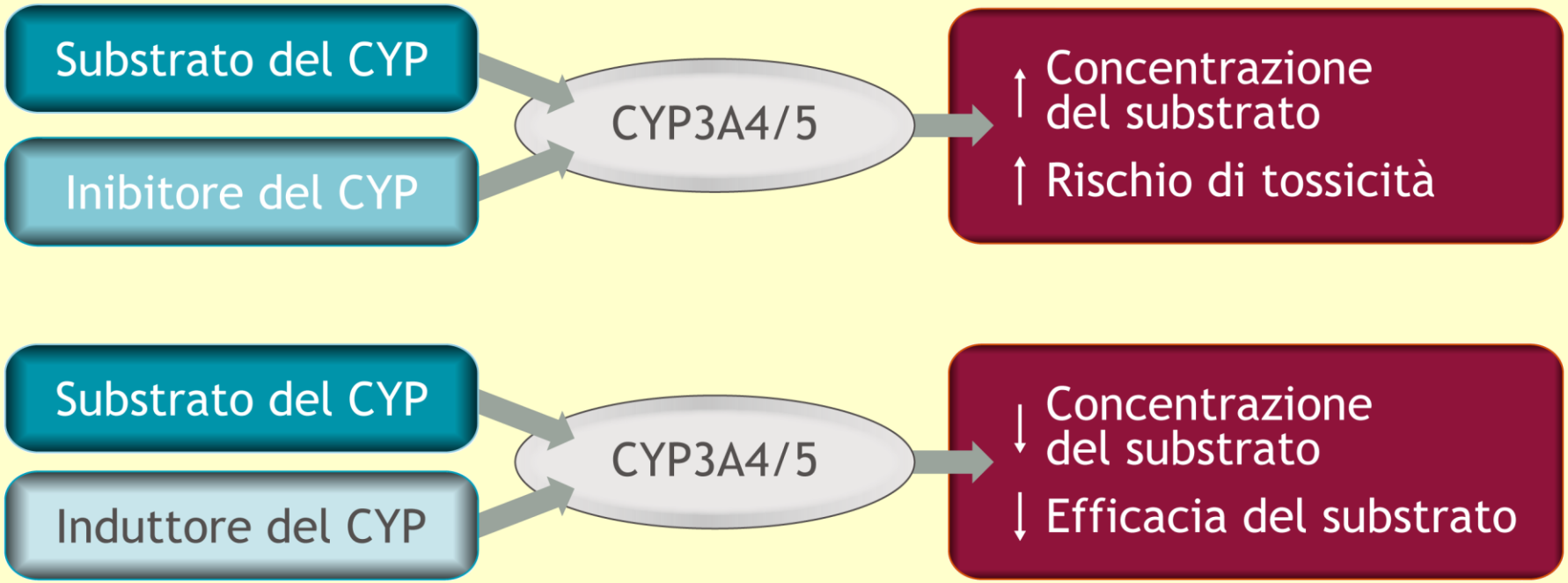


BOCEPREVIR

o

TELAPREVIR

Interazioni con il metabolismo dei farmaci: CYP3A4/5[1]



Elaborato da[1,2]

Abbreviazioni: CYP3A4/5, citocromo P450 3A4/5.

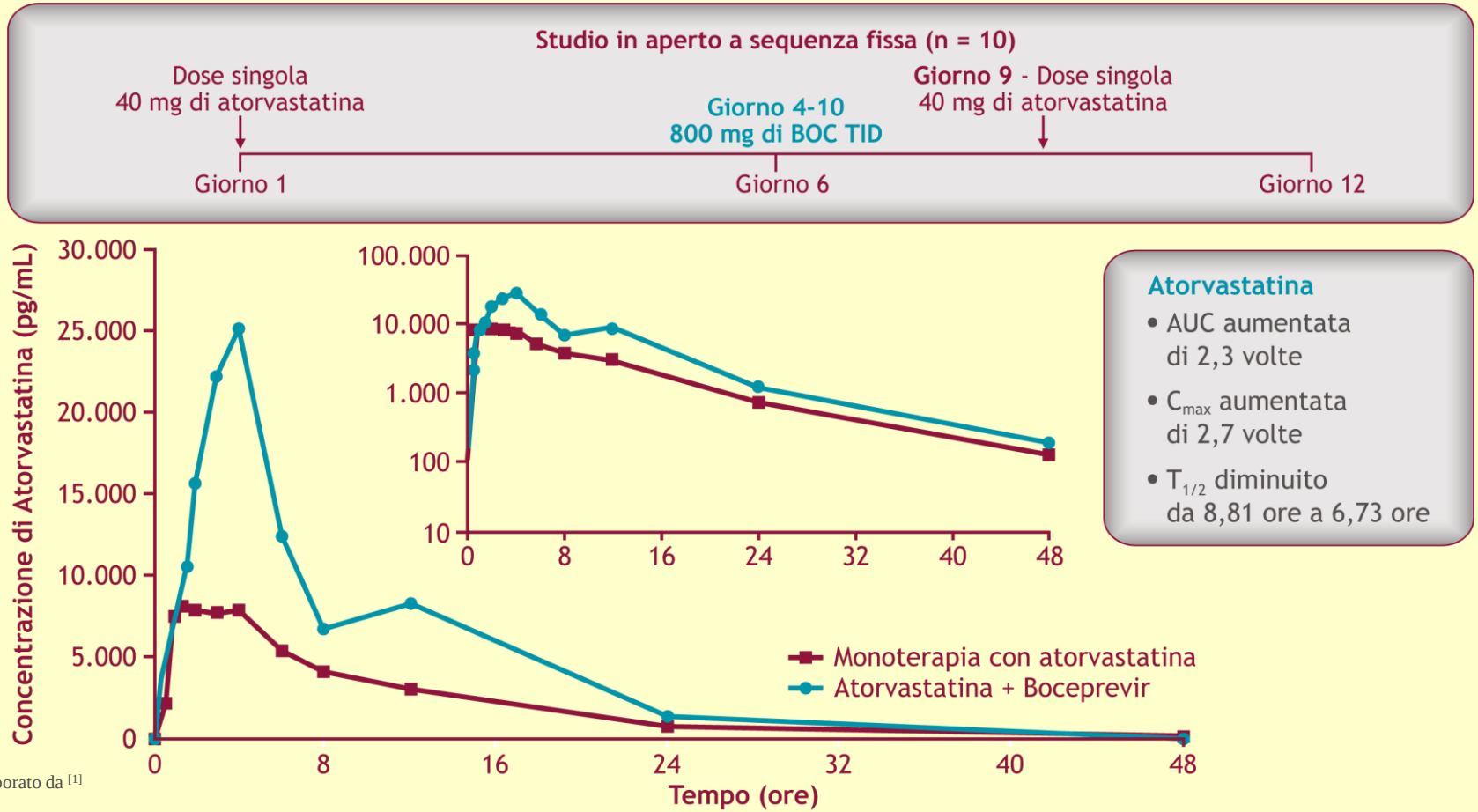
1. VICTRELIS Riassunto delle Caratteristiche del Prodotto. 2. Buxton ILO, Benet LZ. In: Brunton L et al, ed. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12 ed. New York, NY: McGraw Hill Medical; 2011:17–39.

Telaprevir: DDIs with HIV antiretrovirals

HIV antiretroviral	HIV antiretroviral	Recommendation with telaprevir
Darunavir/r (DRV/r)	**PREZISTA**	**Not recommended**
Fosamprenavir/r (FAP/r)	**TELZIR**	**Not recommended**
Lopinavir/r (LPV/r)	**KALETRA**	**Not recommended**

For DRV/r, evolving in vivo and in vitro data is consistent with a protein displacement interaction, but clinical confirmation is needed. We are further investigating this interaction in HIV-HCV coinfected patients.
20 patients on stable DRV/r-based HAART will be allowed in the phase 3 trial INSIGHT (NCT01513941), with mandatory PK substudy (data on file).

Effetto sulla PK di farmaci co-somministrati



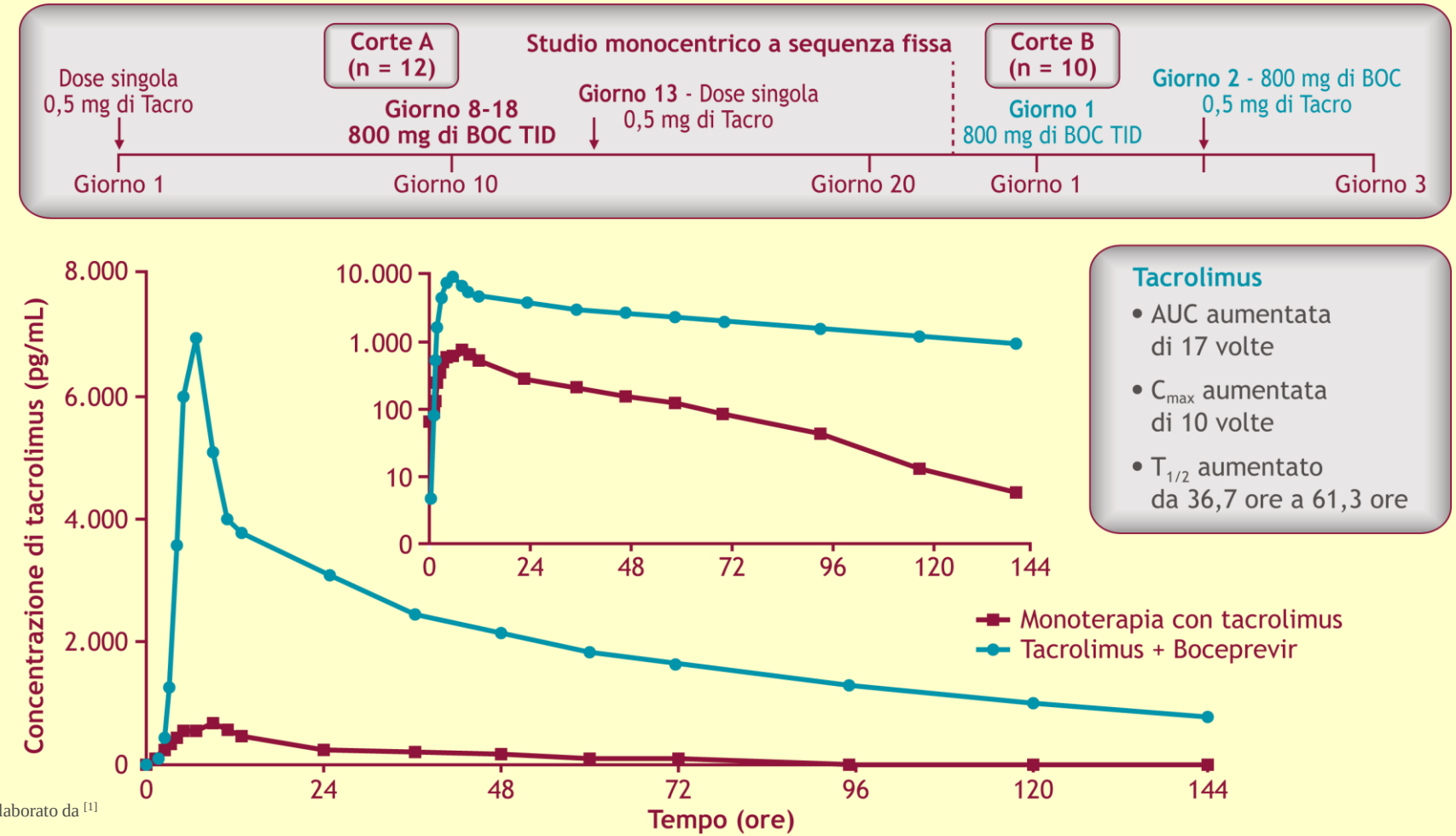
Elaborato da [1]

- Si raccomanda il monitoraggio terapeutico di atorvastatina durante la co-somministrazione.[1]
- La co-somministrazione diboceprevir e simvastatina o lovastatina è controindicata.[1]

Abbreviazioni: AUC, area sotto la curva concentrazione plasmatica-tempo; BOC, boceprevir; C_{max}, concentrazione plasmatica massima (picco) di farmaco; PK, farmacocinetica; $T_{1/2}$, emivita di eliminazione; TID, tre volte al giorno.

1. VICTRELIS Riassunto delle Caratteristiche del Prodotto.

Effetto sulla PK di farmaci co-somministrati



Elaborato da [1]

Si raccomanda il monitoraggio terapeutico di tacrolimus durante la co-somministrazione.[1]

Abbreviazioni: AUC, area sotto la curva concentrazione plasmatica-tempo; BOC, boceprevir; C_{max}, concentrazione plasmatica massima (picco) di farmaco; PK, farmacocinetica; $T_{1/2}$, emivita di eliminazione; Tacro= tacrolimus; TID, tre volte al giorno.

1. VICTRELIS Riassunto delle Caratteristiche del Prodotto.

Counseling should be provided on potential adverse events that may occur

Telaprevir:[1]

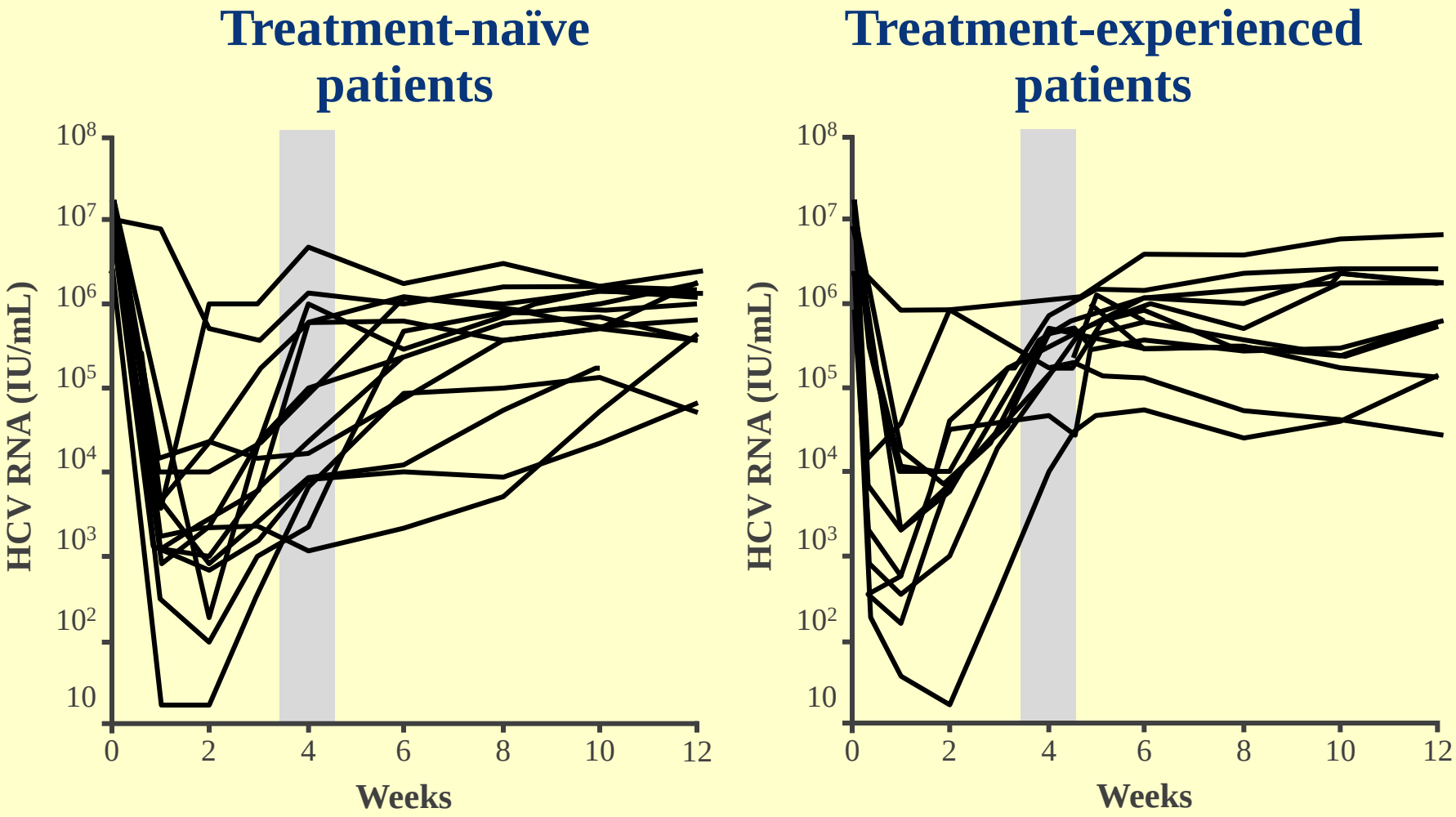
- **Anemia**
- **Nausea**
- **Rash, pruritus**
- **Anorectal signs/symptoms**
- **Diarrhoea**

Boceprevir:[2]

- **Anemia**
- **Nausea**
- **Dysgeusia**
- **Neutropenia**
- **Headache**

1. Telaprevir EU SmPC; 2. Boceprevir EU SmPC

Viral kinetics in patients who met the >1000 IU/mL HCV RNA
Week 4 stopping rule with telaprevir



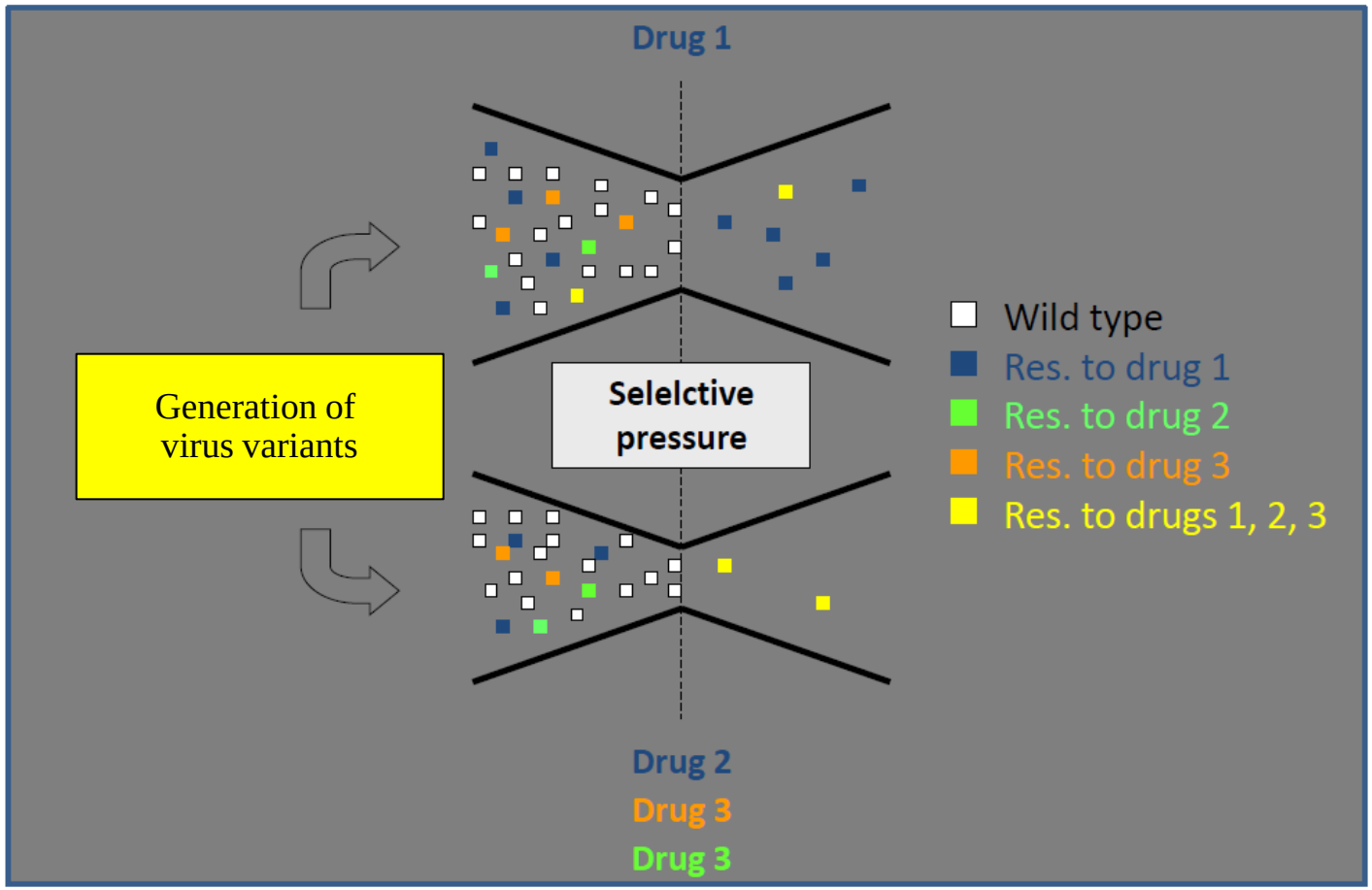
Adda N, et al. HepDART 2011. Abstract 45

Il problema della resistenza ai farmaci antivirali

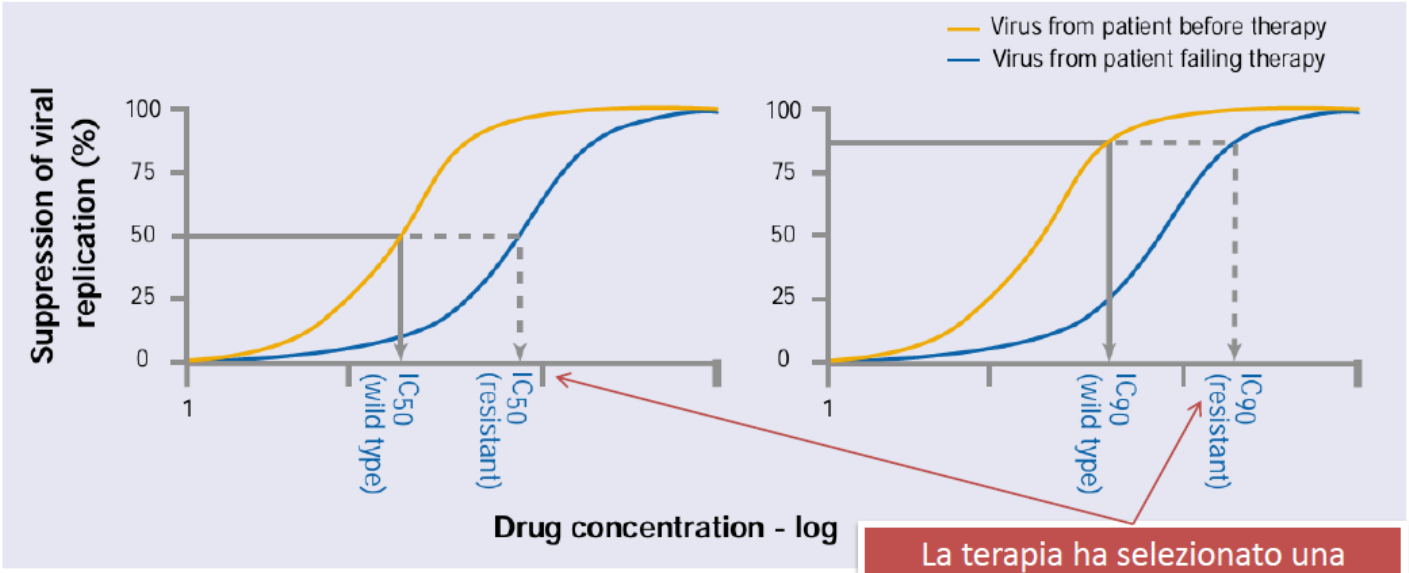
- I virus generano con facilità mutanti

- Un mutante può essere casualmente meno sensibile ad un farmaco
  - Il farmaco seleziona i mutanti ad esso resistenti
  - La selezione opera sul virus in attiva replica
    - Se la replica virale è bloccata anche la generazione e selezione dei mutanti è bloccata
- Mutanti resistenti possono esistere anche prima del contatto con il farmaco a cui sono resistenti
  - Variabilità naturale
  - Trasmissione ceppi resistenti da parte di soggetti in trattamento antivirale

La terapia combinata rallenta la selezione della resistenza



Misurazione dell'attività antivirale in vitro (IC = Inhibitory Concentration)



- IC50, dose di farmaco che inibisce del 50% la produzione di virus
  - Valore meno corrispondente alla reale inibizione ma misurazione più accurata (usato spesso)
- IC90, dose di farmaco che inibisce del 90% la produzione di virus
  - Valore più corrispondente alla reale inibizione ma misurazione poco accurata (usato raramente)

HCV
DAA - direct-acting antiviral agents

Molecules	Class	Genotype	Company	FDA	EMA	AIFA
telaprevir	NS3/4A PI	1	Janssen Cilag	SI	SI	SI
boceprevir	NS3/4A PI	1	MSD	SI	SI	SI
Sofosbuvir	NPI	Pangenotypic	Gilead Sciences	SI	SI	(CNN) Comm. PR
Simeprevir	NS3/4A PI	1	Johnson & Johnson	SI	SI	(CNN) Comm. PR

Adapated from Raymond Schinazi Liver International 2014

22 November 2013
EMA/717004/2013
Press Office

Press release

European Medicines Agency recommends approval of sofosbuvir for the treatment of chronic hepatitis C

First-in-class medicine provides the first interferon-free treatment option

The European Medicines Agency's Committee for Medicinal Products for Human use (CHMP) has recommended granting a marketing authorisation for Sovaldi (sofosbuvir), for use 'in combination with other medicinal products for the treatment of chronic (long-term) hepatitis C in adults'.

Hepatitis C virus (HCV) infection is a major European public-health challenge. It occurs in between 0.4% and 3.5% of the population in different European Union (EU) Member States.

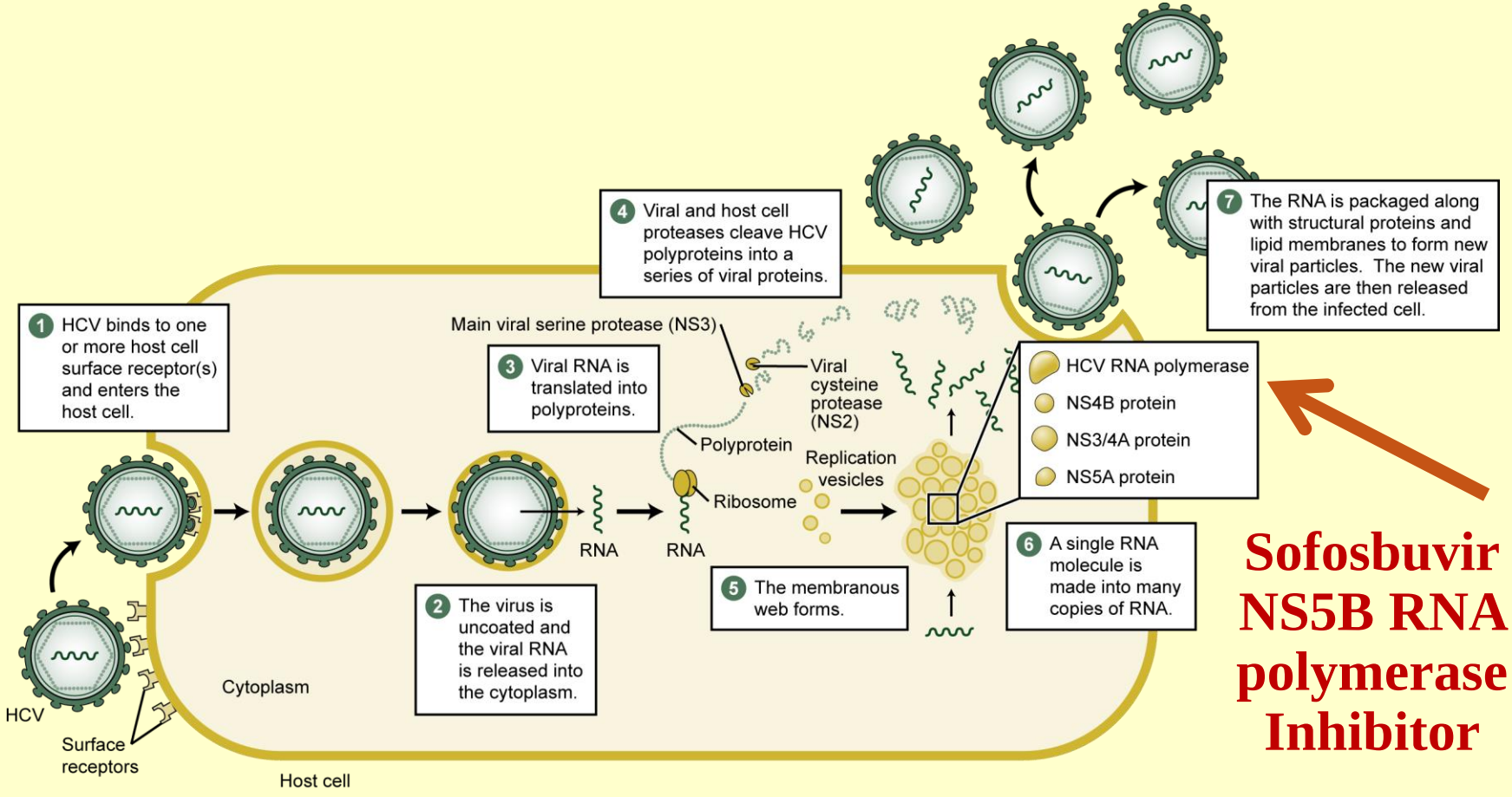
The current standard of care includes a combination of the medicines pegylated interferon and ribavirin, with or without an inhibitor of the viral NS3/4A protease enzyme. However, interferon-based therapies are associated with potentially serious side effects, which are sometimes difficult to manage and also make a considerable proportion of HCV patients ineligible for therapy. This includes patients with very advanced liver disease, as well as patients with psychiatric diseases, autoimmune disorders, etc. For these patients, there is a very clear unmet medical need for new HCV treatment regimens.

The treatment of hepatitis C is a rapidly moving therapeutic area, with several new classes of direct-acting antivirals now in advanced stages of development. The European Medicines Agency is actively supporting the development of these new treatment options for patients through provision of scientific advice and drafting of guidance to developers of these medicines.

Sovaldi is the first representative of a new class of antivirals that act as inhibitors of an essential enzyme of HCV, the NS5B ribonucleic acid polymerase. This medicine provides the first interferon-free treatment option for chronic hepatitis C.

In clinical trials where sofosbuvir was used in combination with ribavirin alone, it has convincingly shown efficacy with a good safety profile. A high proportion of patients had no detectable virus in their

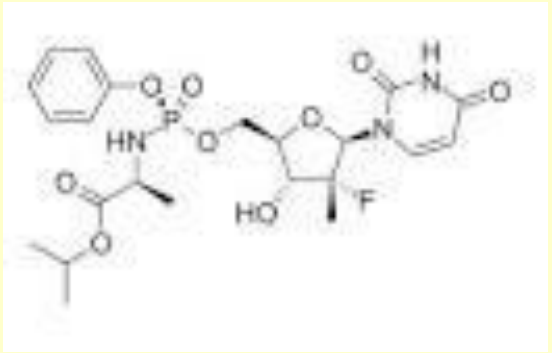
HCV life cycle



Sofosbuvir NS5B RNA polymerase Inhibitor

Adattato da Mandell et al, 2010; Moradpour et al, 2007.

SOFOSBUVIR



Sofosbuvir è un **inibitore pan-genotipico dell'RNA polimerasi NS5B RNA-dipendente dell'HCV**, che è essenziale per la replicazione virale.

Sofosbuvir è un **profarmaco nucleotidico** soggetto a metabolismo intracellulare, che dà origine all'analogo uridinico trifosfato (GS-461203) farmacologicamente attivo, il quale può essere **incorporato nell'HCV RNA dalla polimerasi NS5B e fungere da terminatore di catena.**

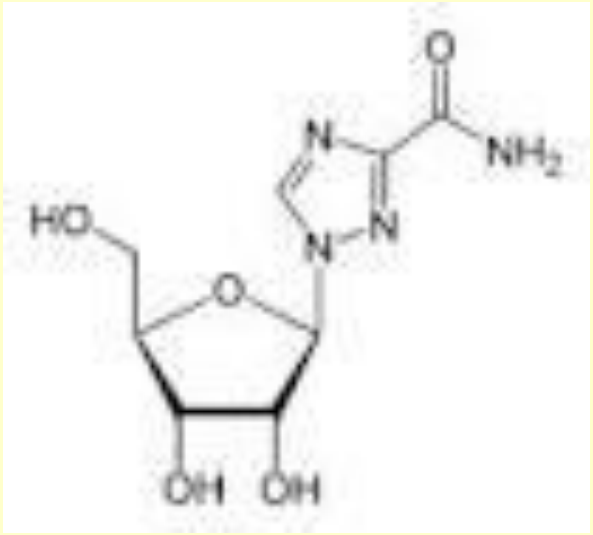
GS-461203 (il metabolita attivo di sofosbuvir) non è un inibitore delle DNA e RNA polimerasi umane, né un inibitore della RNA polimerasi mitocondriale.

Sofosbuvir is a component of the first all-oral, interferon-free regimen approved for treating chronic Hepatitis C

Tucker M (December 6, 2013). "FDA Approves 'Game Changer' Hepatitis C Drug Sofosbuvir". Medscape.

EPAR sofosbuvir

DUPLICE TERAPIA
RIBAVIRINA+PEGIN+DAA



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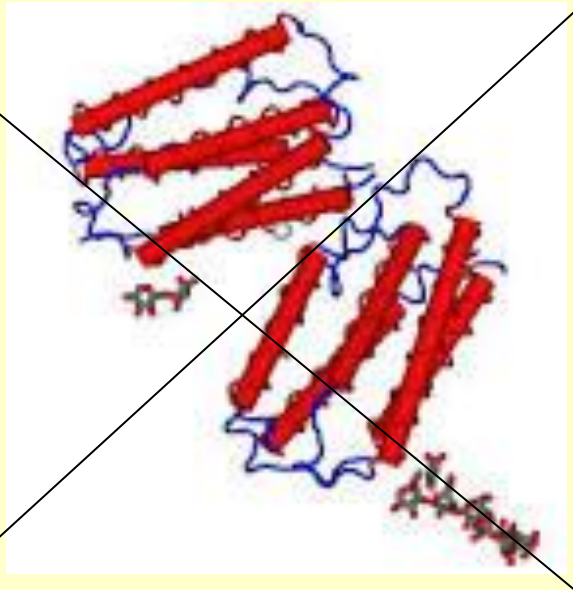


SOFOSBUVIR

Tabella 1: Medicinale(i) raccomandato(i) da somministrare insieme con Sovaldi e durata del trattamento per la terapia di associazione

Popolazione di pazienti*	Trattamento	Durata
Pazienti con CHC di genotipo 1, 4, 5 o 6	Sovaldi + ribavirina + peginterferone alfa	12 settimane[a, b]
	Sovaldi + ribavirina Da utilizzare solo per i pazienti non eleggibili o intolleranti a peginterferone alfa (vedere paragrafo 4.4)	24 settimane
Pazienti con CHC di genotipo 2	Sovaldi + ribavirina	12 settimane[b]
Pazienti con CHC di genotipo 3	Sovaldi + ribavirina + peginterferone alfa	12 settimane[b]
	Sovaldi + ribavirina	24 settimane
Pazienti con CHC in attesa di trapianto di fegato	Sovaldi + ribavirina	Fino al trapianto di fegato[c]

*Include i pazienti con co-infezione da virus dell'immunodeficienza umana (HIV).

a. Per i pazienti con infezione da HCV di genotipo 1 precedentemente trattati, non esistono dati relativi all'associazione di Sovaldi, ribavirina e peginterferone alfa (vedere paragrafo 4.4).

b. Si deve prendere in considerazione la possibilità di estendere la durata della terapia oltre 12 settimane e fino a 24 settimane, specialmente per i sottogruppi che presentano uno o più fattori storicamente associati a bassi tassi di risposta alle terapie a base di interferone (ad es. fibrosi/cirrosi avanzata, concentrazioni virali basali elevate, etnia nera, genotipo IL28B non-CC, precedente assenza di risposta alla terapia con peginterferone alfa e ribavirina).

c. Vedere Popolazioni particolari di pazienti: Pazienti in attesa di trapianto di fegato.

Genotype 2 and 3:
oral dual therapy of sofosbuvir in combination with ribavirin (RBV)

Genotypes 1 and 4:
triple therapy with injected pegylated interferon (pegIFN) and RBV for treatment-naive patients with HCV

Tucker M (December 6, 2013). "FDA Approves 'Game Changer' Hepatitis C Drug Sofosbuvir". Medscape.

EPAR sofosbovir

HCV
DAA - direct-acting antiviral agents

Molecules	Class	Genotype	Company	FDA	EMA	AIFA
telaprevir	NS3/4A PI	1	Janssen Cilag	SI	SI	SI
boceprevir	NS3/4A PI	1	MSD	SI	SI	SI
Sofosbuvir	NPI	Pangenotypic	Gilead Sciences	SI	SI	(CNN) Comm. PR
Simeprevir	NS3/4A PI	1	Johnson & Johnson	SI	SI	(CNN) Comm. PR

Adapated from Raymond Schinazi Liver International 2014

SIMEPREVIR

FDA NEWS RELEASE

For Immediate Release: Nov. 22, 2013
Media Inquiries: Stephanie Yao, 301-796-0394, stephanie.yao@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

En Español

FDA approves new treatment for hepatitis C virus

The U.S. Food and Drug Administration today approved Olysio (simeprevir), a new therapy to treat chronic hepatitis C virus infection.

Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with the hepatitis C virus have no symptoms of the disease until liver damage becomes apparent, which may take several years. Most of these people then go on to develop chronic hepatitis C. Some will also develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections or liver cancer. According to the Centers for Disease Control and Prevention, about 3.2 million Americans are infected with the hepatitis C virus.

Olysio is a protease inhibitor that blocks a specific protein needed by the hepatitis C virus to replicate. It is to be used as a component of a combination antiviral treatment regimen. In clinical studies, Olysio was evaluated in combination with peginterferon-alfa and ribavirin, two drugs also used to treat hepatitis C virus

SIMEPREVIR

Olysio

Opinion | Key facts

On 20 March 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Olysio, 150 mg, hard capsules intended for the treatment of chronic hepatitis C (CHC). The applicant for this medicinal product is Janssen-Cilag International N.V. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Olysio is simeprevir, antivirals for systemic use (J05AE) and a specific inhibitor of the HCV NS3/4A serine protease.

The benefits with Olysio are its efficacy demonstrated in the treatment of chronic hepatitis C in adult patients when used in combination with other medicinal products. The most common side effects (incidence ≥ 5%) are were nausea, rash, pruritus, dyspnoea, blood bilirubin increase and photosensitivity reaction.

A pharmacovigilance plan for Olysio will be implemented as part of the marketing authorisation.

The approved indication is: "*OLYSIO is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients (see sections 4.2, 4.4 and 5.1). For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1.*". It is proposed that Olysio be prescribed by physicians experienced in the treatment of chronic hepatitis C (CHC).

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Olysio and therefore recommends the granting of the marketing authorisation.

Name	Language	First published	Last updated
CHMP summary of positive opinion for Olysio	(English only)	21/03/2014	

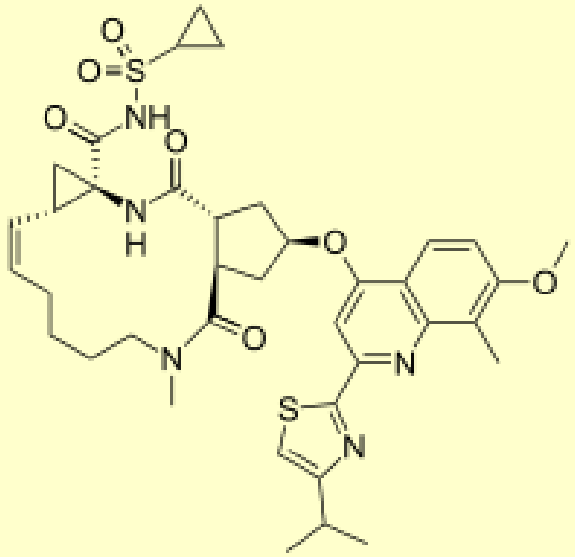
News

- Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 17-20 March 2014 (21/03/2014)

SIMEPREVIR

Simeprevir is an **NS3/4A protease inhibitor**

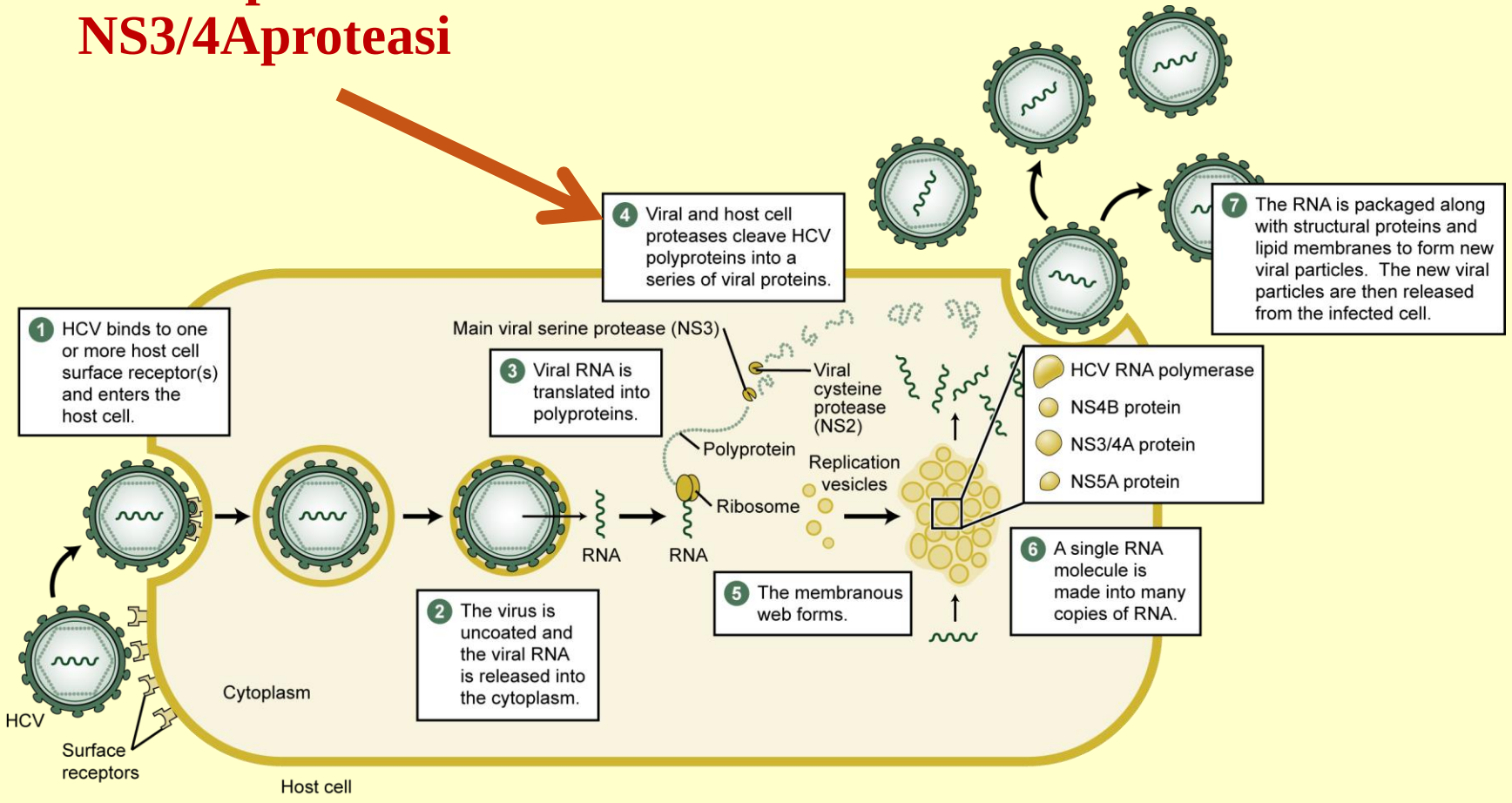
Simeprevir works by blocking the viral protease enzyme that enables the hepatitis C virus (HCV) to replicate in host cells.



FDA simeprevir

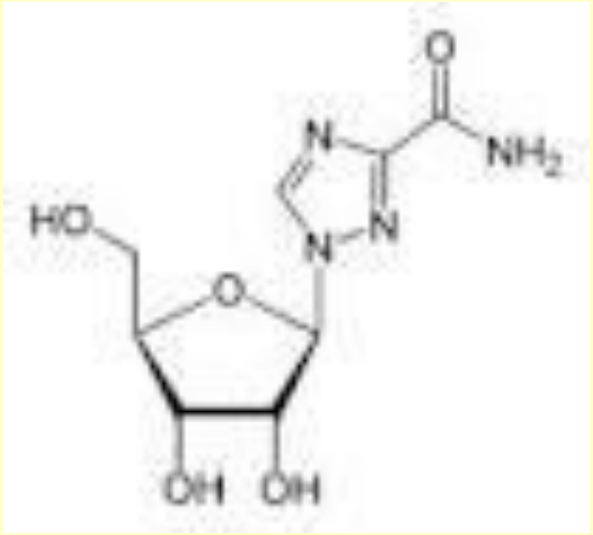
HCV life cycle

simeprevir
NS3/4Aproteasi



Adattato da Mandell et al, 2010; Moradpour et al, 2007.

TRIPLICE TERAPIA
RIBAVIRINA+PEGIN+DAA



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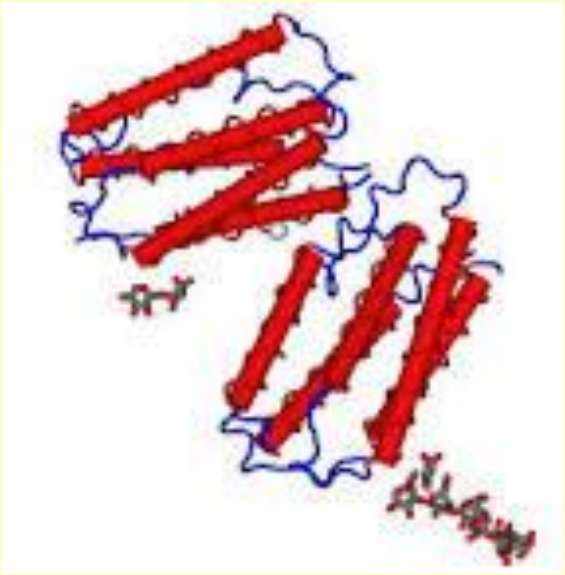

SIMEPREVIR

Hepatitis C pipeline

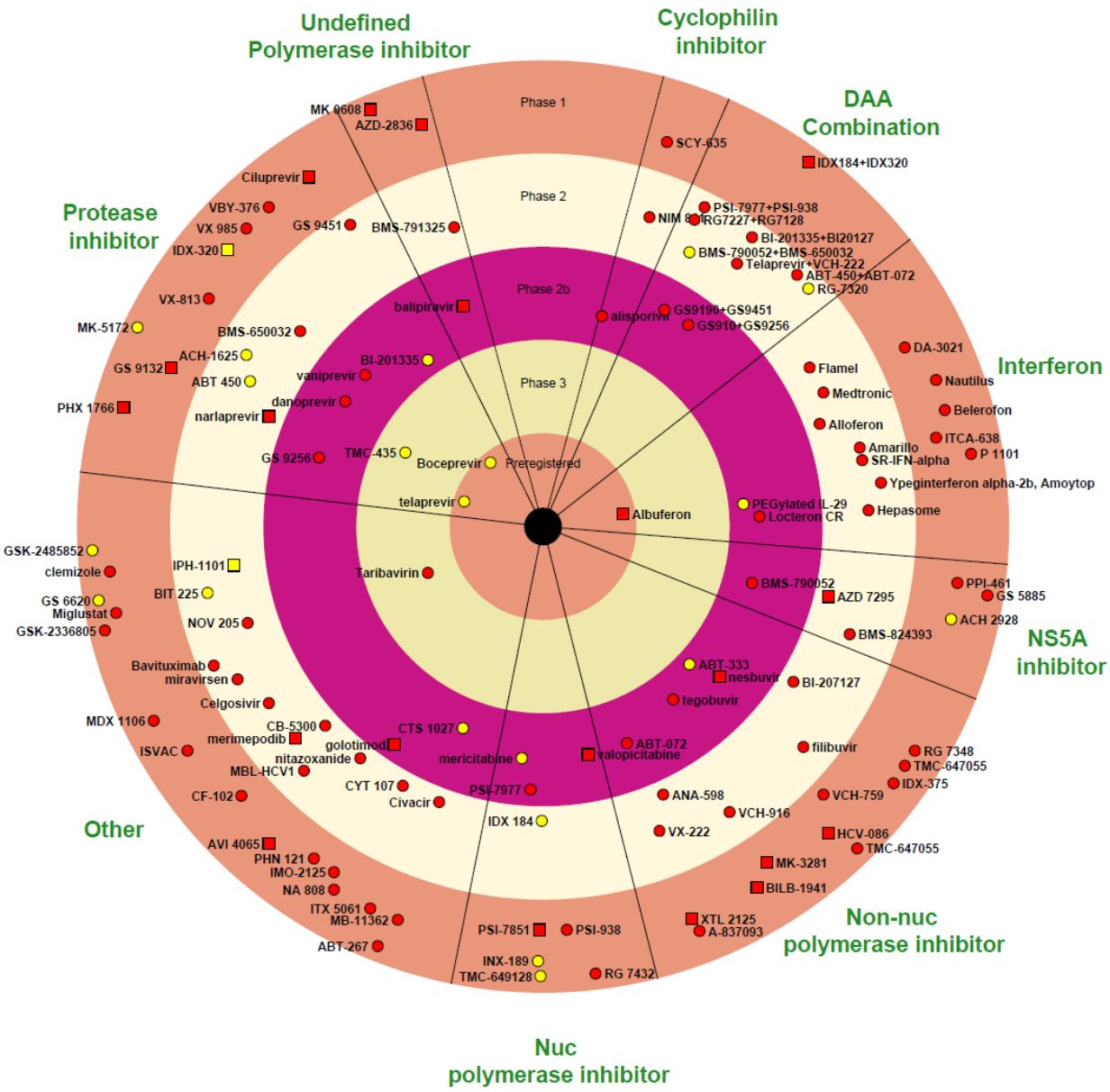

TABLE 6

Direct-acting antiviral drugs for hepatitis C virus infection in clinical development

INHIBITORS OF VIRAL TARGETS

NS3 protease inhibitors
Danoprevir, faldaprevir, asunaprevir, sovaprevir, vaniprevir, GS-9451, GS-9256, ABT-450, MK-5172, BILN-2061, ACH-2684

NS4B inhibitors
Clemizole, silibinin

NS5A inhibitors
Daclatasvir, ledipasvir, ABT-267, GSK-2336805, ACH-2928, BMS824393, IDX719, PPI-461, PPI-668, ACH-3102, MK-8742

NS5B nucleoside inhibitors
Mericitabine, ALS-2200

NS5B Non-nucleoside inhibitors
Tegobuvir, filibuvir, lomibuvir, setrobuvir, MK-3281, GS-9669, BI-207127, TMC-647055, BMS-791325

INHIBITORS OF HOST TARGETS

Cyclophilin A inhibitors
Cyclosporin A, alisporivir, NIM811, SCY-635

MiR122 inhibitors
Miravirsen

Entry inhibitors
ITX5061

HCV direct-acting antiviral agents: the best interferon-free combinations

Molecules	Class	Genotype	Company
MK-5172/8742	NS3/4A /NS5A PI	Pangenotypic	Merck Sharpe&Dohme
Faldaprevir	NS3/4A PI	1	Boehringer Ingelheim
Daclatasvir	NS5A	1	Bristol Myers Squibb
ABT-450/r/ABT-333/ABT-267	Boosted PI/NPI/NS5A PI	1	AbbVie

Adapated from Raymond Schinazi Liver International 2014

GRAZIE PER L'ATTENZIONE