KVCV - Dag van het chemieonderwijs
Chemie & Farmacie
Zaterdag, 17 maart 2012

Integrating diagnostics and therapeutics to fight infectious diseases

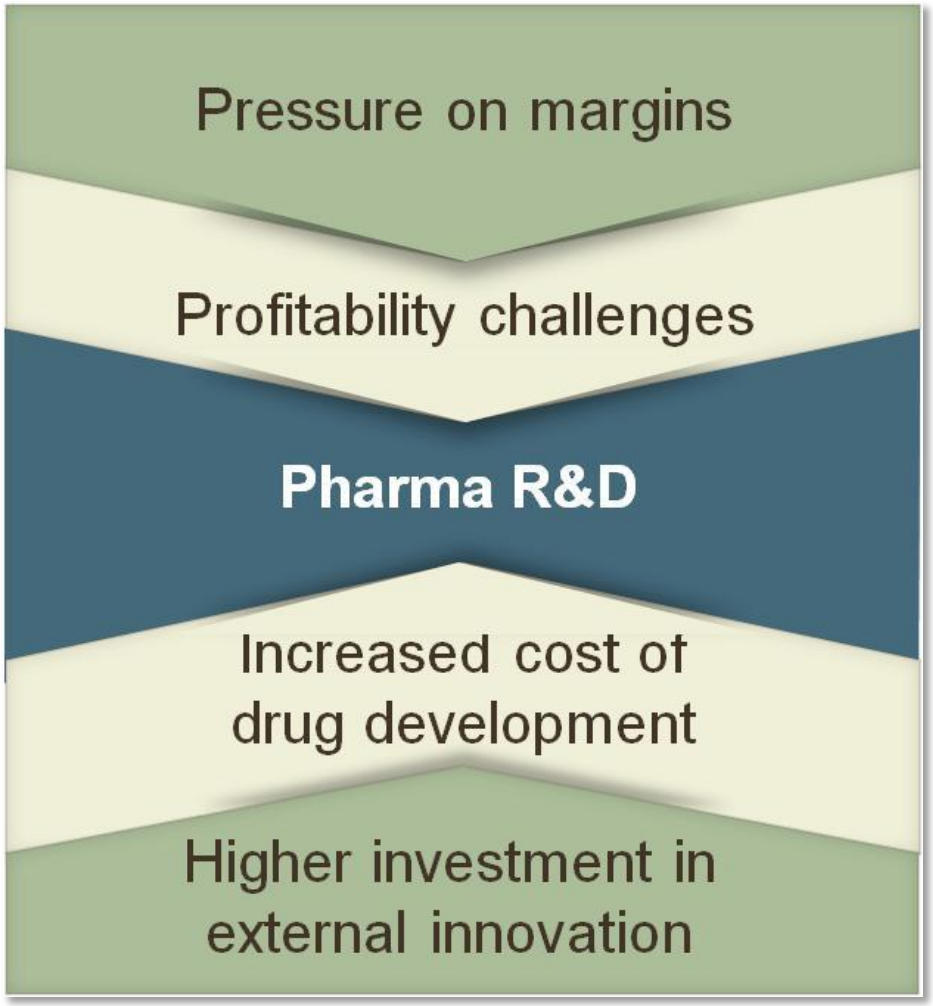
How Pharma R&D can make the difference

Kristof Van Emelen

Before: Tibotec Infectious Disease and Vaccines - J&J
Today: Advanced Chemical Sciences
Janssen C.R.E.A.Te - Community of Research Excellence and Advanced Technologies

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

Dramatic Pressures for R&D



Fighting Infectious Diseases Makes a Real Impact

Infectious Diseases:
2nd leading killer worldwide

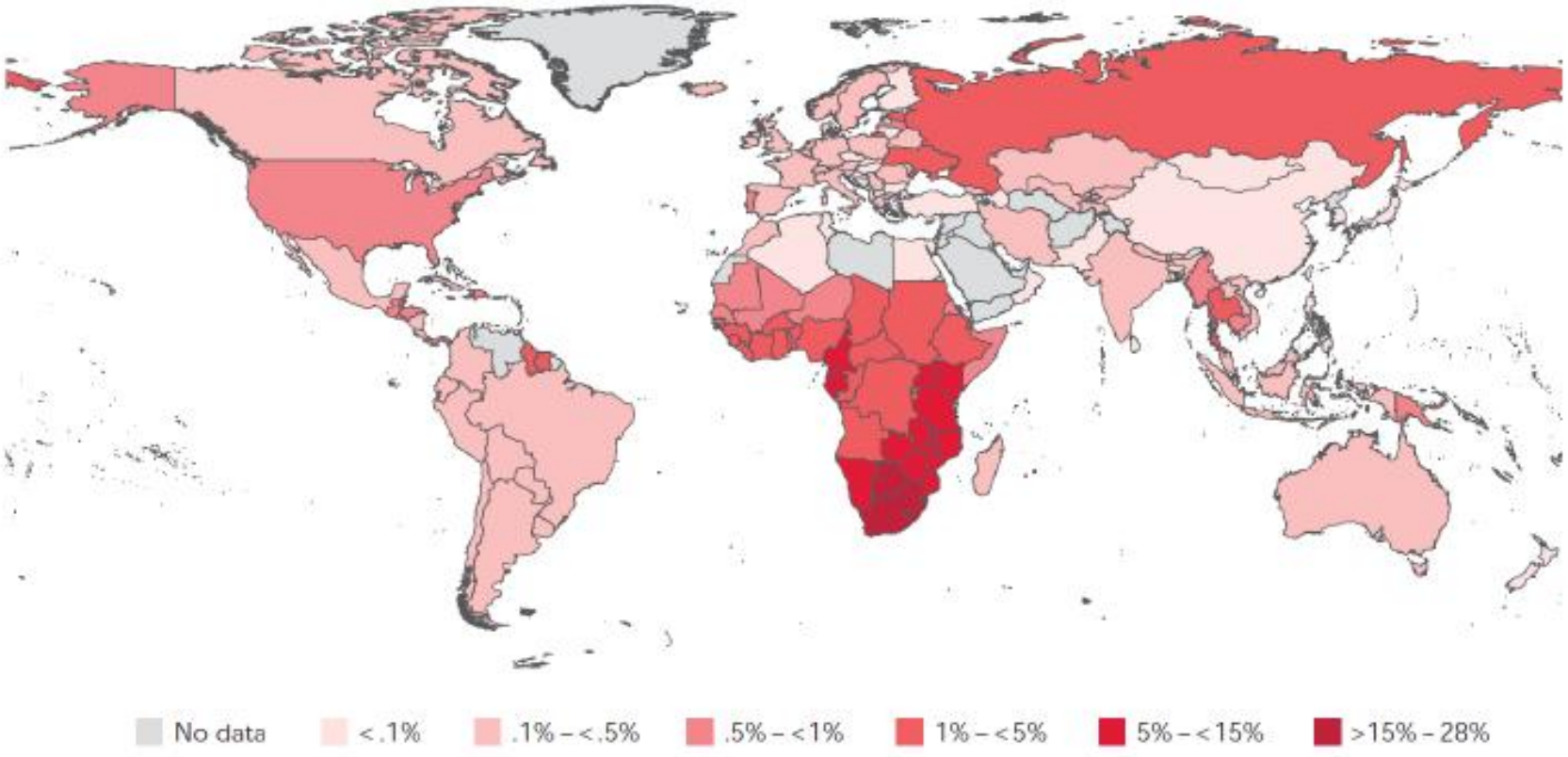
~1500 people die per hour from infectious disease,
and ½ of them are under 5 years old

WHO. Cause Specific Mortality 2008

HIV

From killer disease to sleeping enemy?

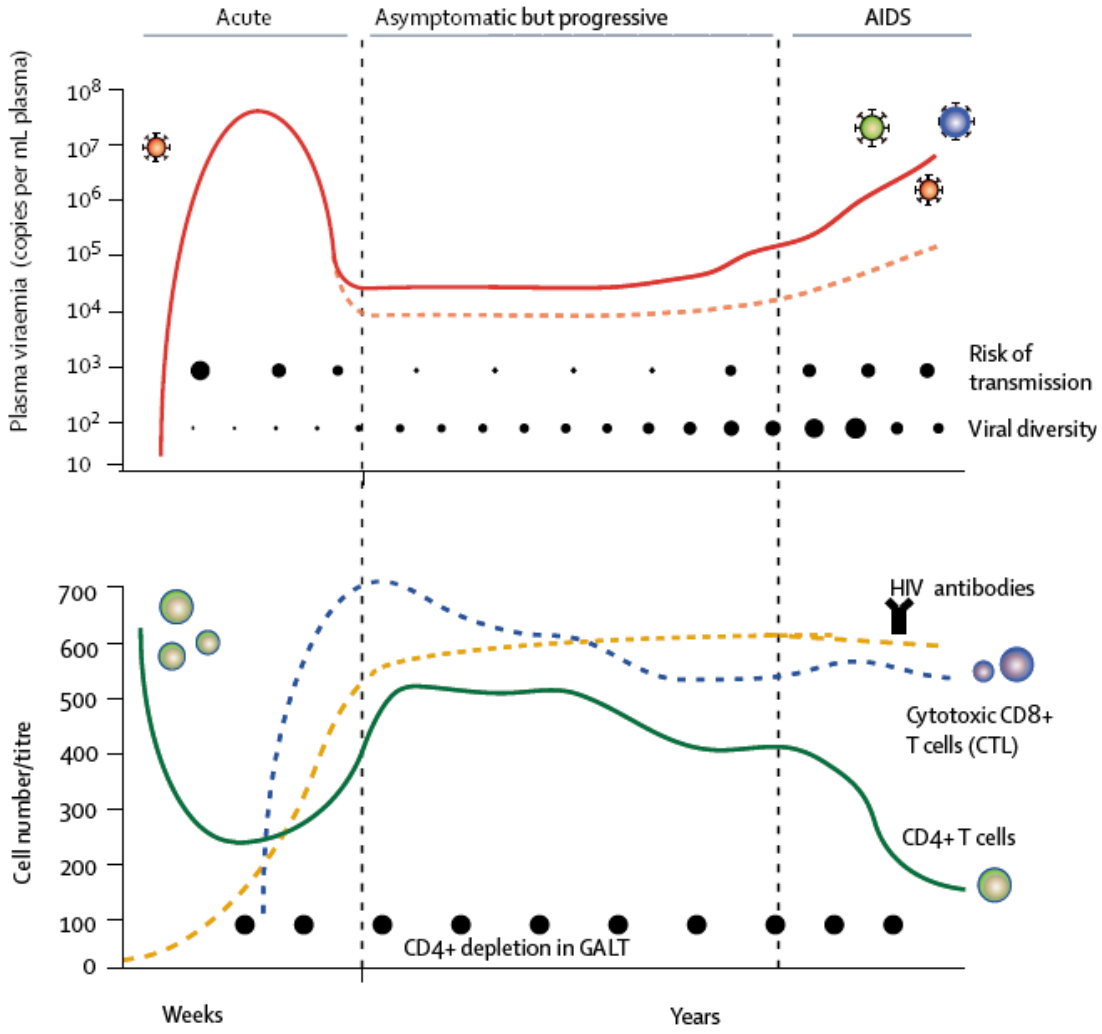
Global Prevalence of HIV, 2009



Number of people living with HIV in 2009

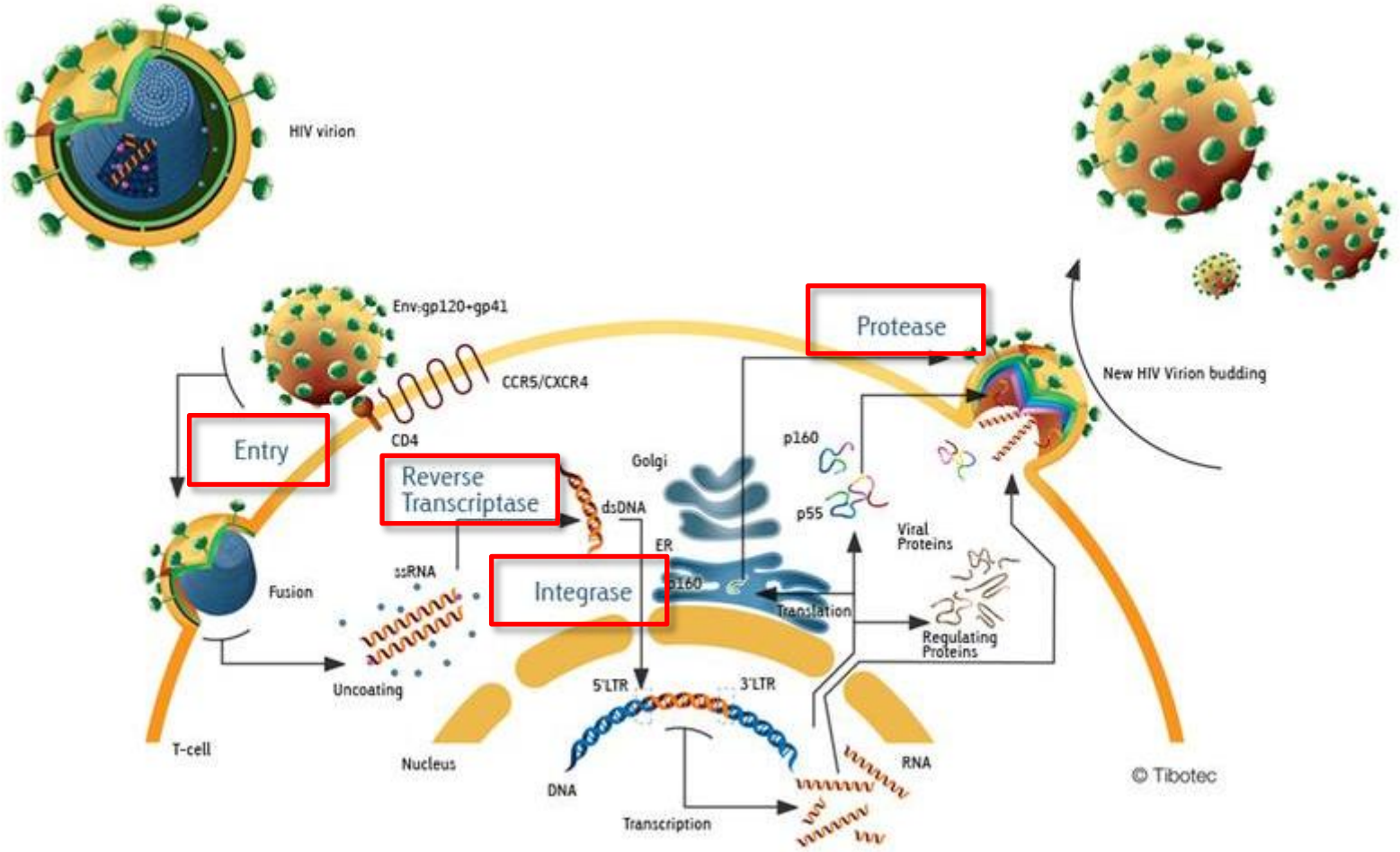
Total	**33.3 million**
Adults	**30.8 million**
Woman	**15.9 million**
Children under 15 years	**2.5 million**

HIV Infection



The Lancet, 2006, 368, 9534, 489-504

HIV – Viral Life Cycle



Medical need for new HIV drugs

Main causes for HIV-therapy failure

- Drug resistance development
- Cross-resistance within same drug class

Side-effects:

- Rash, nausea, headache, diarrhea, …
- Hyperlipidemia, lipodistrophy

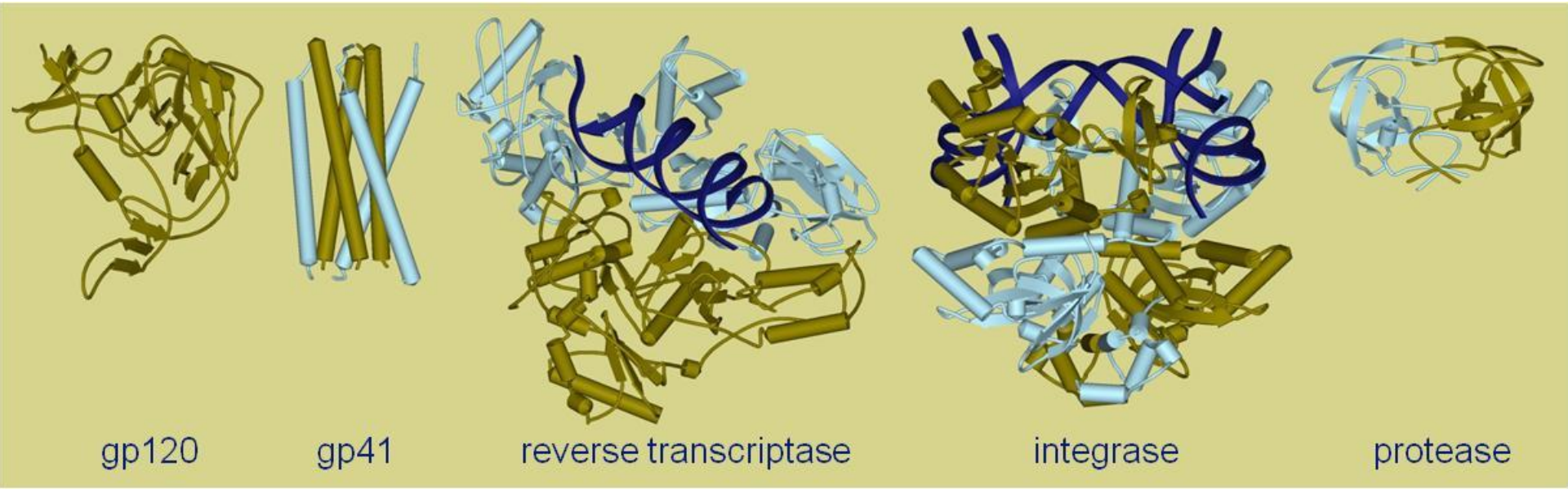
High pill burden (related to HAART therapy)

Janssen next generation HIV drugs

active on HIV-resistant mutants

high genetic barrier for drug resistance

HIV-1 targets



entry
Enfurvirtide

CCR5
Maraviroc

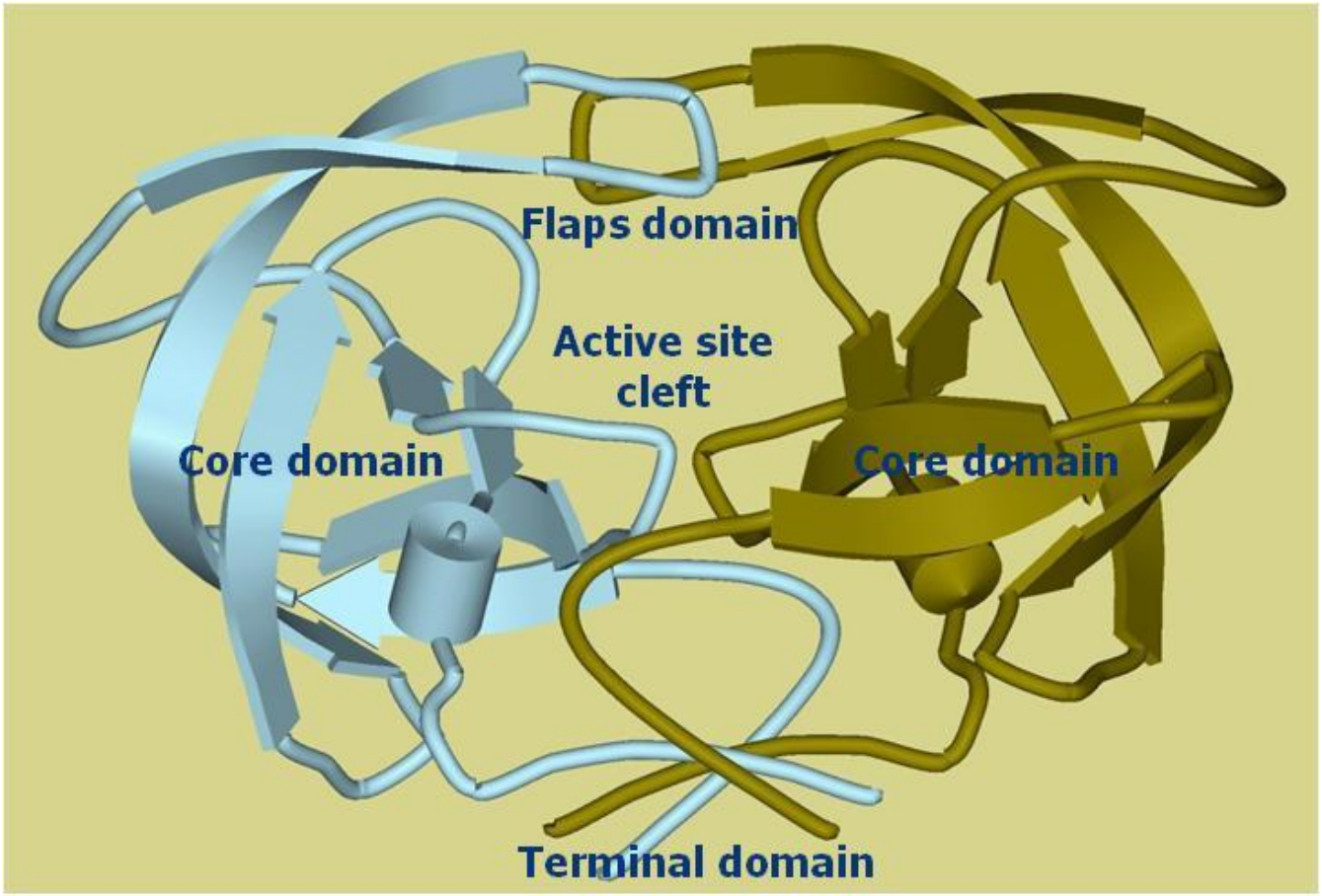
NRTI
AZT
ddI
ddC
d4T
3TC
ABC
TFV
FTC

NNRTI
NVP
DLV
EFV

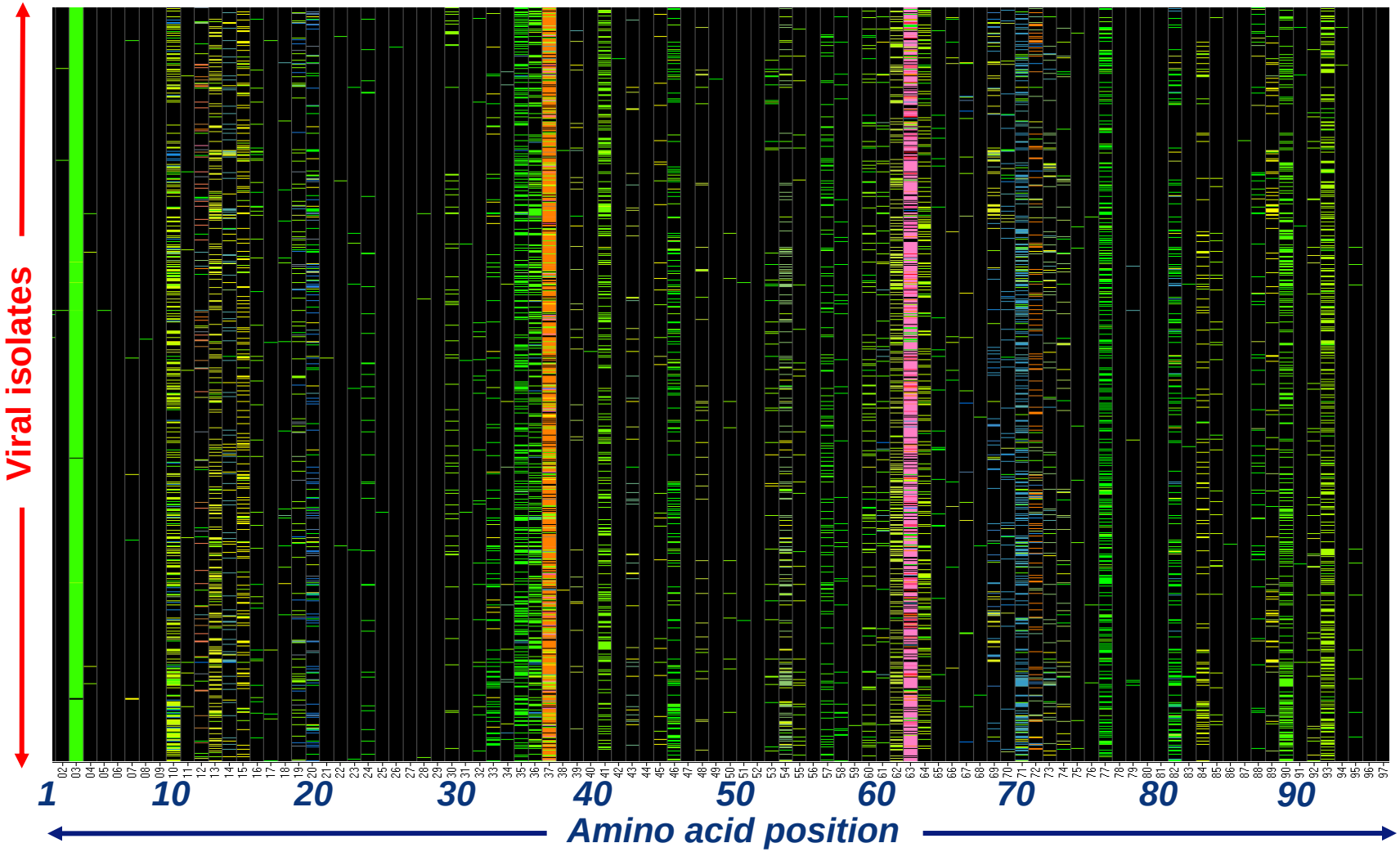
Integrase Inh.
Raltegravir
Elvitegravir

PI
SQV
RTV
IDV
NFV
APV
LPV
ATV
TPV

HIV Protease



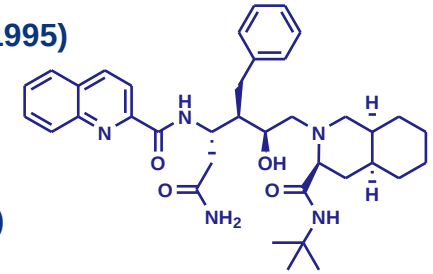
Genetic diversity
of HIV-1 protease in patients



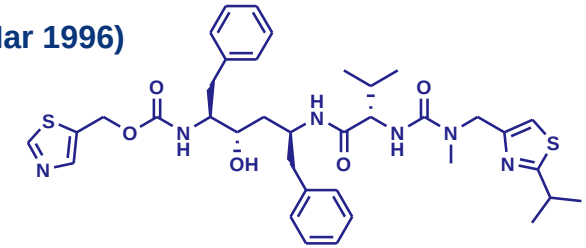
Genetic diversity implies a different optimization strategy

FDA approved HIV protease inhibitors

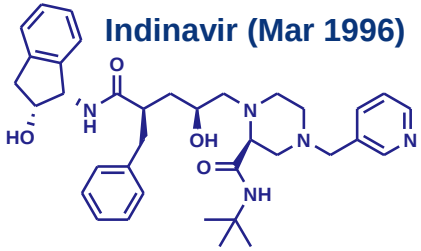
Saquinavir (Dec 1995)



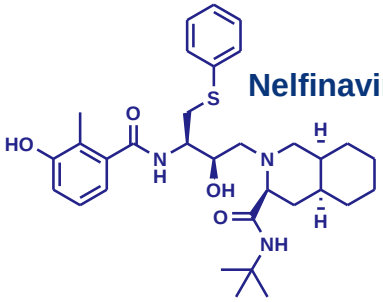
Ritonavir (Mar 1996)

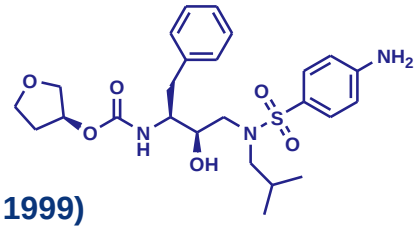


Indinavir (Mar 1996)



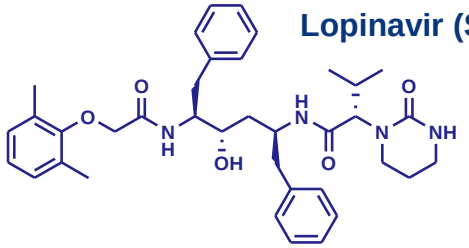
Nelfinavir (Mar 1997)



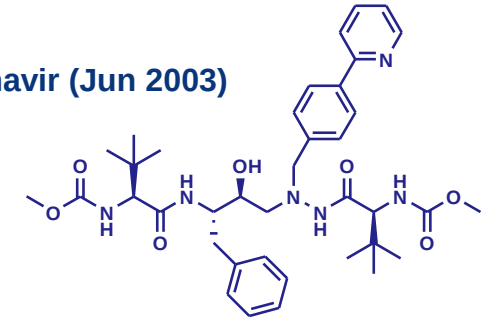


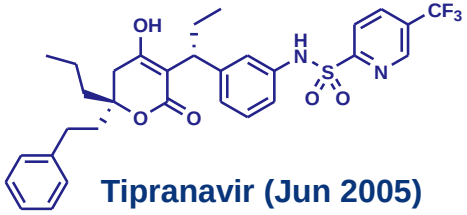
Amprenavir (Apr 1999)

Lopinavir (Sep 2000)

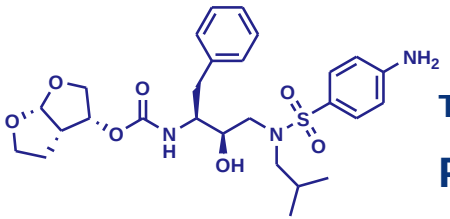


Atazanavir (Jun 2003)





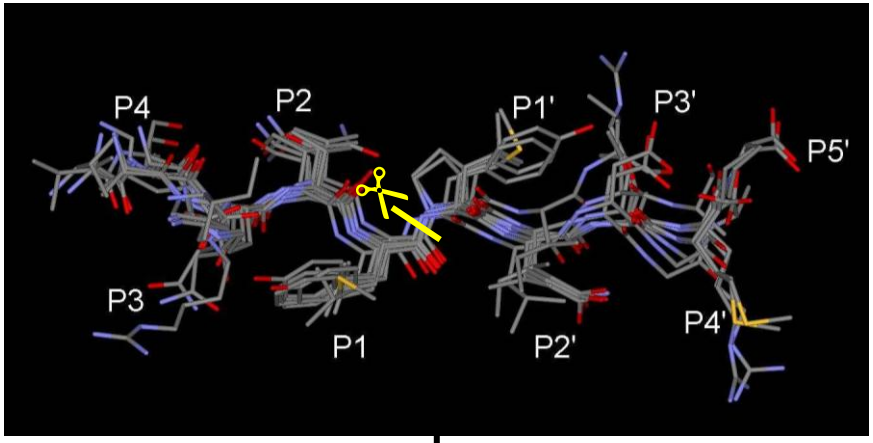
Tipranavir (Jun 2005)

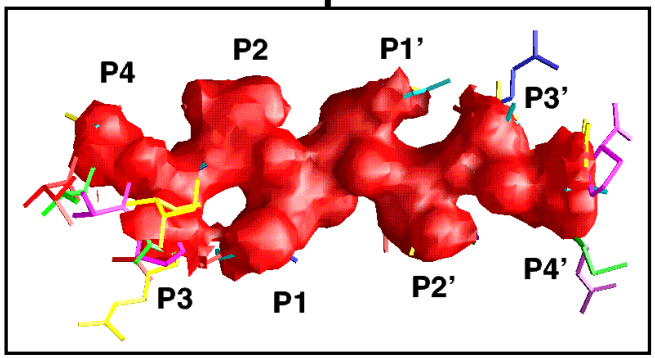


TMC114 - Darunavir

Prezista (Jun 2006)

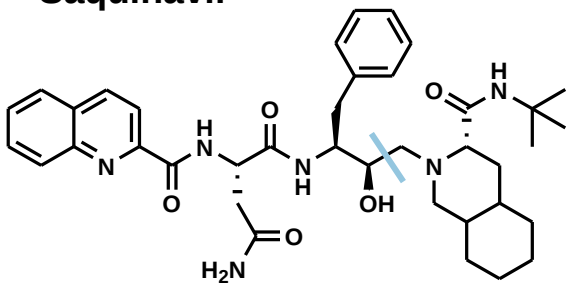
Design of a drug-like broad spectrum PI





Time

Saquinavir

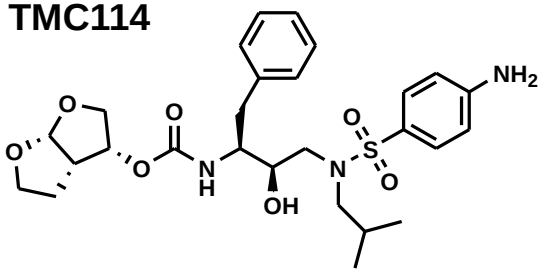


PI design strategies:

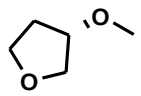
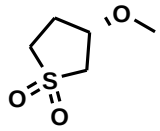
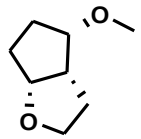
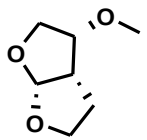
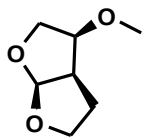
- Non-scissile peptidomimetic scaffold
- Reduce peptide-like character
- Increase # backbone interactions
- Bind only conserved side-chains
- Stay within substrate envelope

Improve drug-likeness and potency on resistant viruses

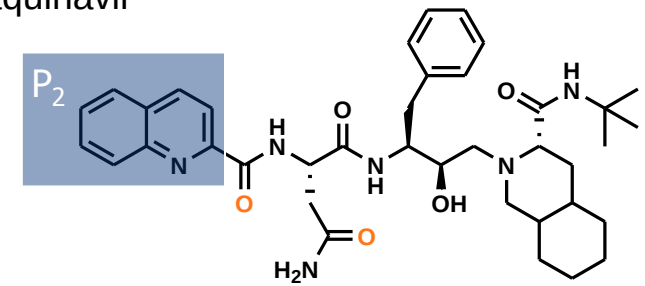
TMC114

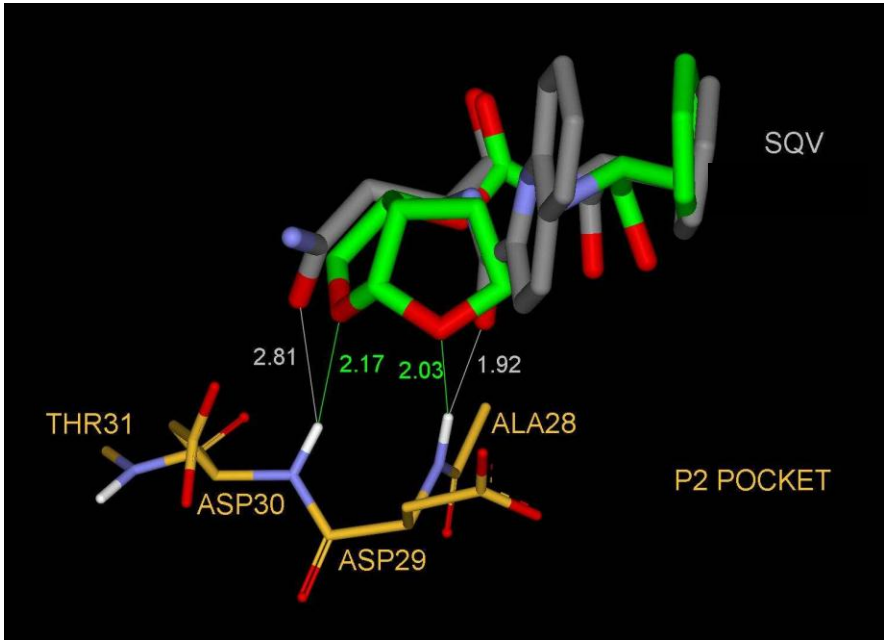


Design of non-peptidic P2 ligands

P_2-ligand	HIV-WT EC_{50} (nM)
	132
	76
	17
	1.8
	6.4

Saquinavir





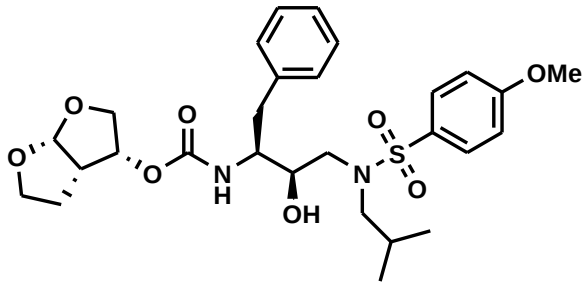
J. Med. Chem. 1996, 39, 3278-3290

Anti-viral profile of the bis-THF derivative

Antiviral activity (pEC_{50}) on a highly PI resistant HIV mutant panel

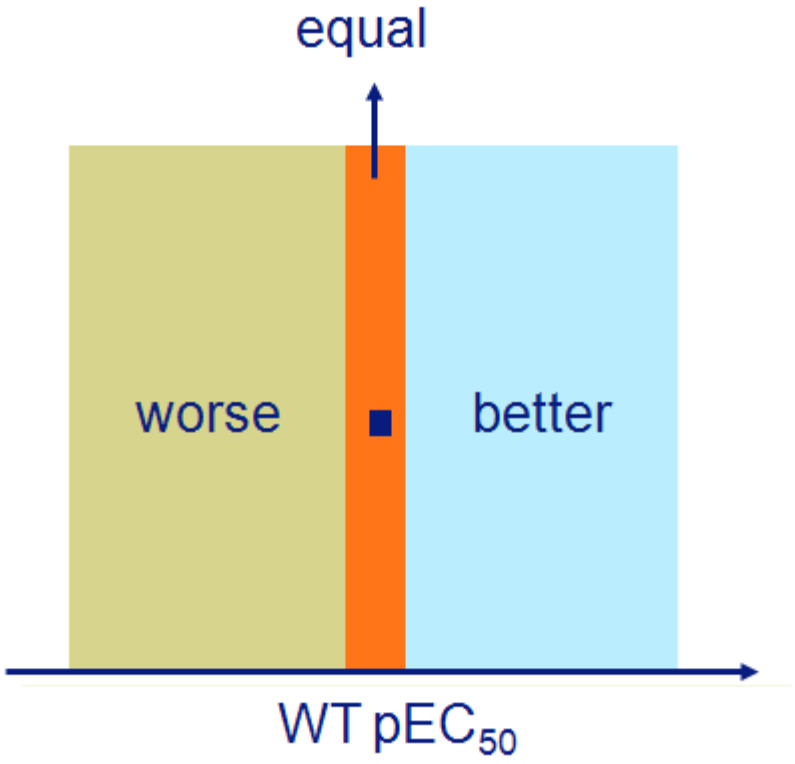
	WT	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18
APV	7.43	6.88	6.68	6.76	6.57	6.62	6.35	6.99	6.48	6.71	6.77	7.37	7.53	6.69	6.74	6.41	7.99	6.38	6.88
SQV	8.00	5.60	6.00	6.21	6.06	5.97	6.97	6.00	5.82	6.48	5.84	6.85	6.37	7.13	7.37	6.06	8.22	6.28	7.63
IDV	7.51	5.98	5.86	5.85	6.08	6.05	5.82	5.62	6.19	6.57	5.91	6.30	6.85	6.60	6.02	6.32	7.92	6.29	6.59
RTV	7.27	5.03	5.00	5.00	5.47	5.63	5.77	5.00	5.48	5.60	5.46	5.54	6.07	5.28	5.42	5.19	7.45	5.66	5.50
NFV	7.45	5.50	5.47	5.33	5.66	5.60	5.14	5.62	5.60	6.12	5.41	5.94	6.40	6.26	5.96	5.77	6.38	5.46	6.15
ATV	8.45	6.71	6.76	6.80	7.03	7.22	6.11	6.88	6.50	7.50	7.12	7.43	7.62	7.54	7.60	6.94	8.81	6.90	7.67
LPV	8.08	6.50	6.46	6.41	7.05	7.28	7.88	6.67	7.01	6.96	7.06	7.52	7.13	6.94	7.09	7.01	8.66	7.23	6.91
Bis-THF der.	9.23	9.04	8.92	8.95	8.28	8.29	7.61	9.34	8.22	8.65	8.32	9.56	9.88	9.49	9.01	8.54	9.72	8.45	9.47

pEC50
< 7
7 - 8
> 8

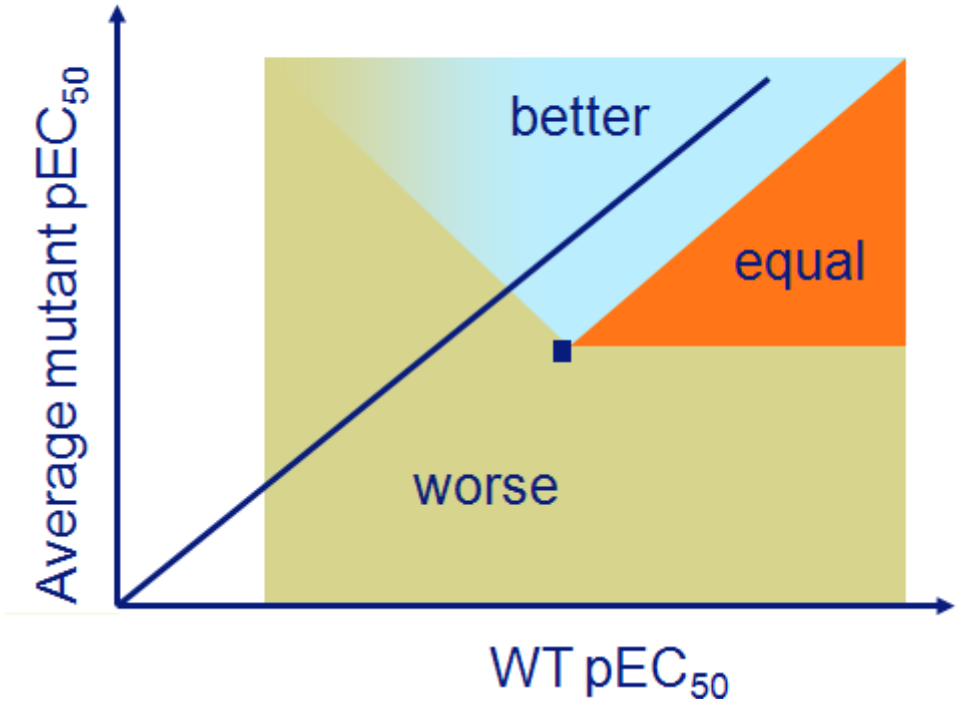


Profiling of HIV-1 protease inhibitors

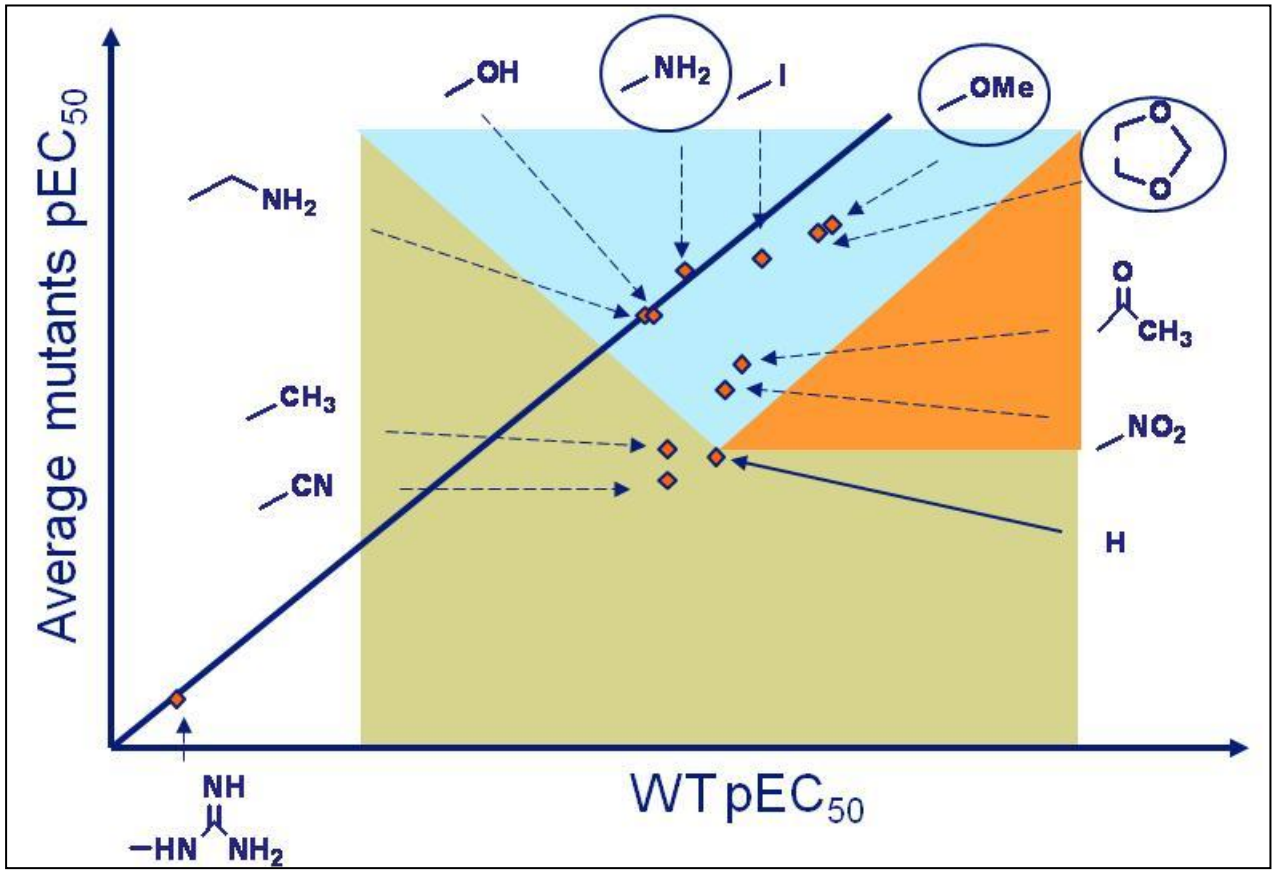
1st Generation PI profiling

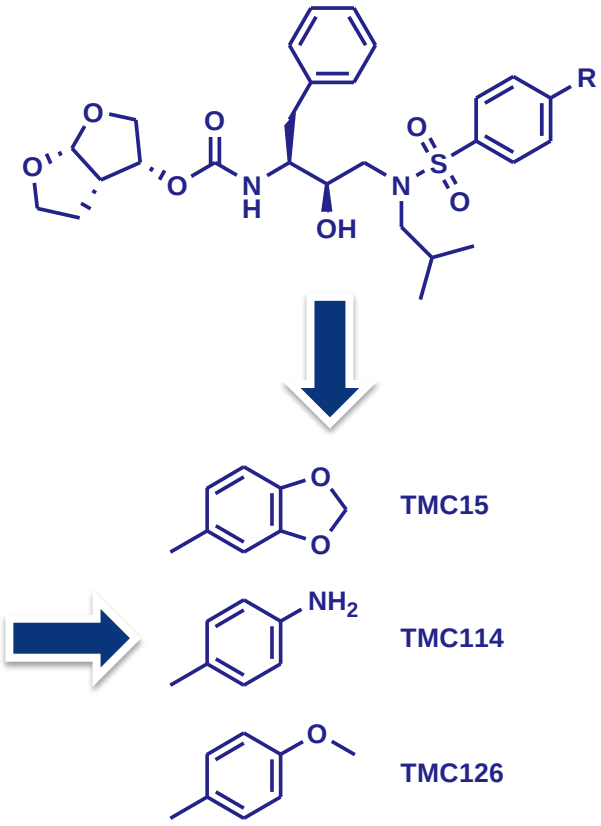


Broad-spectrum PI profiling



Broad spectrum optimization

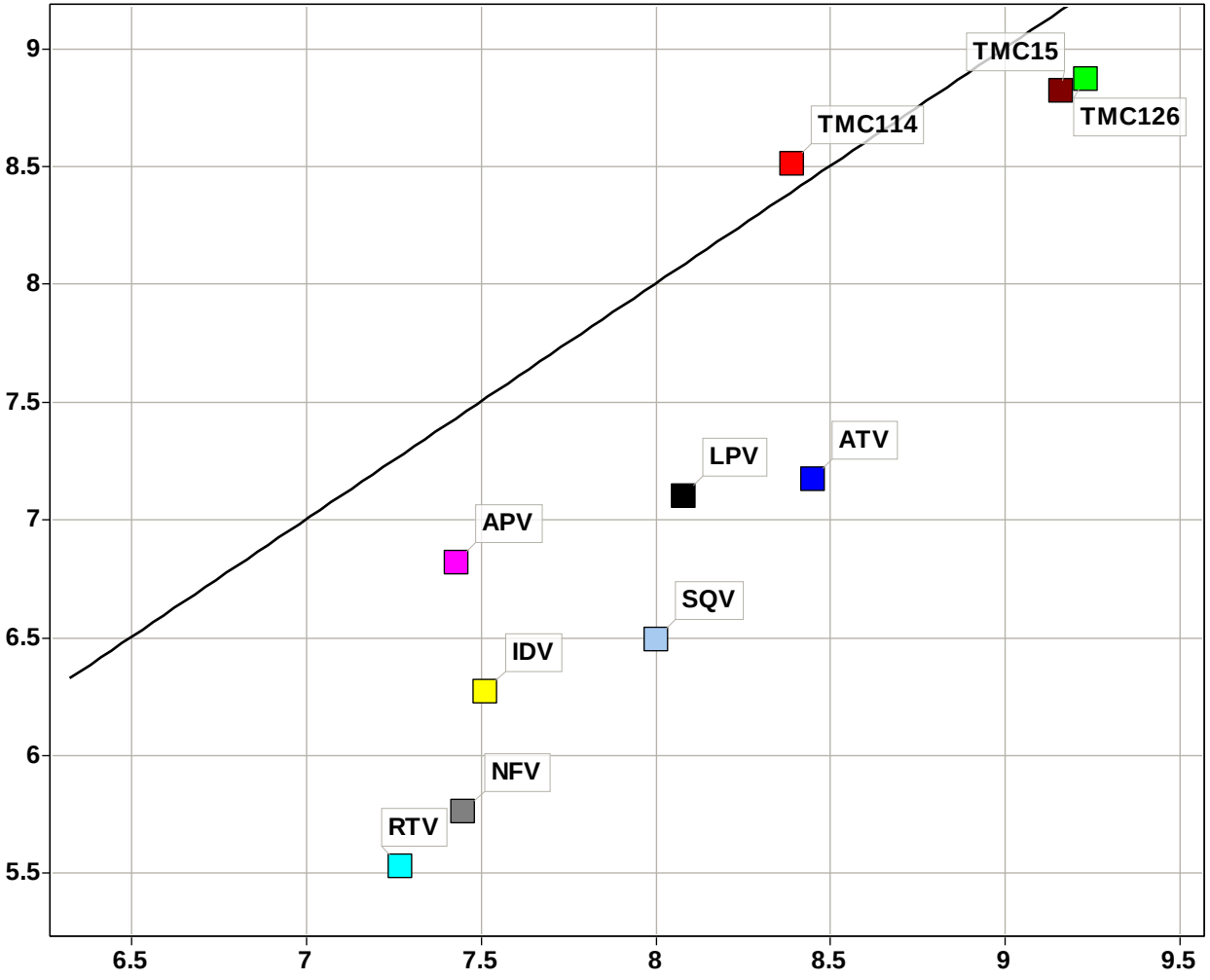




NME selection

Antiviral resistance profile

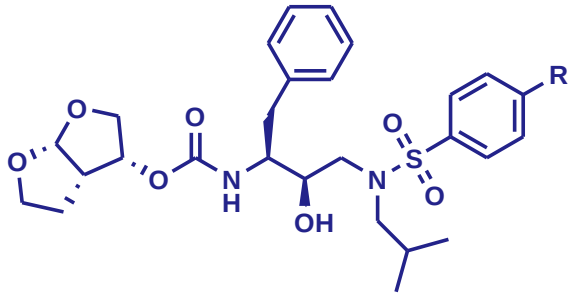
Average MT (pEC_{50})



WT (pEC_{50})

NME selection

ADME profile



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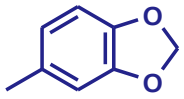
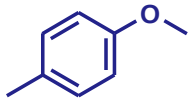
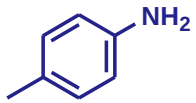


TMC15



TMC126



TMC114

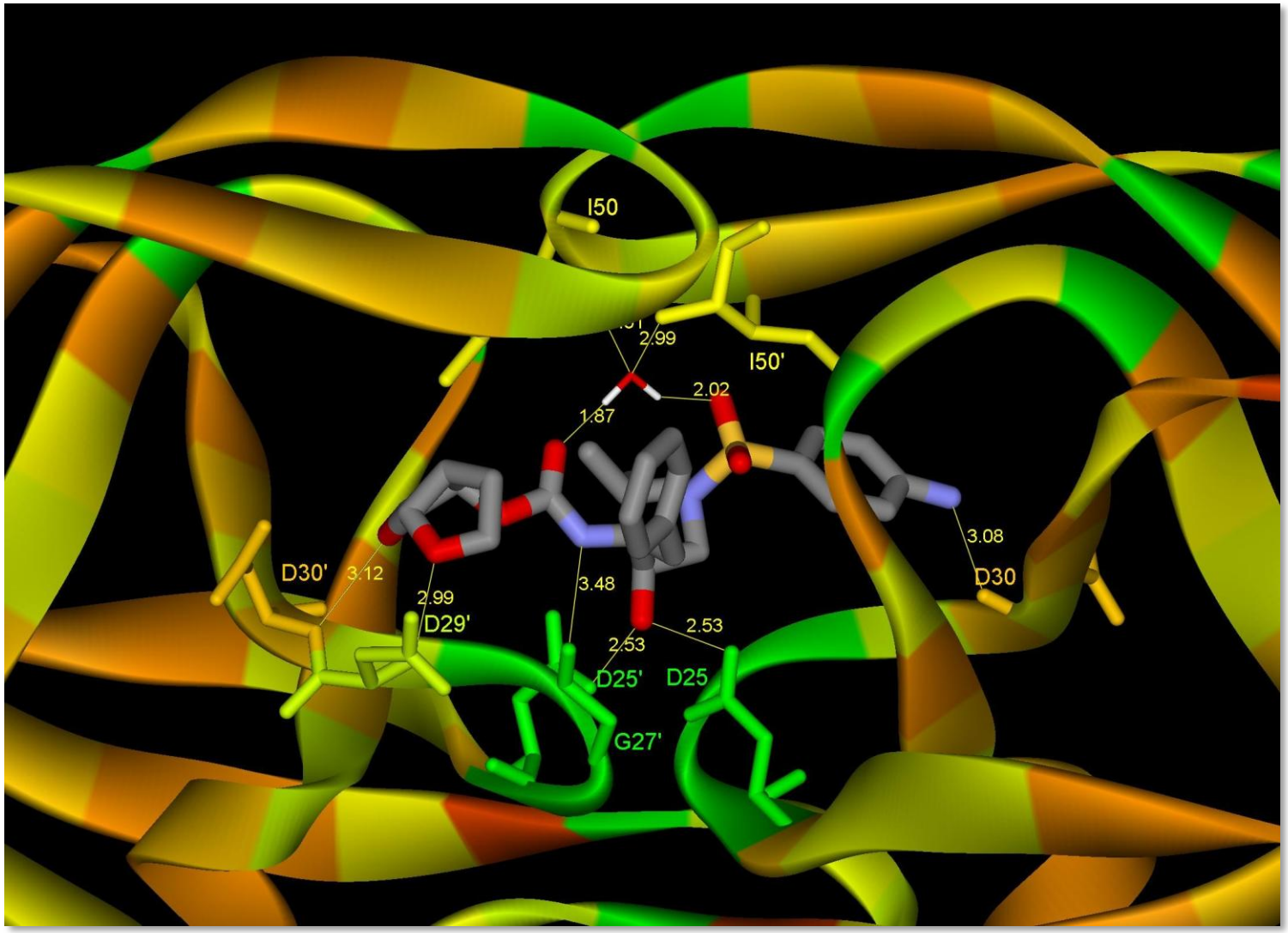
	IN VITRO			
	Solubility pH7 (mg/mL)	Metabolism HLM (% metabolised, 30 min)	Permeability CaCo-2 AP-BL (nm/s)	BL-AP (nm/s)
TMC15	0.12	48	368	285
TMC126	0.07	44	355	283
TMC114	0.17	15	112	328

	IN VIVO			
	Cmax (ng/mL)	Tmax (h)	AUC_{last} (ng h/mL)	T½ (h)
TMC15	3778 (±639)	2.5 (±1.0)	18111 (±3906)	2.1 (±0.5)
TMC126	1181 (±750)	0.6 (±0.3)	2695 (±1972)	1.5 (±0.7)
TMC114	19100 (±5919)	1.0 (±0.4)	74081 (±39355)	0.8 (±0.2)

PK data in dog at 80 mg/kg as a PEG400 solution

J. Med. Chem. 2005, 48(6), 1813-1822

Conserved binding pocket of TMC114

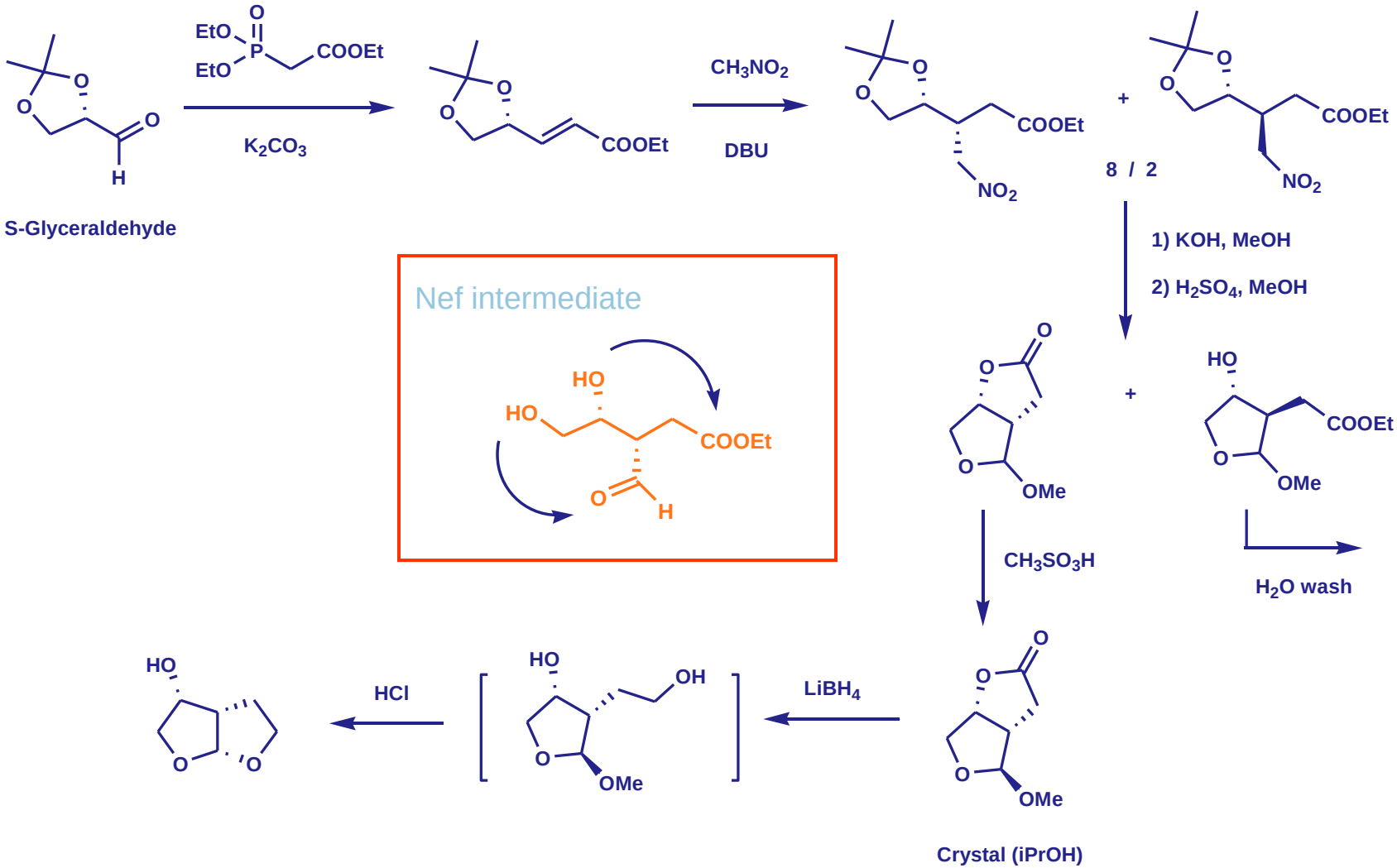


mutation frequency

- < 0.1%
- 0.1 - 0.3%
- 0.3 - 1%
- 1 - 3.2%
- 3.2 - 10%
- 10 - 32%
- 32 - 100%

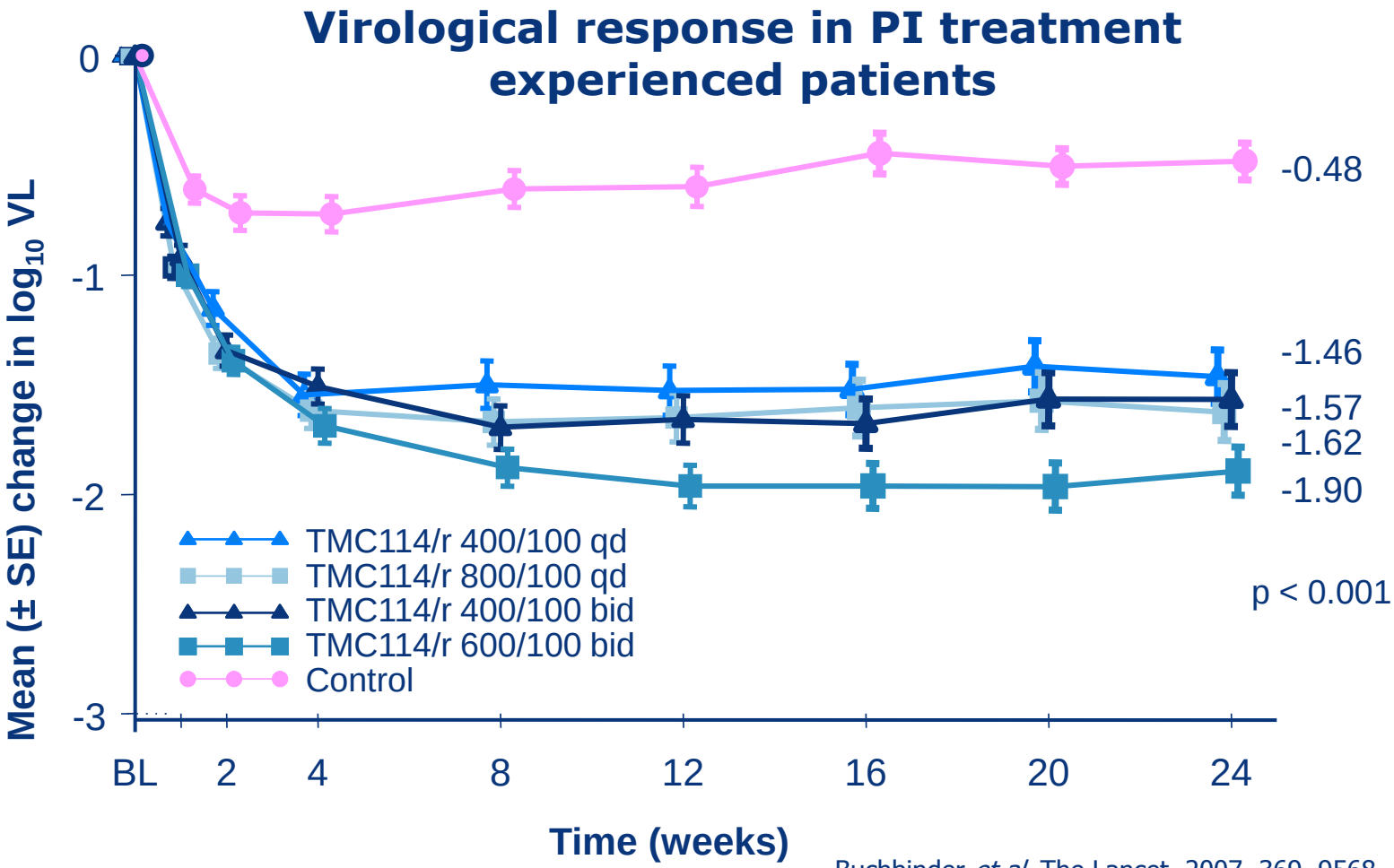
bis-THF

An industrial process



Org. Lett. 2005, 7, 5917-5920

POWER IIb
Virological response

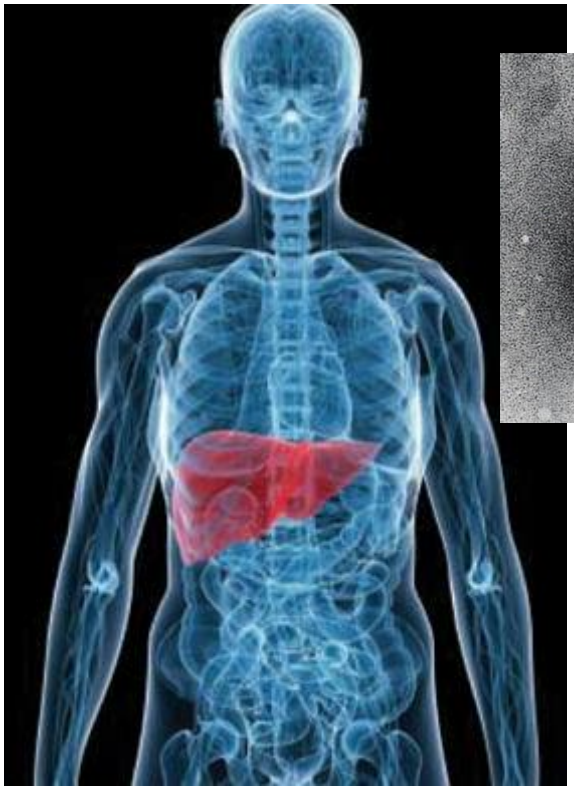


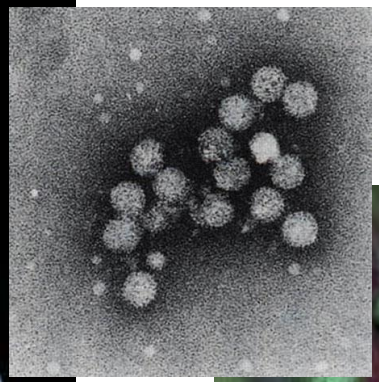
Buchbinder *et al*, The Lancet, 2007, 369, 9568, 1169 - 1178
Katlama C, *et al,* 3rd IAS, 2005. Abstract WeOaLB0102.
Wilkin T, *et al,* 45th ICAAC, 2005. Abstract H-413.

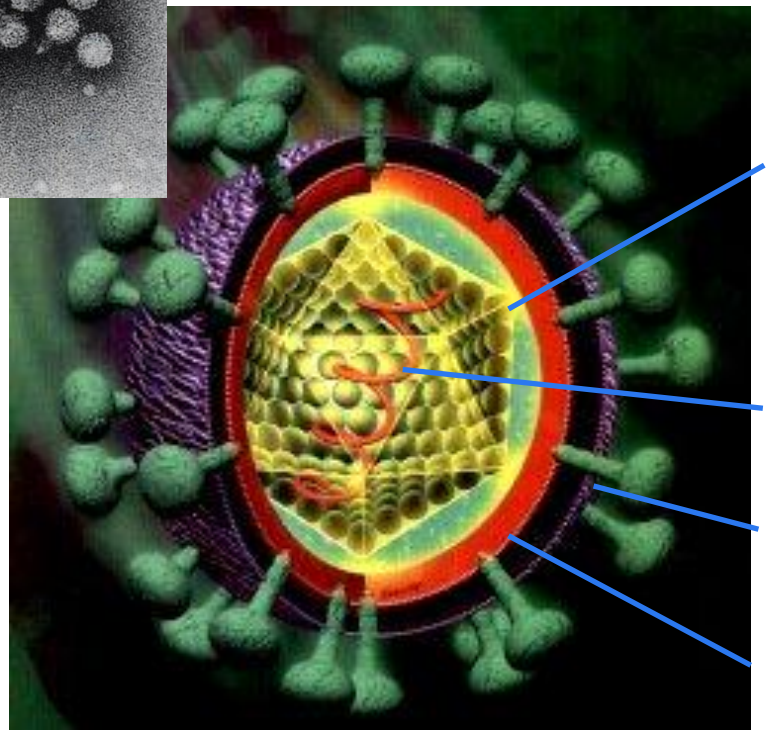
TMC435

A Step Closer to Hepatitis C Remedy

Identification of Hepatitis C Virus (HCV)

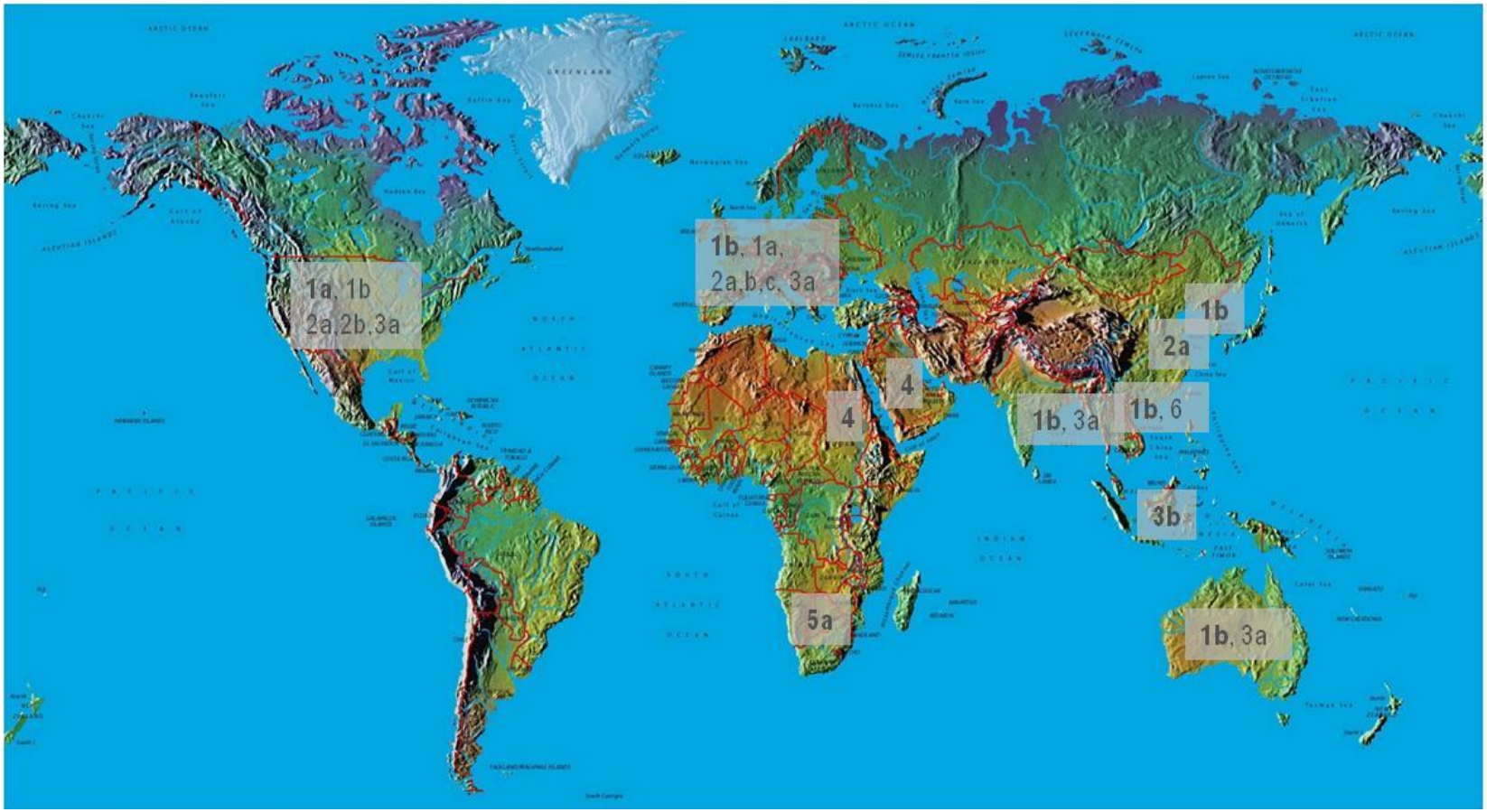






Hepacivirus (*Flaviviridae*) identified in 1989 as agent of non-A non-B hepatitis

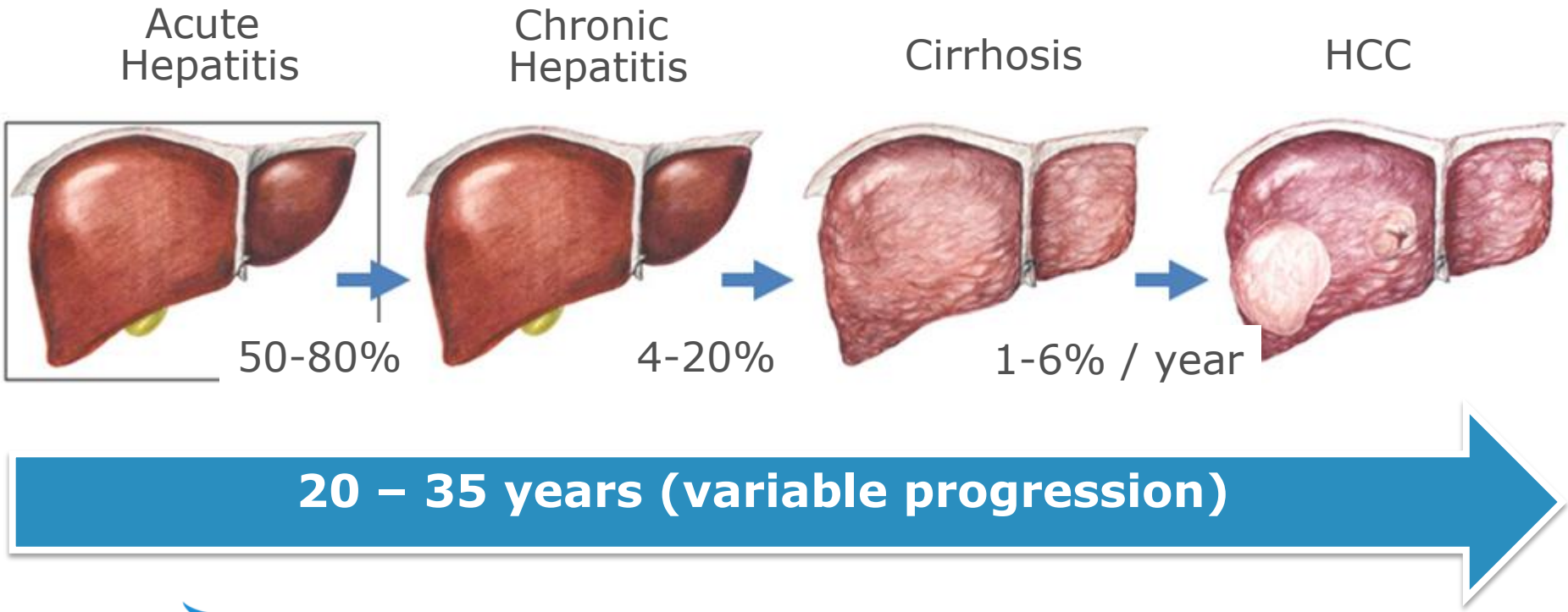
Hepatitis C (HCV) epidemiology



170 Million individuals (3-4% of the World population) are chronically infected by HCV
6 major genotypes (each with subtypes), G1a/b is the most abundant

HCV pathogenesis

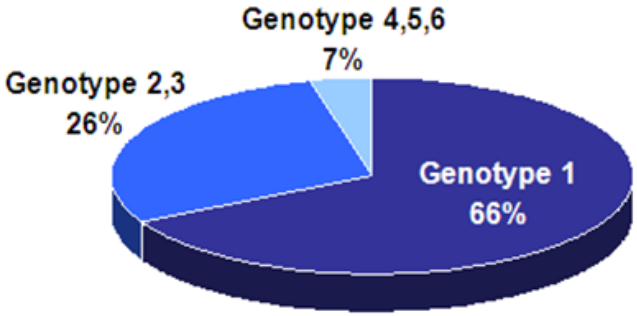
- US #1 cause of liver transplants (~2000/year, 17K waiting list)
- 13,000 deaths / year in the US (to triple in next 10-20 years)
- Health care burden ~ $5 bn / year in the US

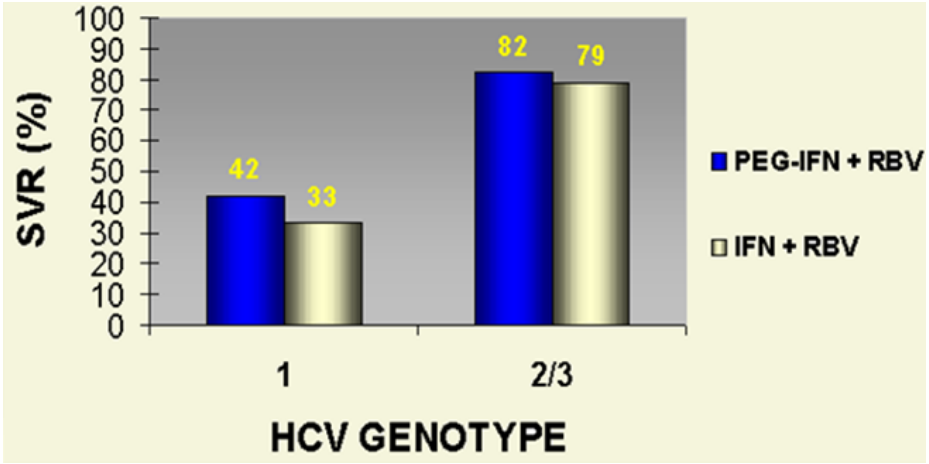


Limitations
of the current Standard Of Care therapy

PEG-IFNα2 (180 µg SC weekly injection)
Ribavirin (800-1200 mg BID orally)

- Long treatment duration (24 weeks for G2/3, 48 weeks for G1, 4/6)
- Poor tolerability (Anemia, Flu-like syndrome, psychiatric disease, …)
- Limited efficacy:

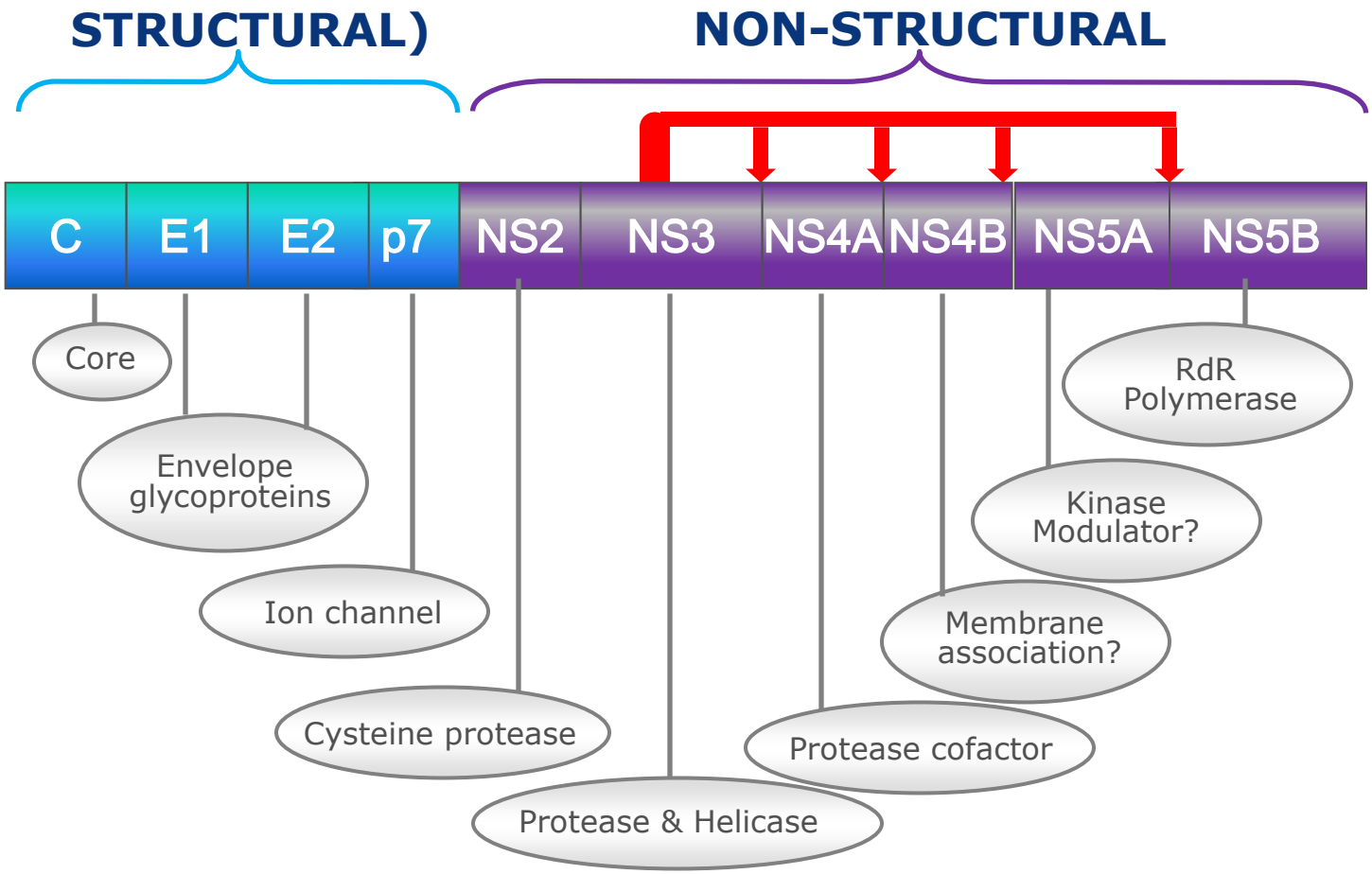




Differentiating therapies

- High SVR rate and good genotypic coverage
- Shortened duration of treatment
- Improved safety and tolerability
- Convenient oral/once daily dosing regimen

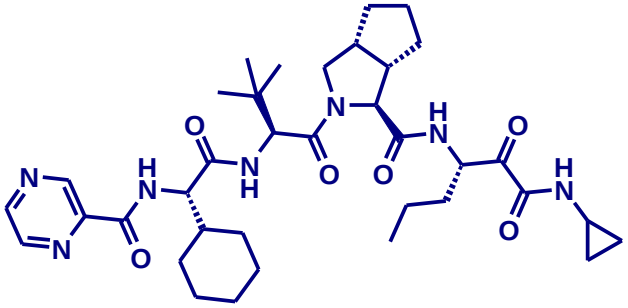
NS3/4A biological functions



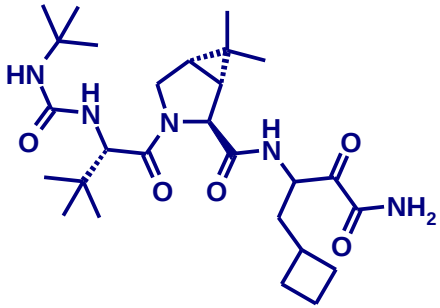
- NS3/4A essential for viral replication
- NS3/4A suppresses innate immunity
- NS3/4A target has been clinically validated (BILN-2061, Telaprevir, Boceprevir, TMC435)

Structure of NS3/4A protease inhibitors

Covalent inhibitors

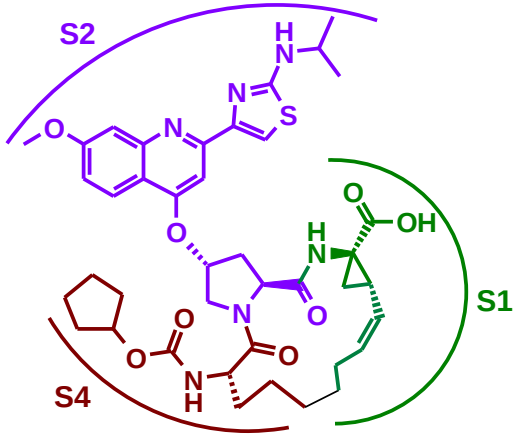


Telaprevir
(VX-950; PhIII)



Boceprevir
(SCH 503034; PhIII)

Non-covalent inhibitors

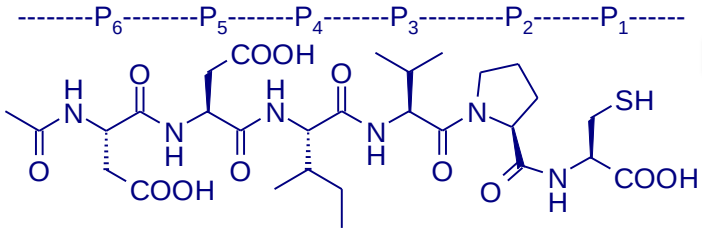


BILN 2061 (discontinued)

Tibotec/Medivir
Boehringer Ingelheim
Bristol-Myers Squibb
Intermune/Roche
Enanta/Abbott
Phenomix
…

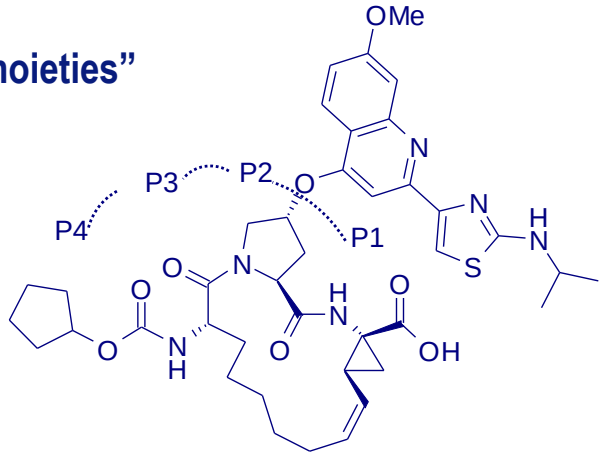
Discovery of BILN-2061 and cyclopentane lead compound

- **Successive truncations**
- **Replacement of "non drug-like moieties"**
- **Macrocyclization**

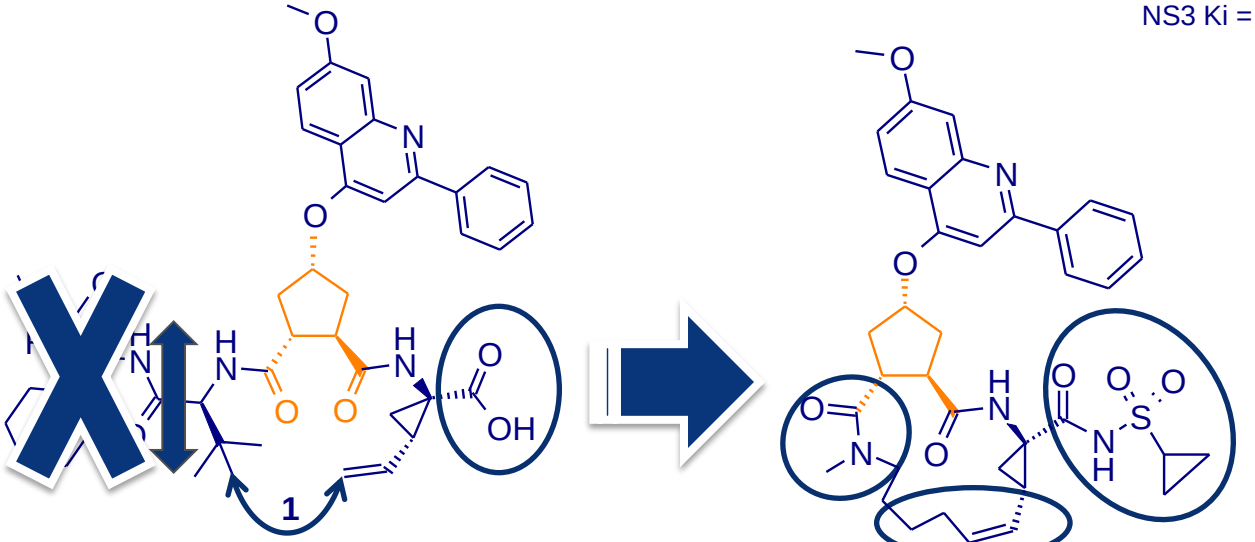


1 (NS5A/NS5B product)
NS3 Ki = 71 μM

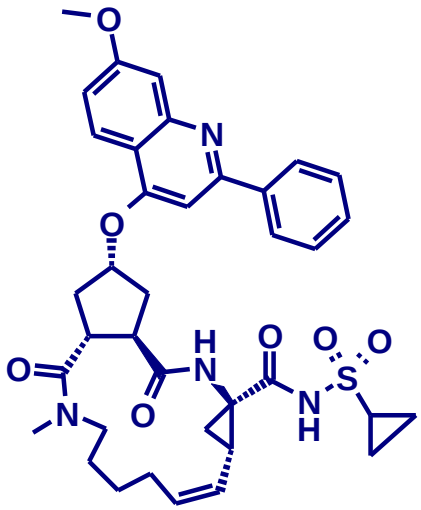
potency x 100 000



BILN-2061
NS3 Ki = 0.66 nM



Characteristics of the lead compound



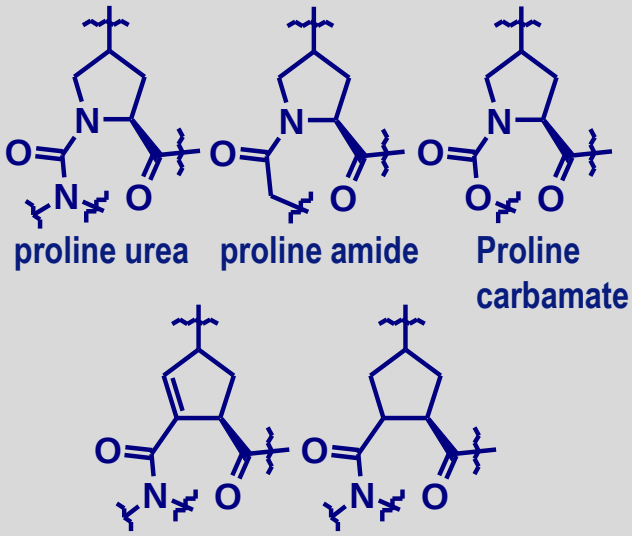
Lead compound

- ✓ Potent and specific HCV NS3/4A protease inhibitor (Ki = 0.41 nM, EC_{50} = 9 nM)
- ✓ Good CACO-2 permeability (P_{app} = 3.8 10^{-6} cm/s)
- ✓ Limited intrinsic clearance in human liver microsomes (Cl_{int} = 40 µL/min/mg)
- X Poor pharmacokinetic profile in rats (F = 2.5 %, Cl = 2.79 L/h/kg)
- X Extensively excreted in the bile (95 % after 1h)

Bioorg. Med. Chem. **2006**, *14*, 5136–5151
Bioorganic & Medicinal Chemistry, **2007**, *15*, 7184-7202

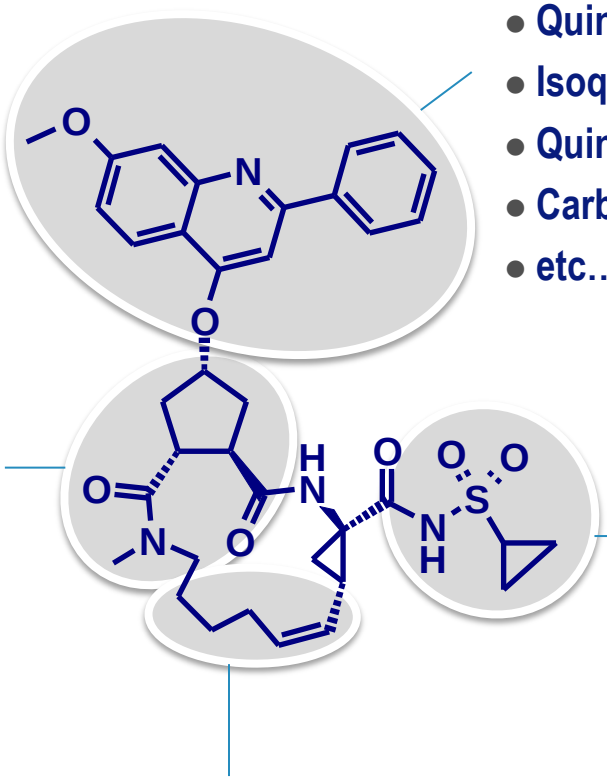
Lead Optimization Strategy

Parallel LO on 5 series



Modification of the P2 heterocycle:

- Quinolines
- Isoquinolines
- Quinazolines
- Carbamates
- etc…

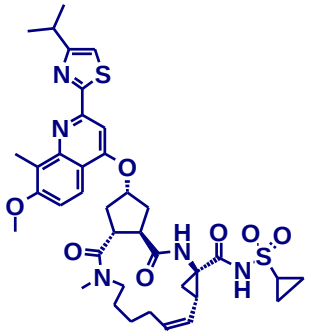


Bioisosteres of the P1 acid.

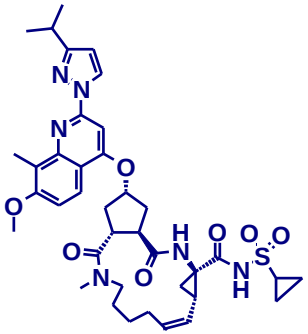
Optimization of the macrocycle:

- Ring size (14-16 mb).
- Incorporation of heteroatoms.

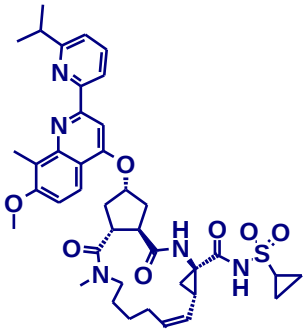
Rat PK profile for selected compounds



TMC435



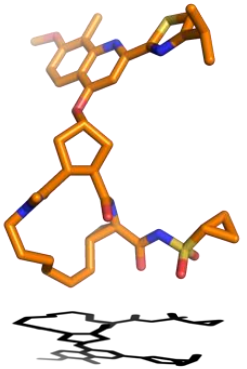
18



19

		TMC435	18	19
iv (2mg/kg, n = 2)	Cl (L/h/kg)	0.505	2.5	1.4
	Vd_{ss} (L/kg)	0.49	4.6	0.70
	AUC (μM.h)	5.21	1.05	1.36
	Liver/Plasma ratio	63.5	23.5	ND
oral (10mg/kg, n = 2)	AUC (μM.h)	2.79	1.30	1.4
	Cmax (μM)	0.73	0.31	0.30
	Tmax (h)	3.0	1.5	2.0
	$T_{1/2}$	2.8	2.2	5.8
	F (%)	11	25	31
	Liver/Plasma ratio	32	44	ND

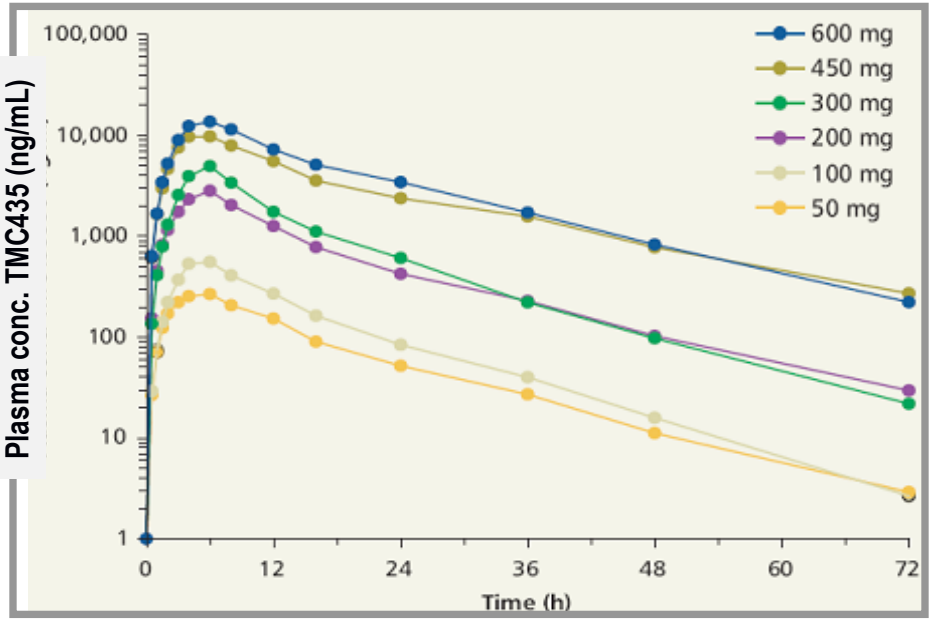
TMC435 *in vitro* profile



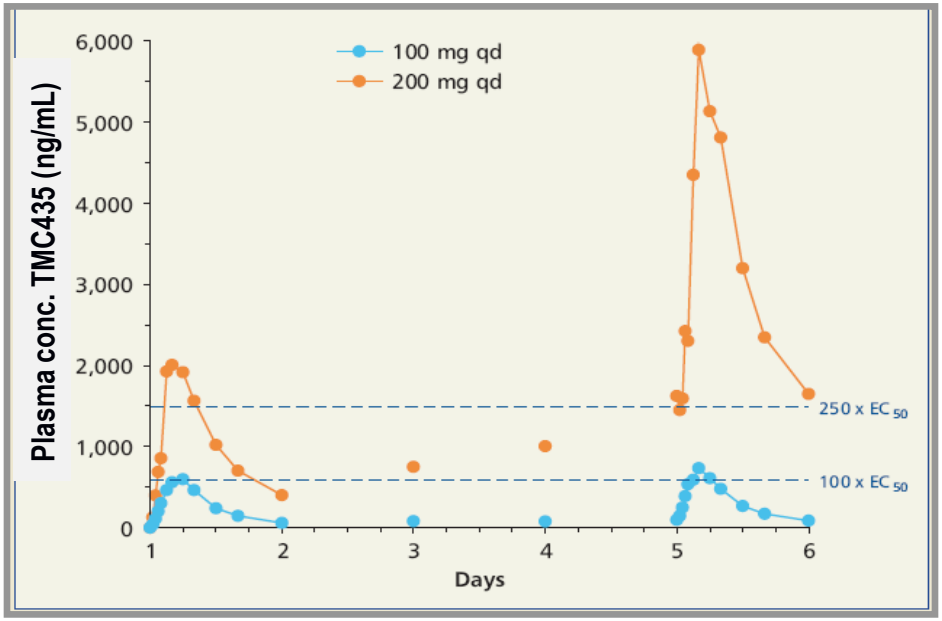
- Enzymatic activity
  - Enzymatic assay: K_i (G1a) = 0.4 nM; K_i (G1b) = 0.5 nM
  - Selectivity against selected human proteases >1,000
- Cellular activity
  - HCV: luciferase replicon (G1b): EC_{50} = 8 nM
  - Quantitative RNA detection: EC_{50} on G1a, G1b replicons (13-27 nM)
  - Selectivity Index (SI) = EC_{50}/CC_{50} on selected human cell lines >2000
  - Inactive against a broad panel of other RNA/DNA viruses
- Functional Protein Binding
  - Limited effect of protein binding: replicon EC_{50} increased 2 fold after addition of 50% human serum to culture medium
- Good PK profile consistent with QD dosing
- Safe in preclinical species (including cardiosafety)

PK profile in healthy volunteers after single and repeated dosing

Plasma concentrations of TMC435 after single dosing



Mean plasma concentrations of TMC435 after repeated dosing



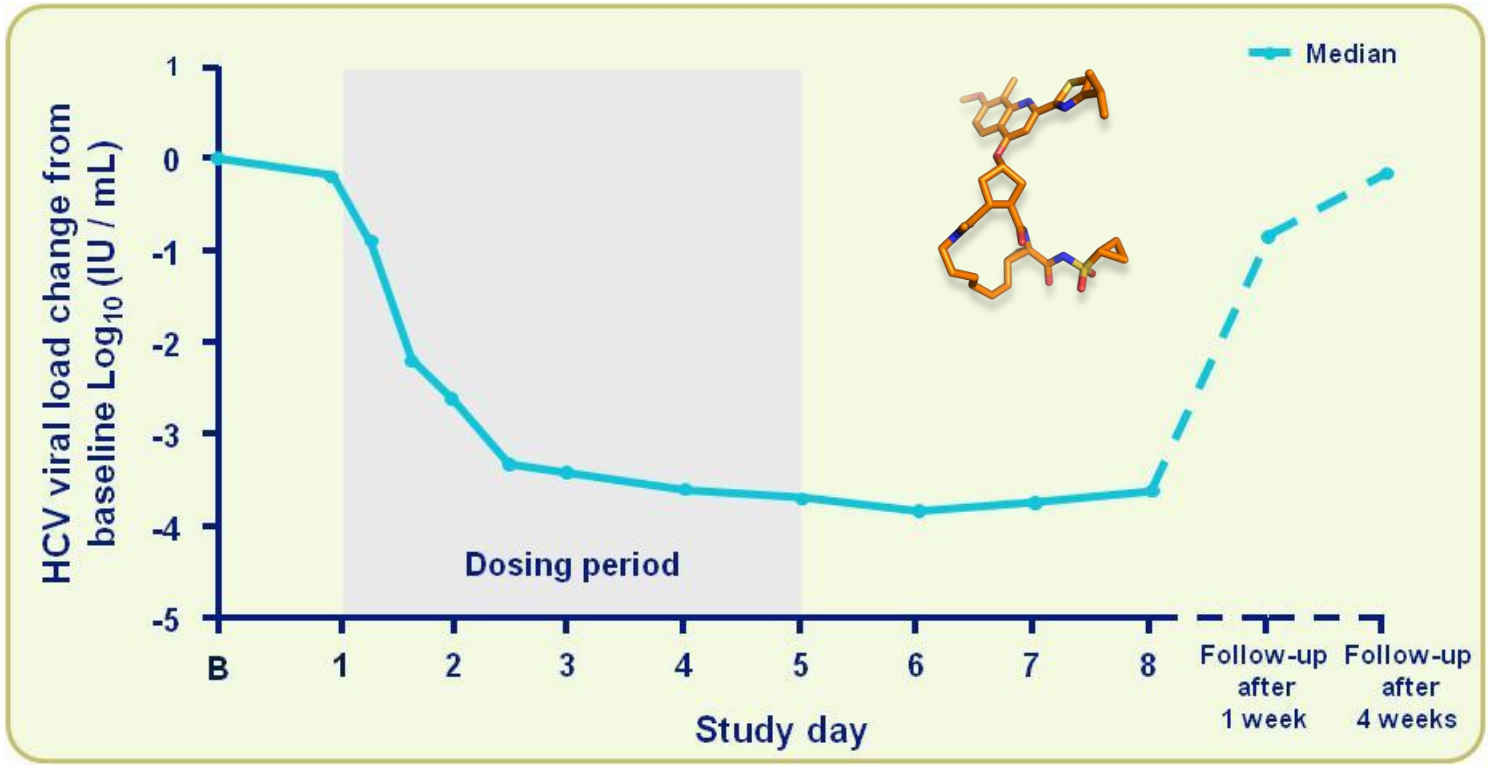
TMC435 was **safe and well-tolerated** in the study, when given to HCV-negative healthy volunteers at single oral doses up to 600 mg and at 5 days of oral doses up to 200 mg once-daily.

The pharmacokinetic profile of TMC435 supports **once-daily dosing**.

Minor (grade 1 only) adverse events, mainly gastrointestinal tract related and transient photosensitive reaction in some subjects (mild, short-lasting erythema).

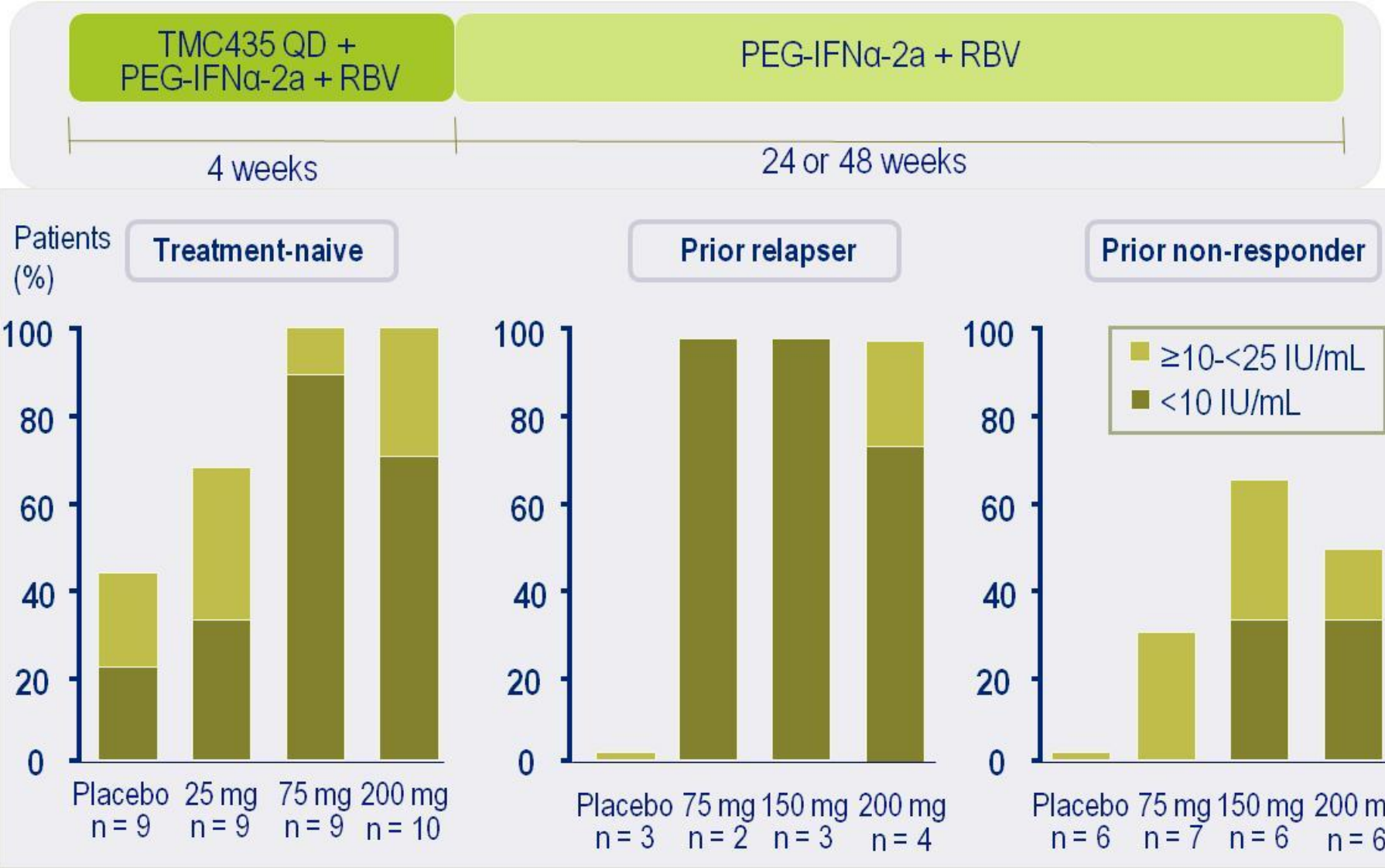
No dose-dependent increase in AE incidence was observed.

Median change from baseline HCV RNA
in patients (n = 6) treated with TMC435 (mono-therapy)

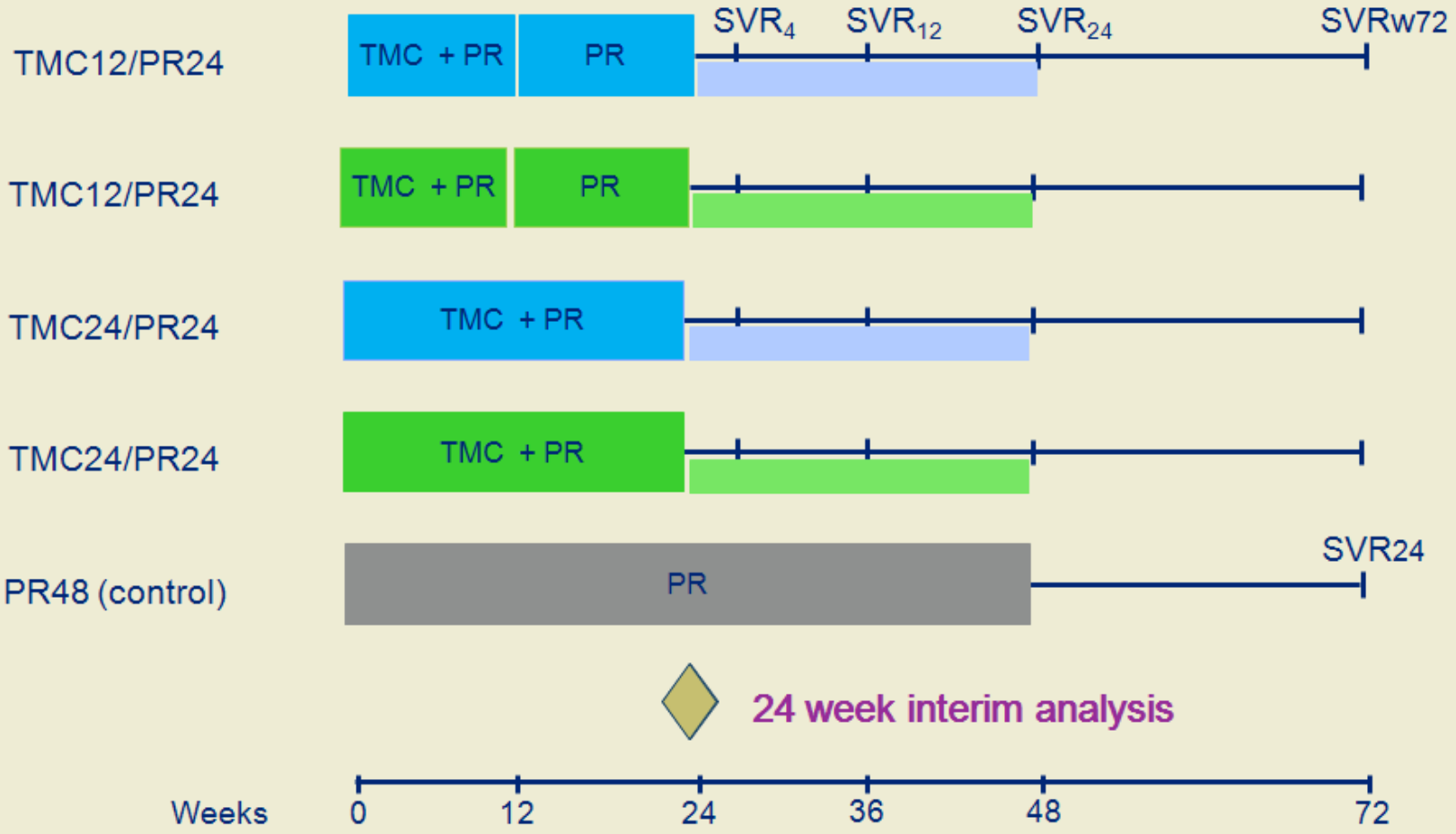


Five-day treatment with TMC435 200 mg QD resulted in **a maximal median decrease in HCV viral load of 3.9 Log10** IU/mL (range 2.9 - 4.1 Log10, IU/mL) observed at day 6
No difference in response between genotype 1a and 1b
No viral breakthrough observed

OPERA-1: PhIIa
response to treatment at Day 28

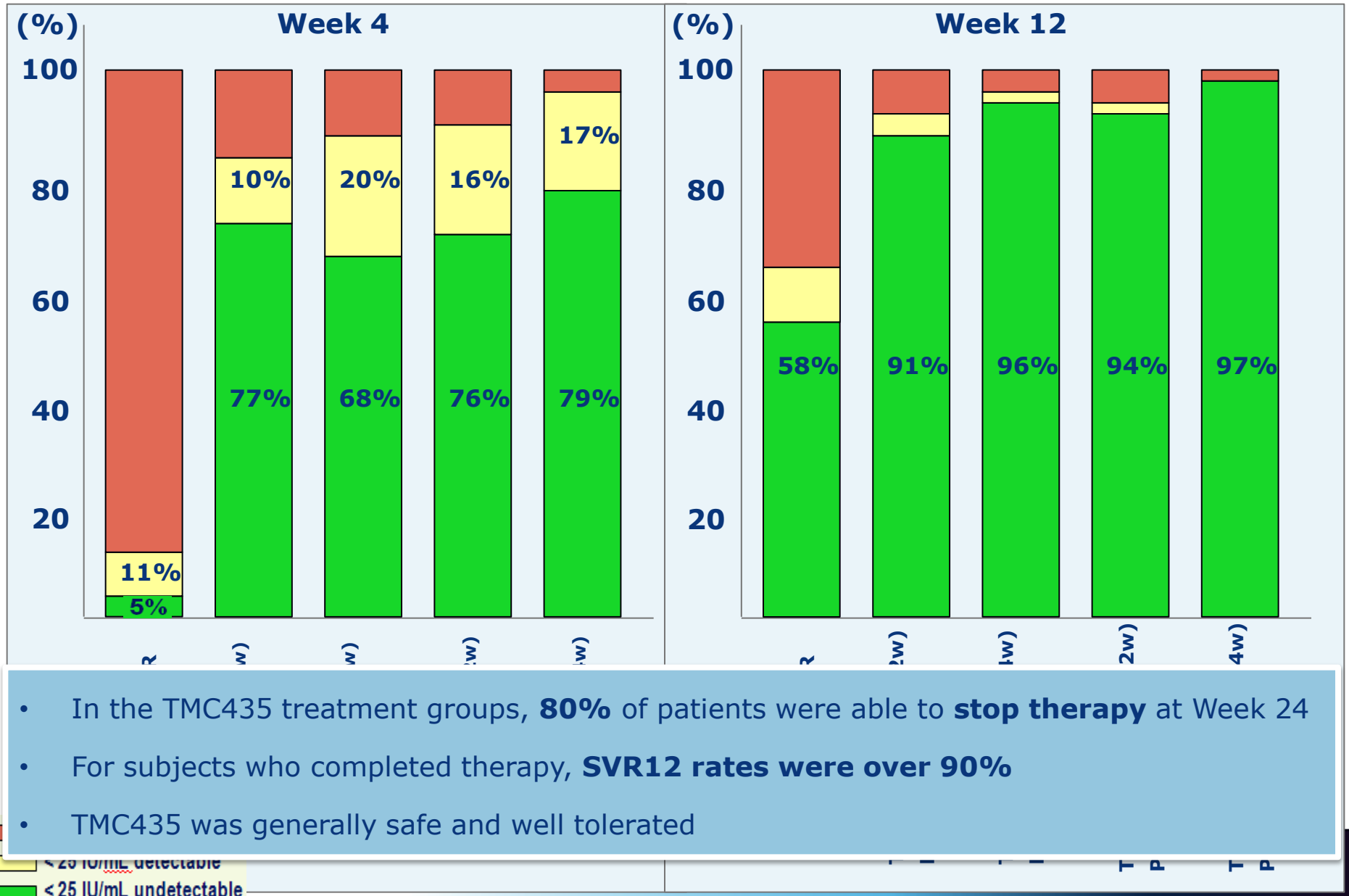


PILLAR: PhIIb
in a treatment- naive G1 patients



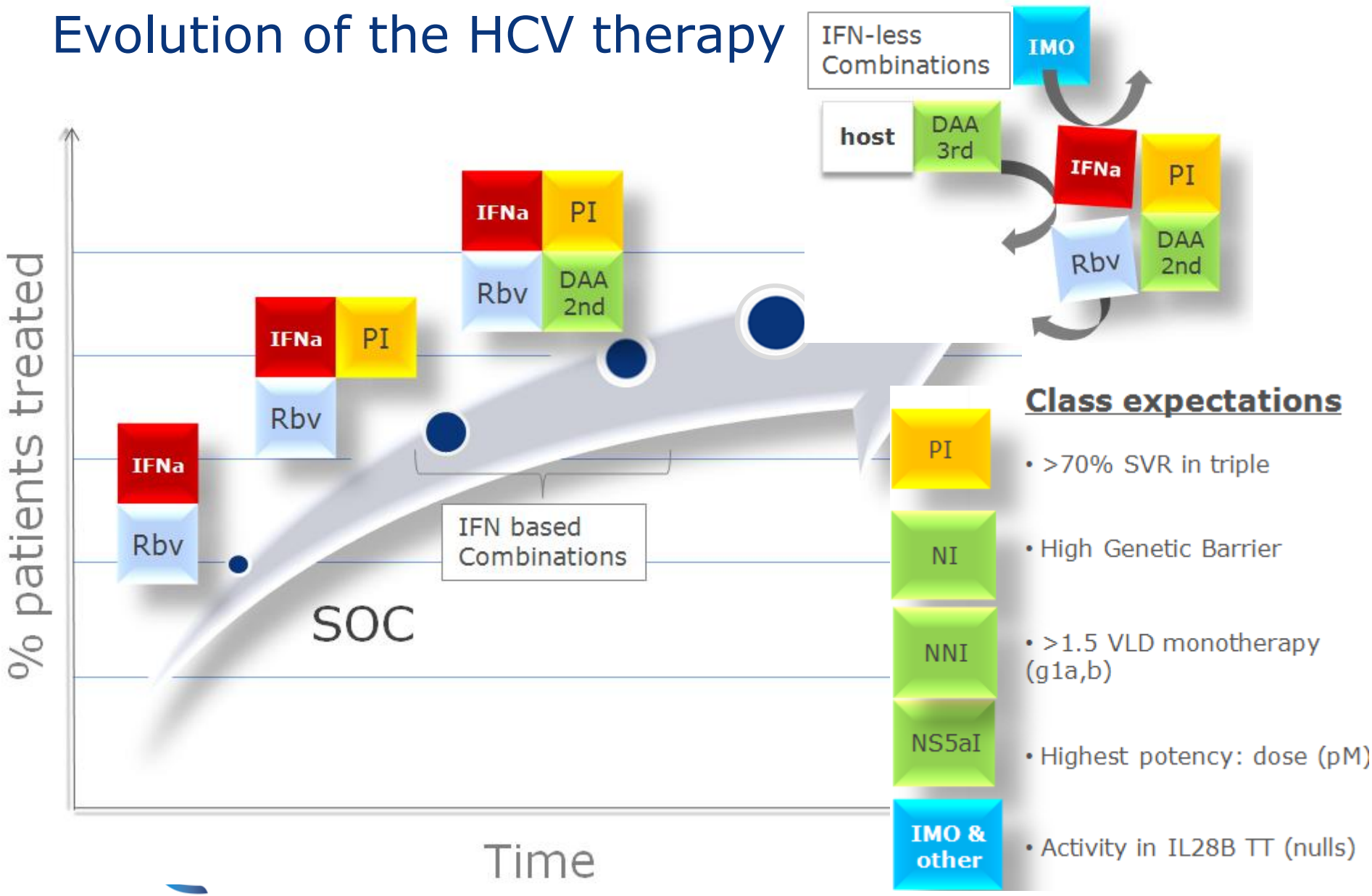
TMC435 arms: patients who do not achieve HCV RNA <25IU/mL and undetectable HCV RNA (<25IU/mL undetectable) at Wk12,16 and 20 continue PR until Wk48; (P) Peg-IFN = pegylated interferon alfa-2a 180 µg/wk; (R) RBV = ribavirin 1,000 or 1,200 mg/day; (TMC) TMC = TMC435 ; TMC435 75 mg q.d. (blue) or 150 mg q.d. (green)

PILLAR: Highlights 24-wk Interim Analysis

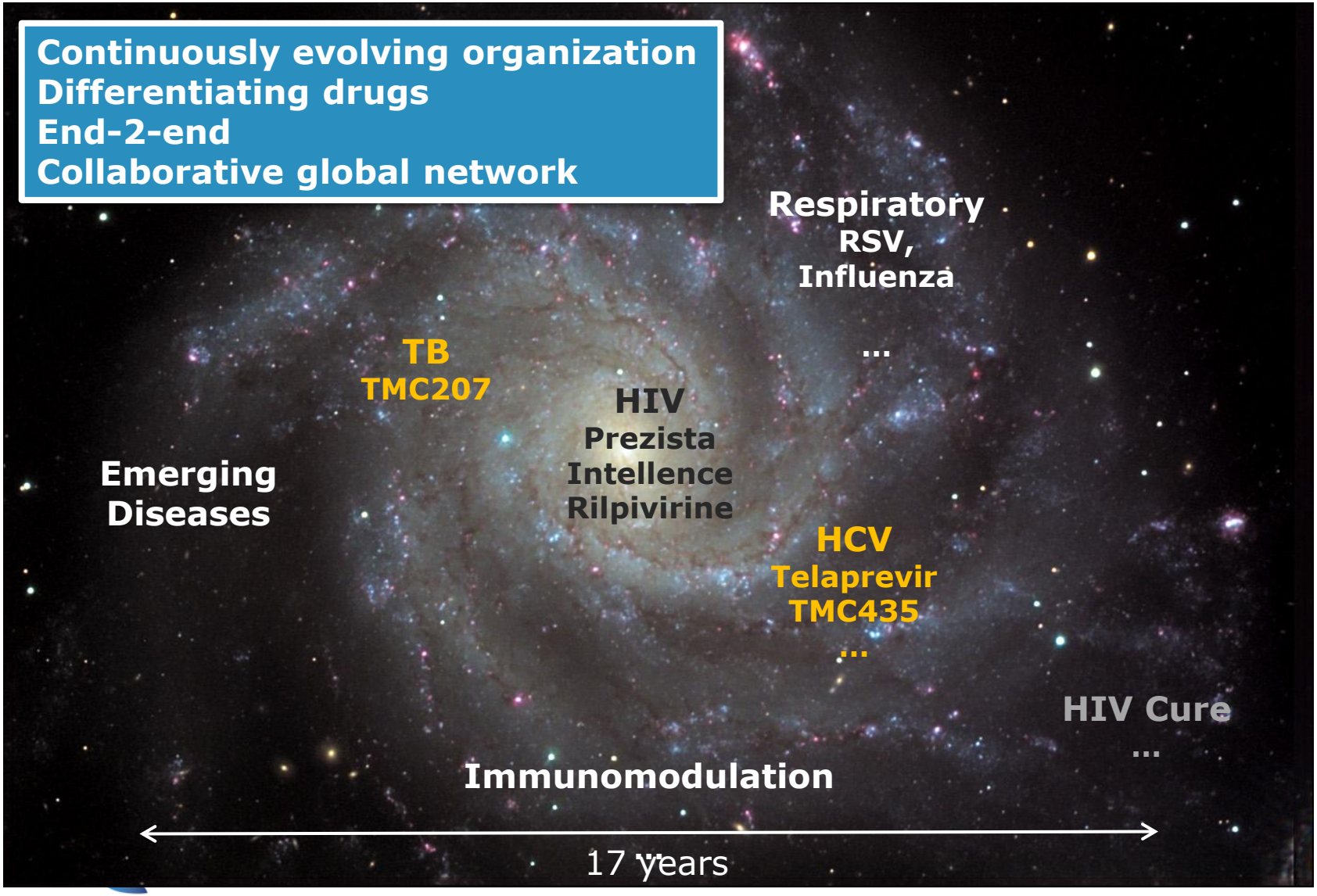


- In the TMC435 treatment groups, **80%** of patients were able to **stop therapy** at Week 24
- For subjects who completed therapy, **SVR12 rates were over 90%**
- TMC435 was generally safe and well tolerated

Evolution of the HCV therapy



In conclusion



Acknowledgements

- **Patients**
- **External collaborators**
- **Tibotec & Janssen R&D Teams**