SISET

Siset Training Center:

CORSO MALATTIE EMORRAGICHE

Firenze, 26-30 settembre 2016

Lunedì 26 settembre – sessione teorica

16.30 **Il trattamento delle complicanze infettive nell'emofilia** *Dario Bartolozzi (Firenze)*

OVVERO….

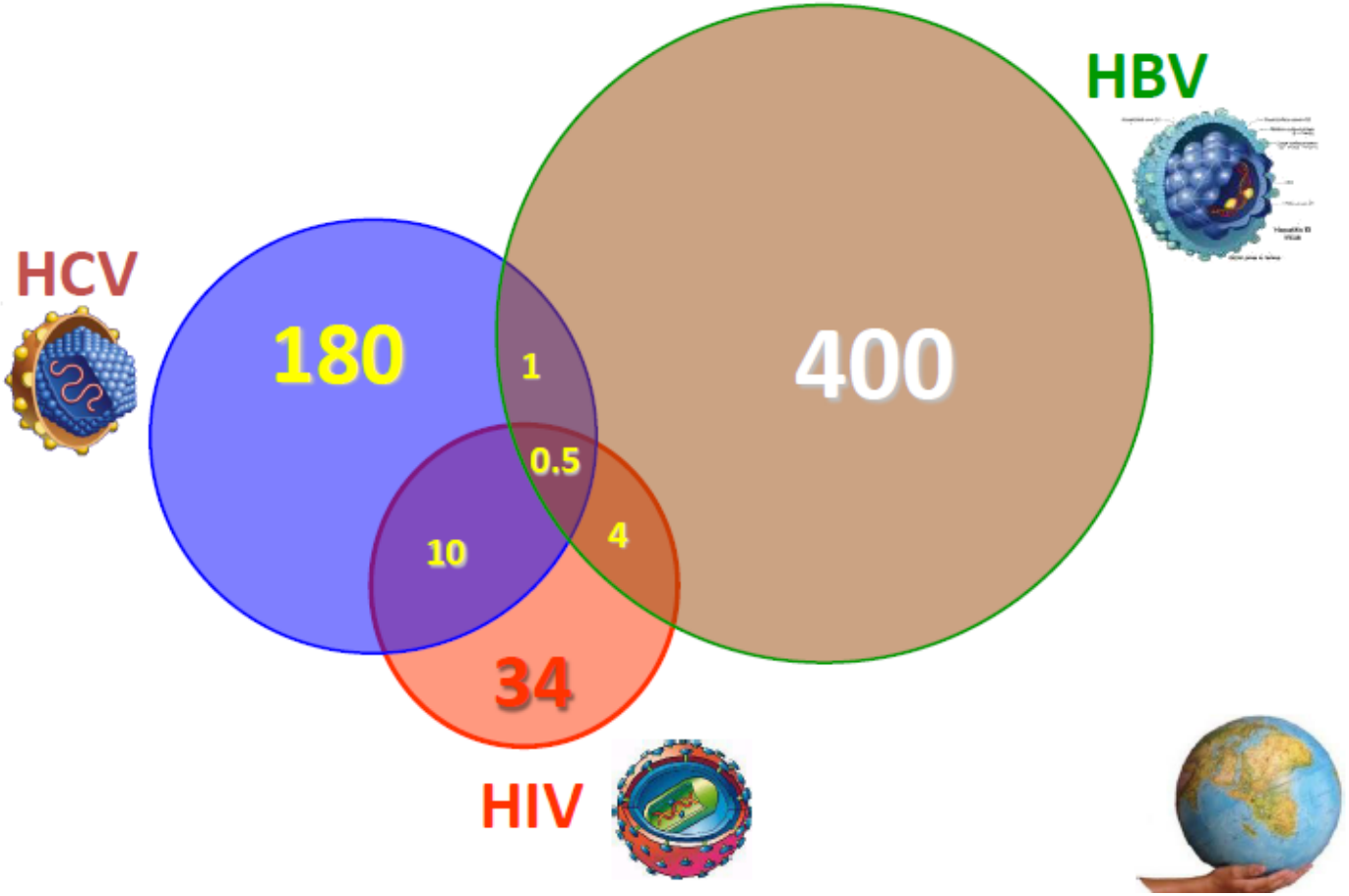
NEWS SUI TRATTAMENTI

DEI TRE VIRUS

(2015 forse un anno da ricordare)

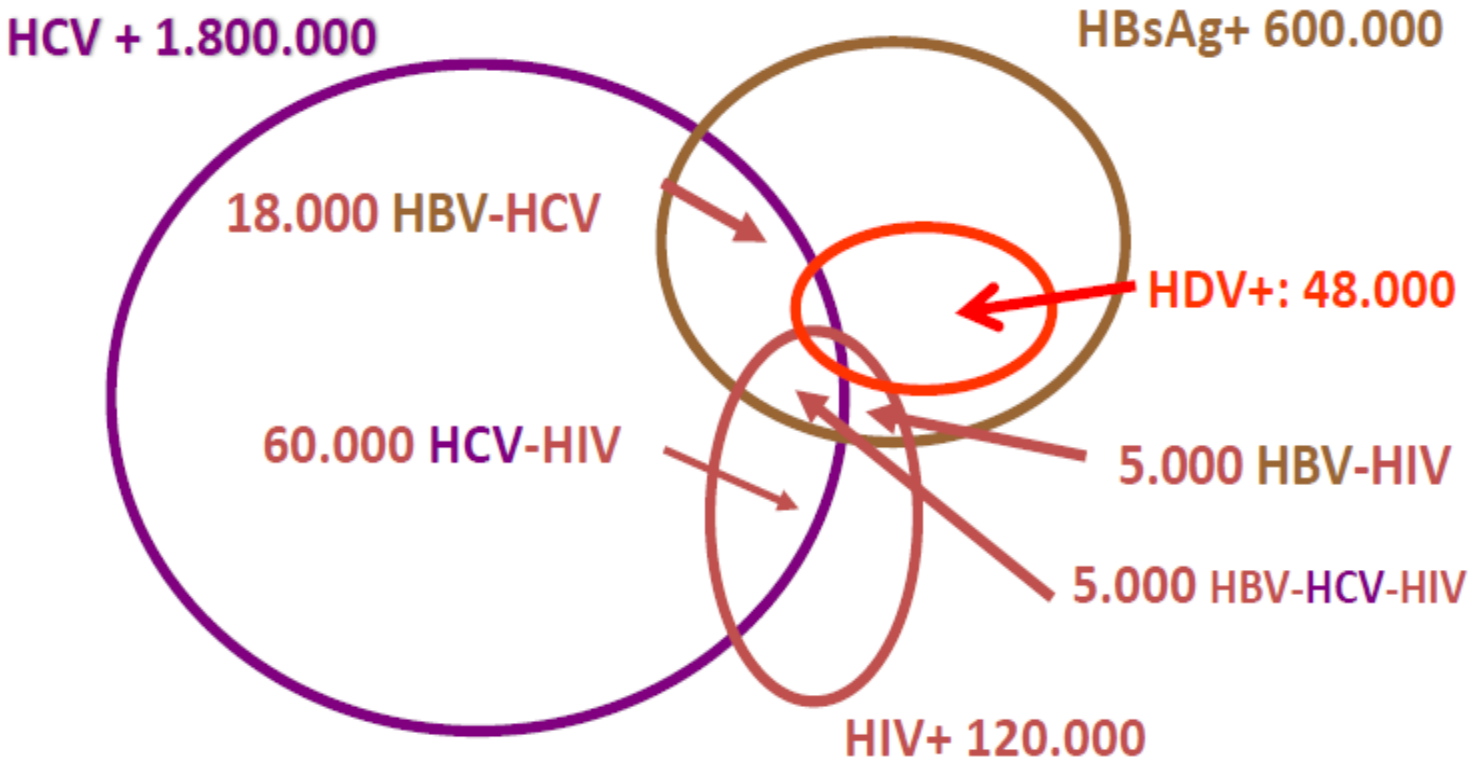
Soriano V et al., AIDS REV 2013

Background



Of the 34 million people living with HIV worldwide, around 20% (~8-10 million) had chronic hepatitis C

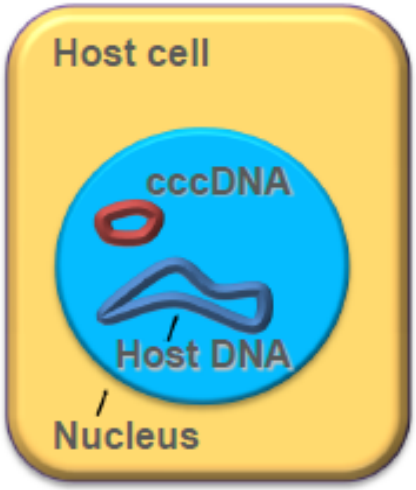
HIV – HBV – HCV – HDV coinfection in Italy



> 80% of HIV-positive individuals with positive HCV antibodies → HCV RNA is detected in the blood

Database Master e ICoNA

HBV
(Latent Reservoir)

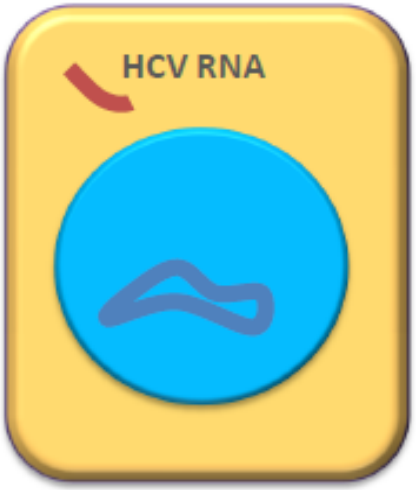


Long-Term Reduction of Viral Replication to Lowest Possible Level

HIV
(Latent Reservoir)

Lifelong Suppression of Viral Replication

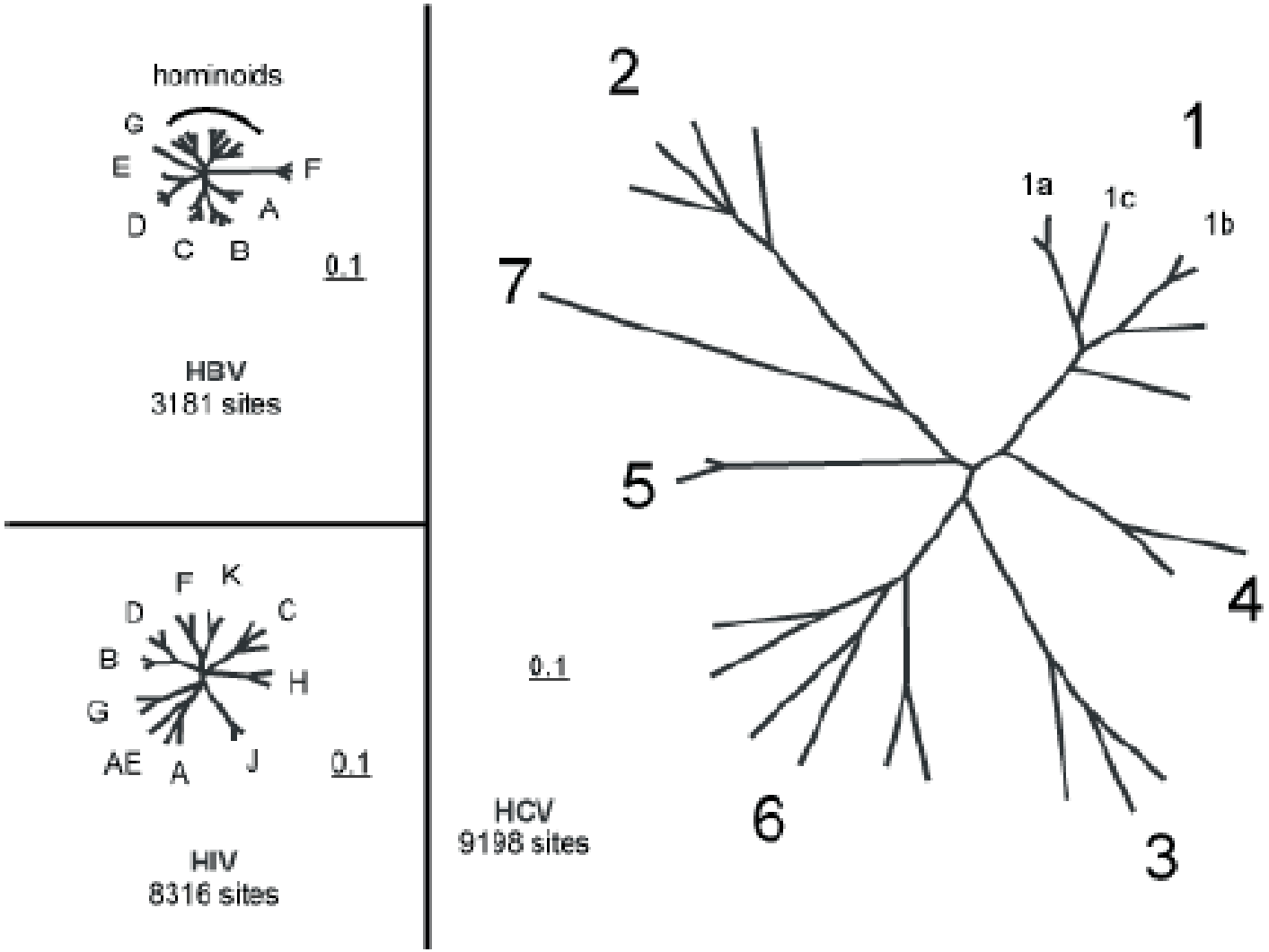
HCV
(No Latent Reservoir)



Definitive Viral Clearance: Cure is possible for HCV

cccDNA = covalently closed circular DNA.

Kieffer TL, et al. *J Antimicrob Chemother*. 2010;65:202-212.


hominoids
G
E
F
D
A
C
B
0.1
HBV
3181 sites
F
K
D
C
B
H
G
AE
A
J
0.1
HIV
8316 sites
2
1
1a
1c
1b
7
5
4
0.1
6
3
HCV
9198 sites

HIV

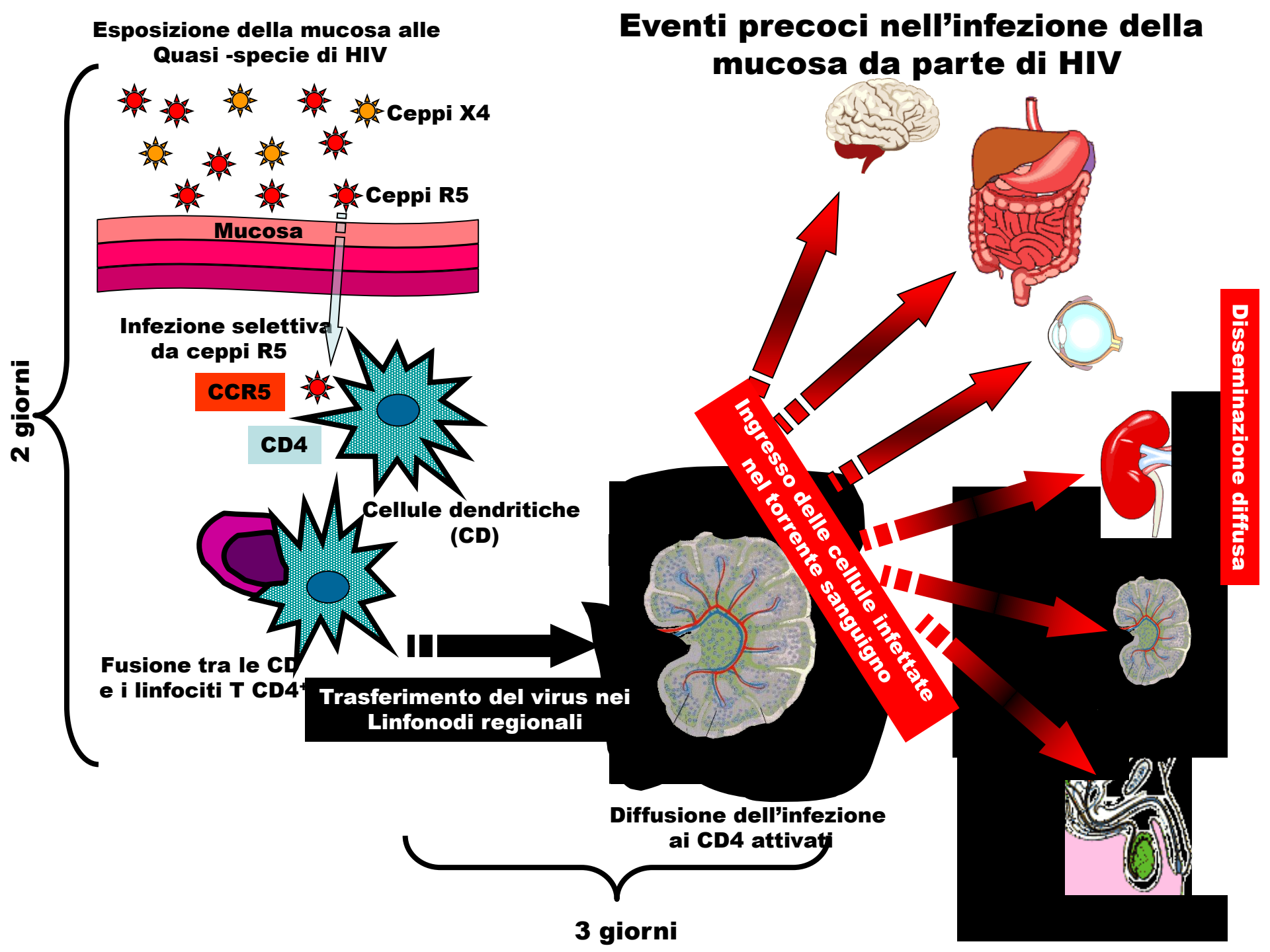
(Latent Reservoir)

Lifelong Suppression of
Viral Replication

c

Kieffer TL, et al. *J Antimicrob Chemother*. 2010;65:202-212.

Eventi precoci nell'infezione della mucosa da parte di HIV



Viral blitzkrieg

R. Paul Johnson and Amitinder Kaur

It takes years for AIDS to develop from the damage inflicted on the immune system by HIV or its simian counterpart. Surprisingly, as many as half of the body's memory T cells may die at a very early stage of infection.

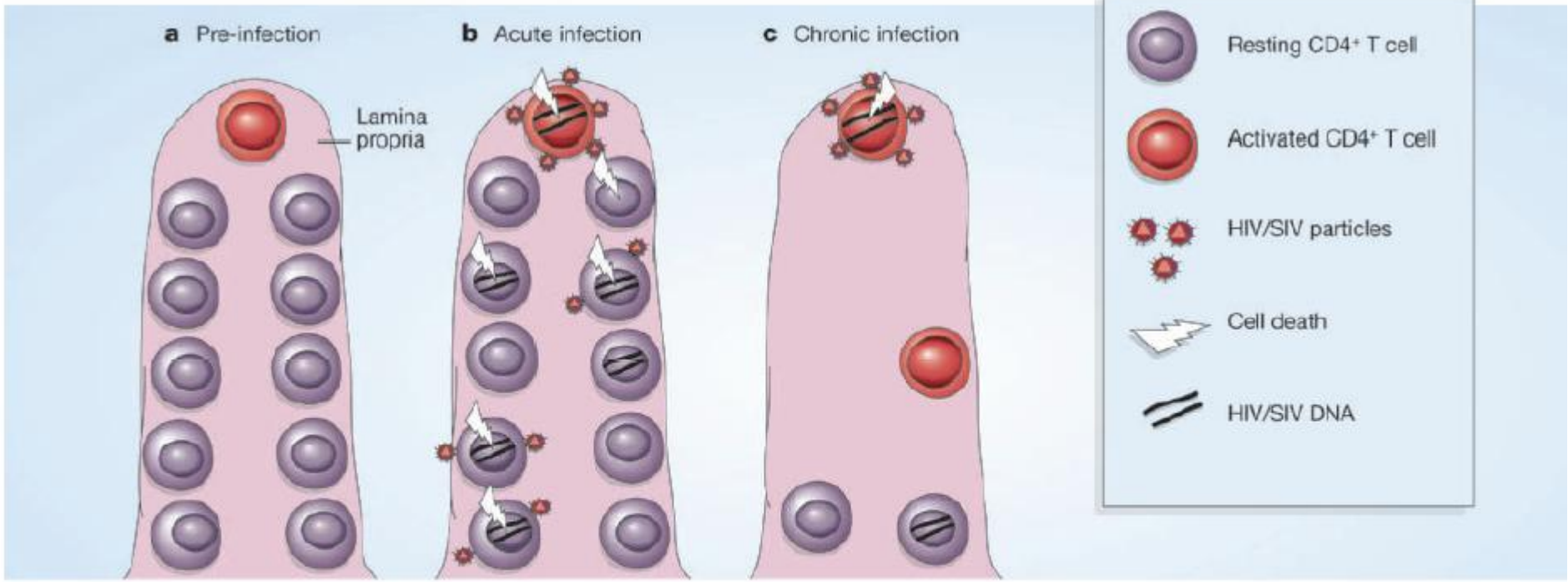
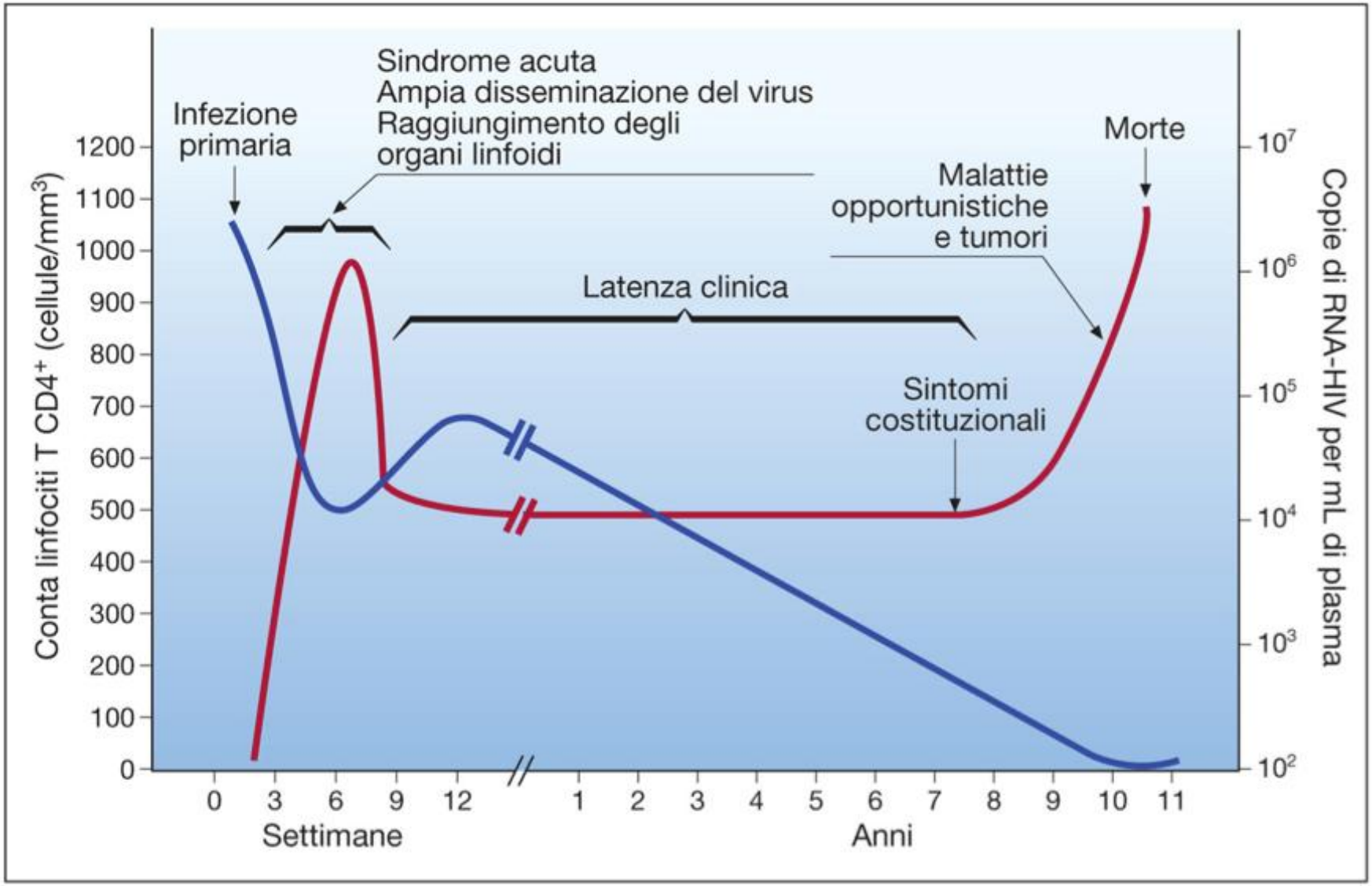


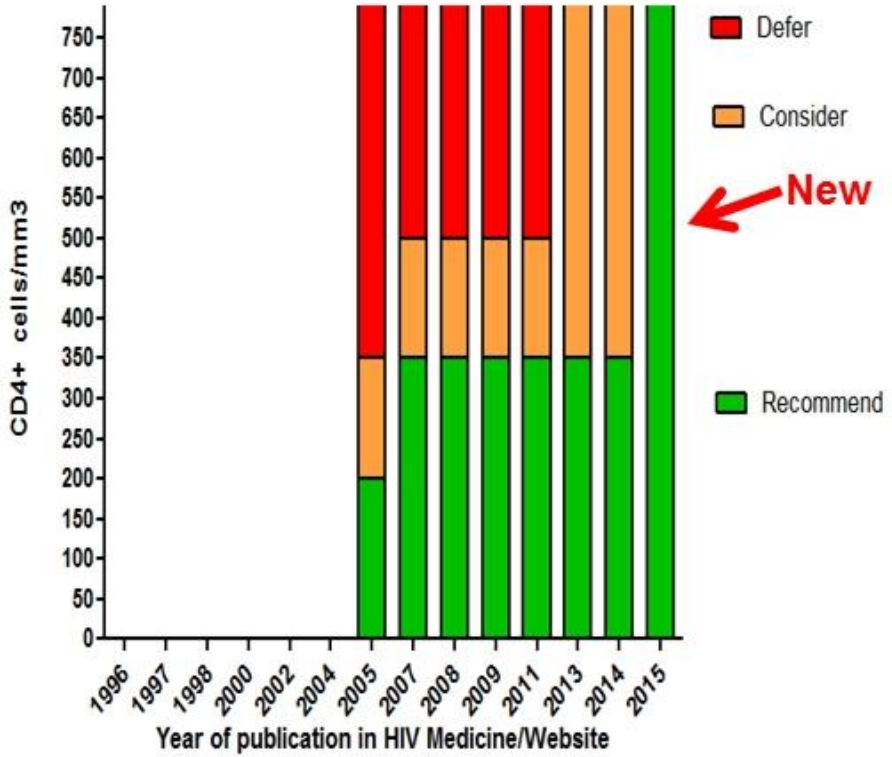
Figure 1 **Model for the depletion of gut CD4-expressing T lymphocytes by SIV. Most of the body's memory CD4$^+$ T helper cells are found in the gut, mainly in a compartment known as the lamina propria. a, Before infection, non-dividing (resting) CD4$^+$ T cells in the lamina propria outnumber activated T cells by 70-fold or more. b, In the initial (acute) phase of infection, the CD4$^+$ T-cell population in the gut is eliminated rapidly; the new papers reveal that up to 60% of these T cells are infected with SIV[1] and that most of the infected cells are resting rather than activated[2]. Only a subset of infected cells that contain SIV DNA will express SIV RNA and produce viral particles. Such 'productively infected' cells, cells that contain viral DNA but not RNA, and uninfected cells may all be killed as a result of SIV infection, although the relative numbers of each are not known. c, During chronic infection, in response to the depletion of resting cells, the number of activated cells increases slightly. These cells now represent the dominant site of viral replication.**

Storia naturale dell'infezione da HIV



When to Start ART

ART in asymptomatic chronic HIV infection with detectable viral load (EACS)



EACS European AIDS Clinical Society

Recommendation 1: When to start ART among people living with HIV

Target population	Specific recommendation	Strength of the recommendation	Quality of the evidence
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED
Adolescents (10–19 years old)	ART should be initiated in all adolescents living with HIV at any CD4 cell count	*Conditional*	*Low* NEW
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*

2015 Update: EACS Guidelines for Treatment of HIV-Infected Pts in Europe

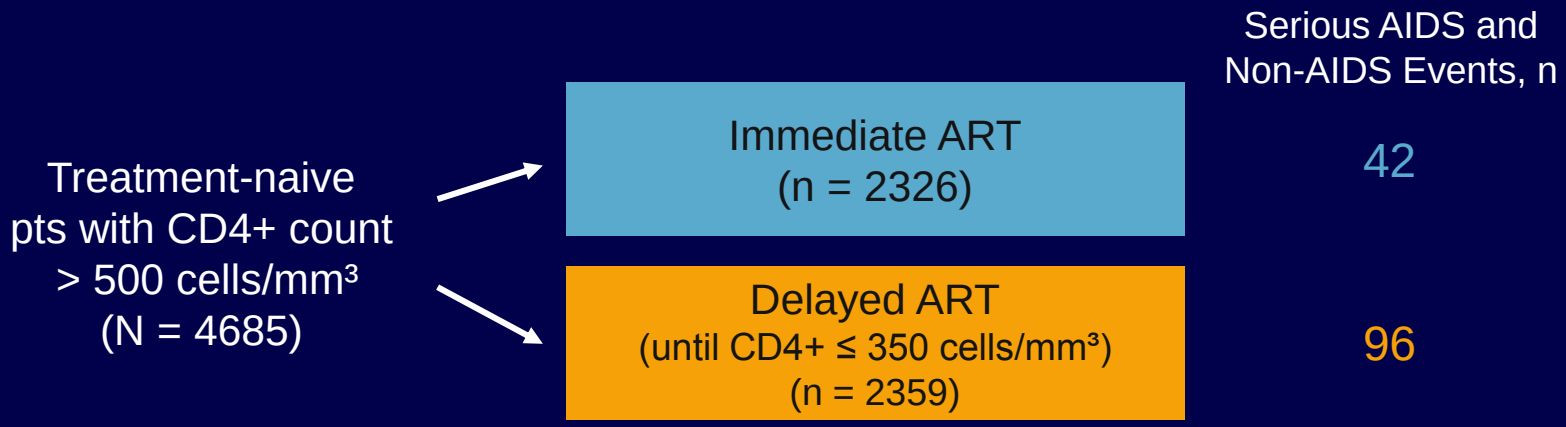
- ART initiation now recommended for all pts, regardless of CD4+ cell count

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count, cells/mm^3		
		< 350	350-500	> 500
EACS[1]	**Yes**	**Yes**	**Yes**	**Yes**
DHHS[2]	Yes	Yes	Yes	Yes
IAS-USA[3]	Yes	Yes	Yes	Yes
WHO[4]	Yes	Yes	Yes	Yes

1. EACS HIV Guidelines. V 8.0. October 2015. 2. DHHS Guidelines. April 2015.
3. Günthard H, et al. JAMA. 2014;312:410-425. 4. WHO When to Start Guidelines. September 2015.

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized phase IV study involving 215 sites in 35 countries



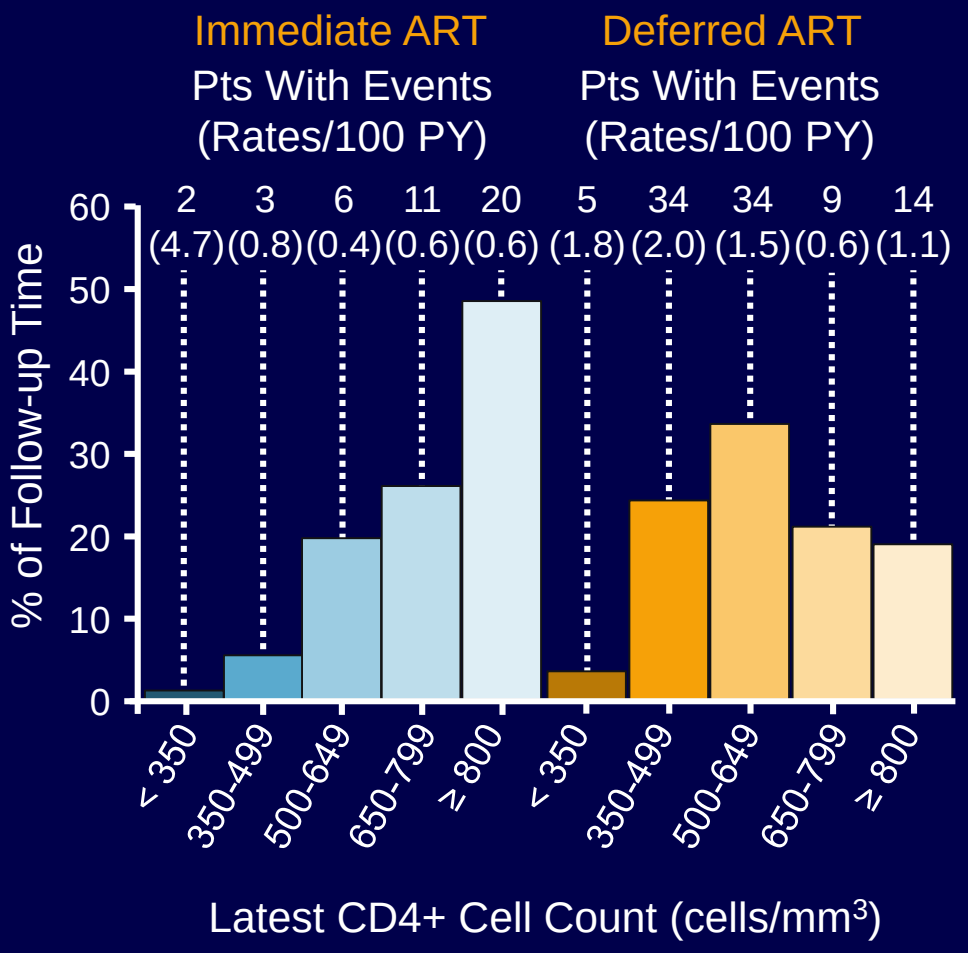
- Study stopped by DSMB following results of interim analysis
  - Overall HR: 0.43 (*P* < .001)
    - HR for serious AIDS-related events: 0.28 (*P* < .001)
      HR for non-AIDS–related events: 0.61 (*P* = .04)
- Similar HIV-1 RNA suppression rates 12 mos after starting ART in both arms (immediate: 98%; delayed: 97%)

Lundgren JD, et al. N Engl J Med. 2015;373:795-807.

START: Primary Endpoint Events by Latest CD4+ Cell Count

Latest CD4+ count > 500 cells/mm^3

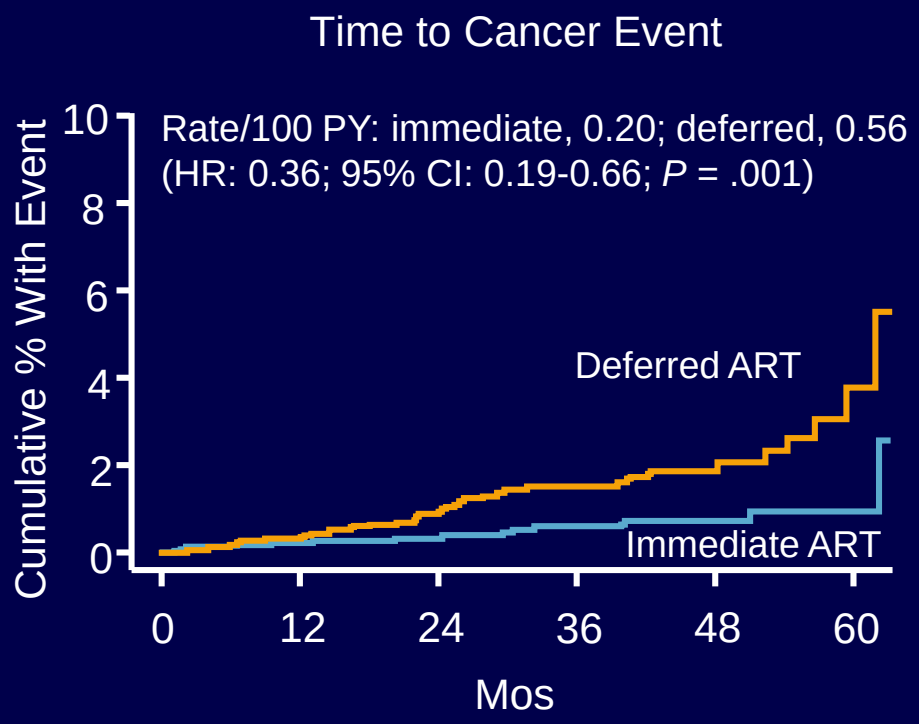
	Immediate ART	Deferred ART
Primary events, % (n/N)	88 (37/42)	59 (57/96)
Rate/100 PY	0.6	1.1



Lundgren JD, et al. N Engl J Med. 2015;373:795-807.

START: Cancer Events With Immediate vs Deferred ART

Cancer Event, n	Immediate ART (n = 2326)	Deferred ART (n = 2359)
Total	**14**	**39**
Kaposi's sarcoma	1	11
Lymphoma, NHL + HL	3	10
Prostate cancer	2	3
Lung cancer	2	2
Anal cancer	1	2
Cervical or testis cancer	1	2
Other types*	4	9

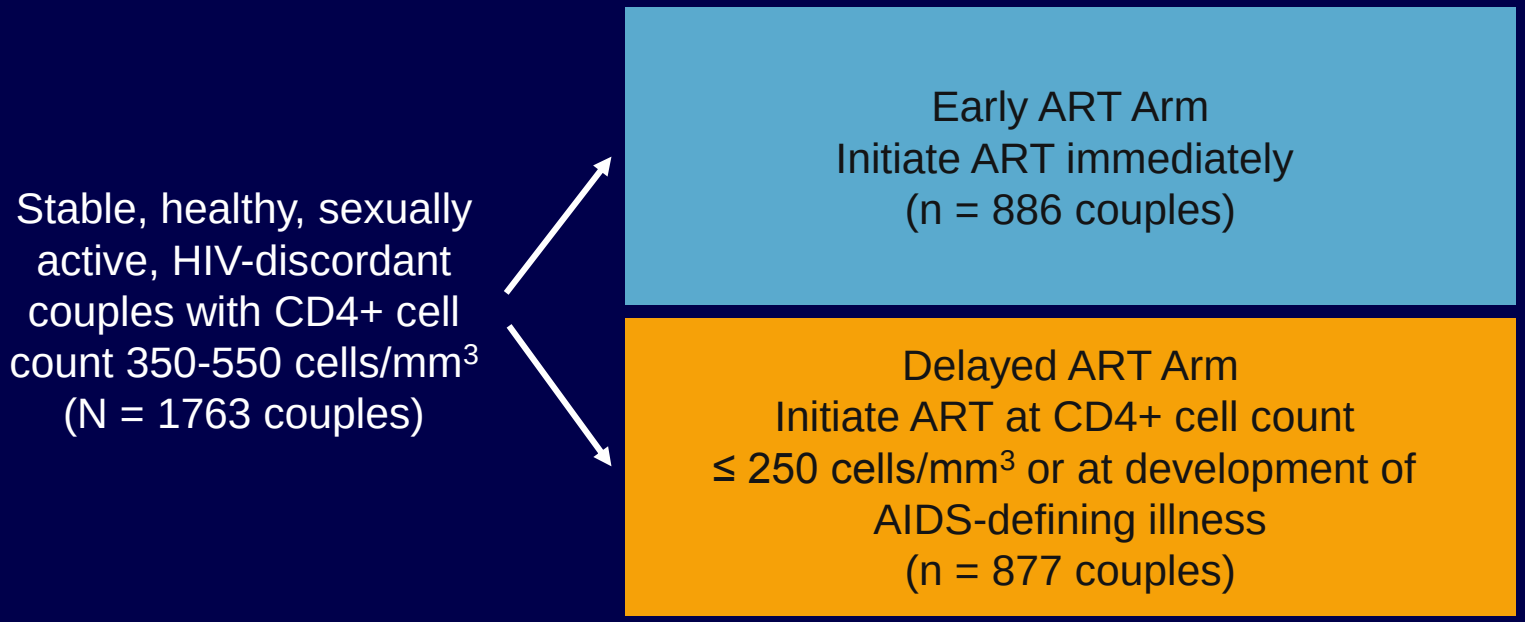


*Immediate ART: squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma. Deferred ART: gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

Lundgren JD, et al. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

HPTN 052: ART for Prevention of HIV Transmission in Serodiscordant Couples

- International, randomized, controlled trial



Grinsztejn B, et al. Lancet Infect Dis. 2014;14:281-290.

HPTN 052: Reduced Risk of Partner Infection

- ART offered to all index pts in delayed ART arm from May 2011 after interim results
- 8 linked HIV infections diagnosed after seropositive patient started ART
  - All occurred before or soon after initiation or after virologic failure
- No linked HIV transmissions observed when index participant stably suppressed on ART

Partner Infections, n (rate per 100 PY)	Overall (April 2005 - May 2015)	
	Early (4314 PY F/U)	Delayed (4180 PY F/U)
All	19 (0.44)	59 (1.41)
Linked	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %		
All infections	69	--
Linked infections	93	--

Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

Part II

ART of HIV-positive Persons	6
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Drug-drug Interactions between Contraceptives/Hormone Replacement Therapy and ARVs	(22)
Drug-drug Interactions between Corticosteroids and ARVs	(23)
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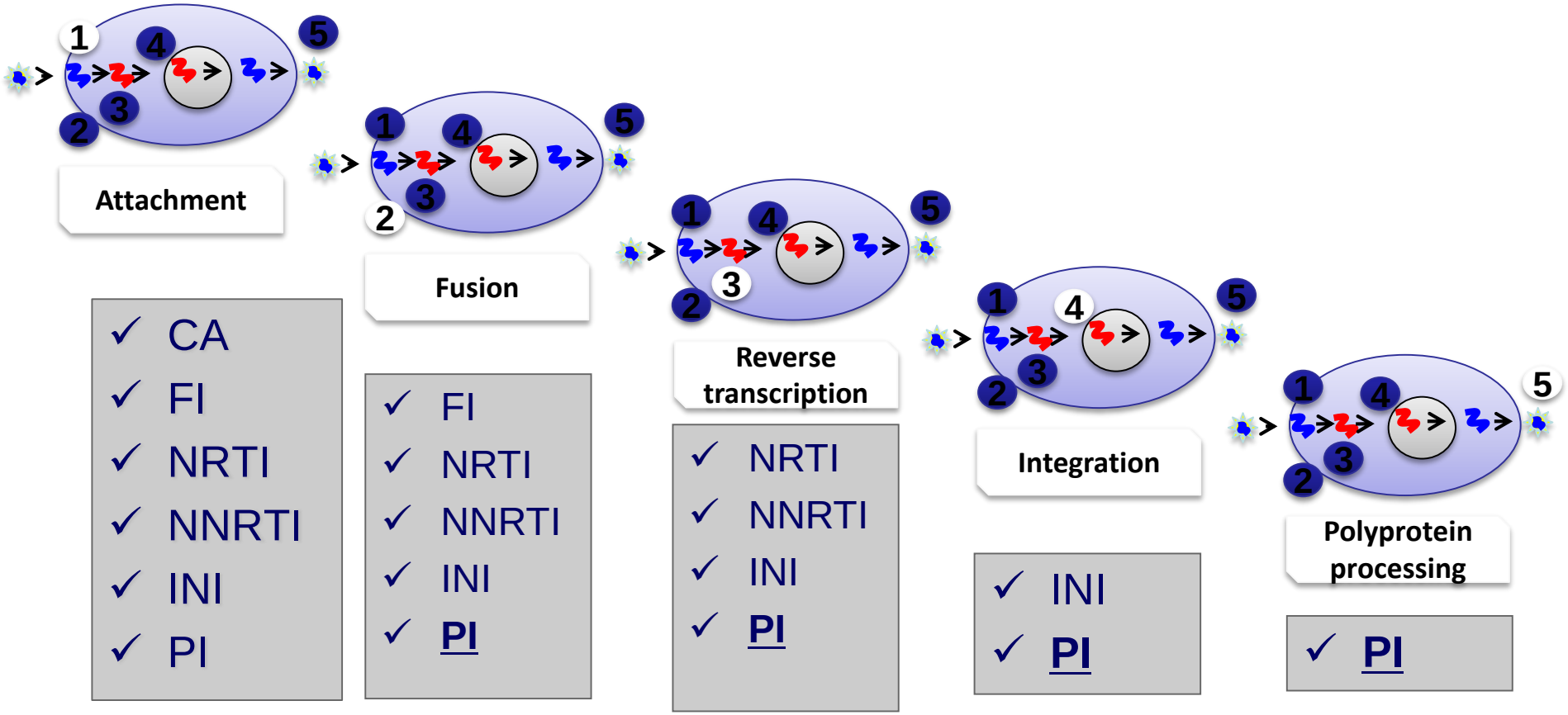
EACS European AIDS Clinical Society

What to Start

Stage-dependent inhibition of HIV replication by individual drugs



As long as HIV cycle proceeds virus production is halted by later acting drug classes

At the time of drug addiction, drugs that act later will have more available target cells in which to prevent viral replication than drugs that act earlier. (Donahue, AAC 2010)

Comparison of Current International Guidelines for Treatment-Naive Pts

Regimen	DHHS[1]	EACS[2]	BHIVA[3]	IAS-USA[4]	GeSIDA[5]
DTG/3TC/ABC*					
DTG + FTC/TDF					
EVG/COBI/FTC/TDF†					
EVG/COBI/FTC/TAF‡					
RAL + FTC/TDF					
ATV/RTV + FTC/TDF					
DRV/RTV + FTC/TDF					
EFV/FTC/TDF					
RPV/FTC/TDF §					

*Only if HLA-B*5701 negative. †Only if CrCl ≥ 70 mL/min. ‡Only if CrCl ≥ 30 mL/min. §Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3.

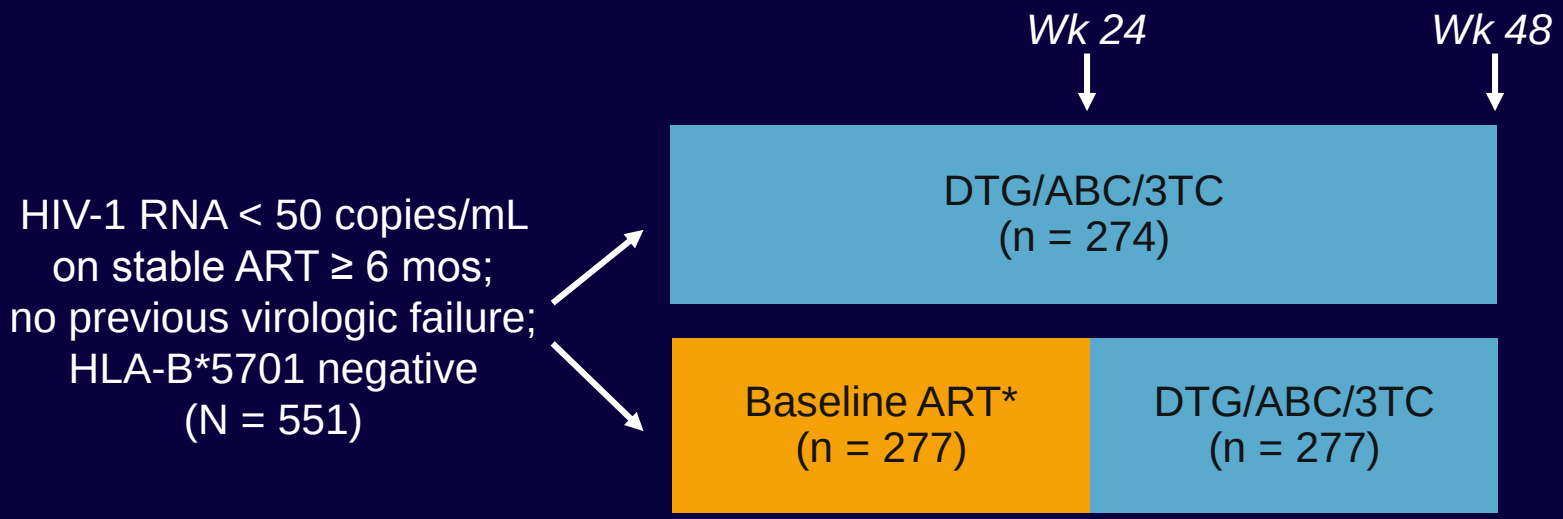
Recommended Alternative Not included

1. DHHS Guidelines. January 2016.
2. EACS HIV Guidelines. V 8.0. October 2015.
3. BHIVA Guidelines. 2015.
4. Günthard H, et al. JAMA. 2014;312:410-425.
5. GeSIDA. January 2016.

Switch Strategies

STRIIVING: Switch From Suppressive ART to Fixed-Dose DTG/ABC/3TC

- Ongoing randomized, open-label phase IIIB study
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

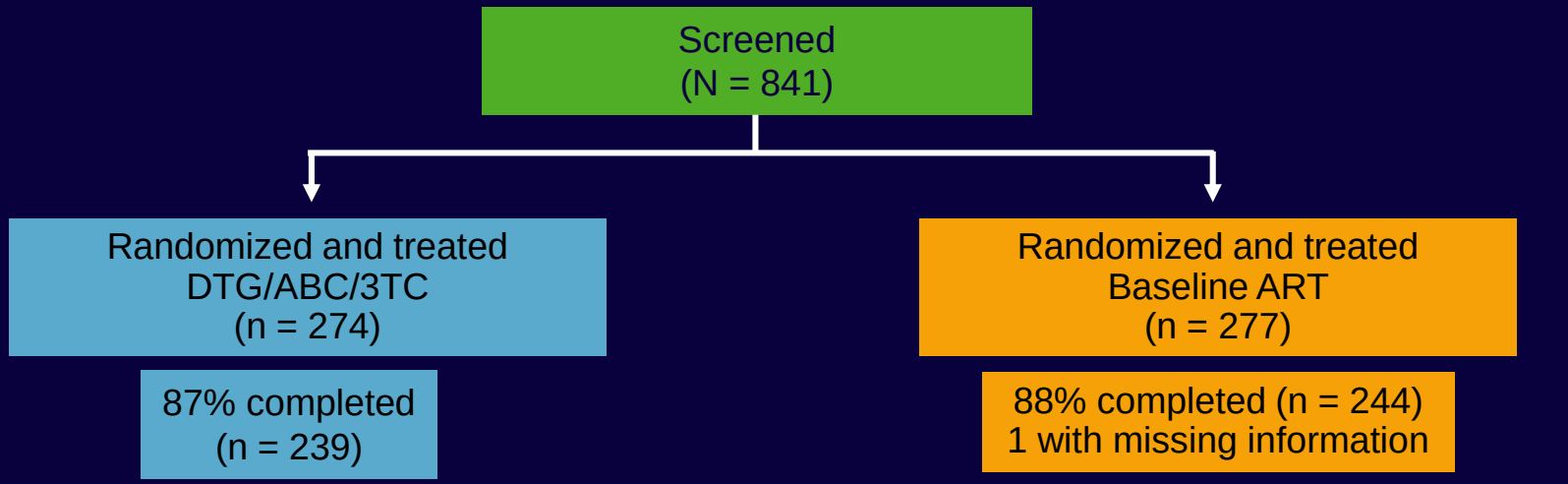


*Containing 2 NRTIs plus NNRTI, PI, or INSTI.

	PI	NNRTI	INSTI	TDF/FTC
BL ART use, %	42	31	26	77

Trottier B, et al. ICAAC 2015.

STRIIVING: Study Disposition at Wk 24



13% of subjects withdrawn (n = 35)	
Adverse event	**10 (4%)**
Lack of efficacy (virologic failure)	0
Protocol deviation	**15 (5%)**
Stopping criteria met	0
Lost to follow-up	3 (1%)
Investigator discretion	3 (1%)
Withdrew consent	4 (1%)

12% of subjects withdrawn (n = 32)	
Adverse event	**0**
Lack of efficacy (virologic failure)	0
Protocol deviation	**17 (6%)**
Stopping criteria met	0
Lost to follow-up	3 (1%)
Investigator discretion	3 (1%)
Withdrew consent	9 (3%)

Trottier B, et al. ICAAC 2015. Reproduced with permission.

Switch From Suppressive ART to Dolutegravir Monotherapy

- 97% of pts maintained virologic suppression at Wk 24[1]
- Reasons for switch improved in most pts from BL to 24 wks[1]
  - T-scores unchanged in 2 pts with osteoporosis
  - In single pt with renal disease, eGFR ↓ from 59 mL/min at BL to 52 mL/min/ at Wk 24; urine protein:creatinine ratio ↓ from 330 to 146 mg/mg

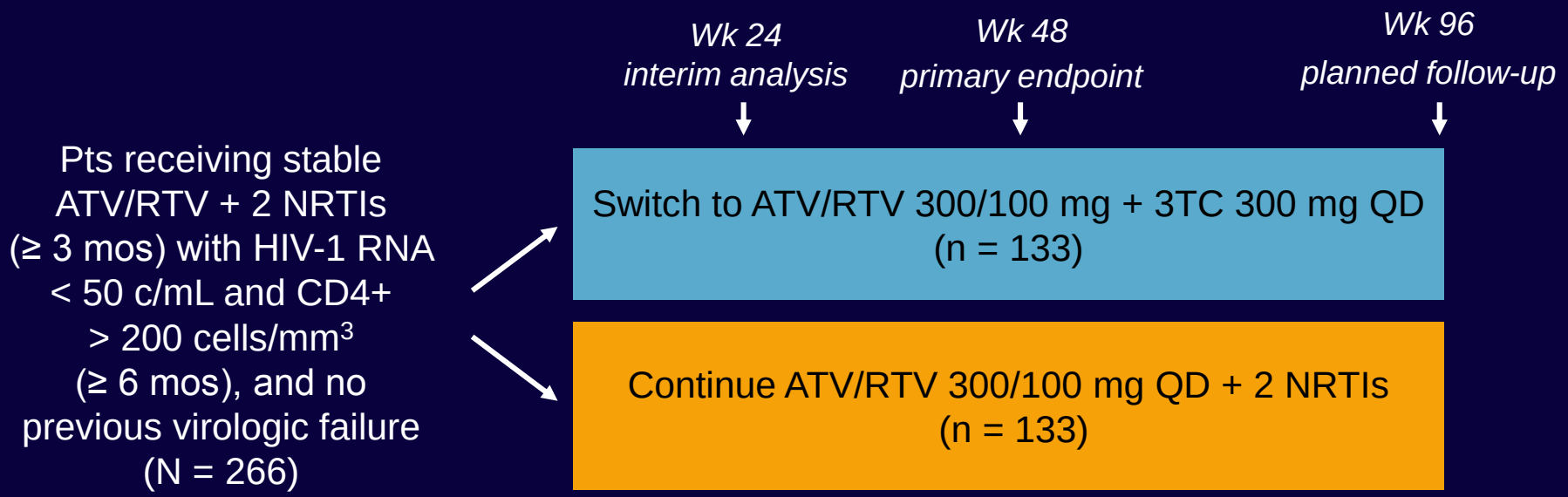
Reason for Switch	Pts at Risk, n	Outcome Improved/ Avoided, n
DDIs	13	13
GI symptoms	11	9
Dyslipidemia	9	9
High Framingham score	3	3

- In separate study of switch from suppressive ART to DTG monotherapy, 89% of pts maintained virologic suppression 24 wks after switch[2]

1. Rojas J, et al. EACS 2015. Abstract 1108. 2. Katlama C, et al. EACS 2015. Abstract 714.

ATLAS-M: Switch From Suppressive ATV/RTV + 2 NRTIs to ATV/RTV + 3TC

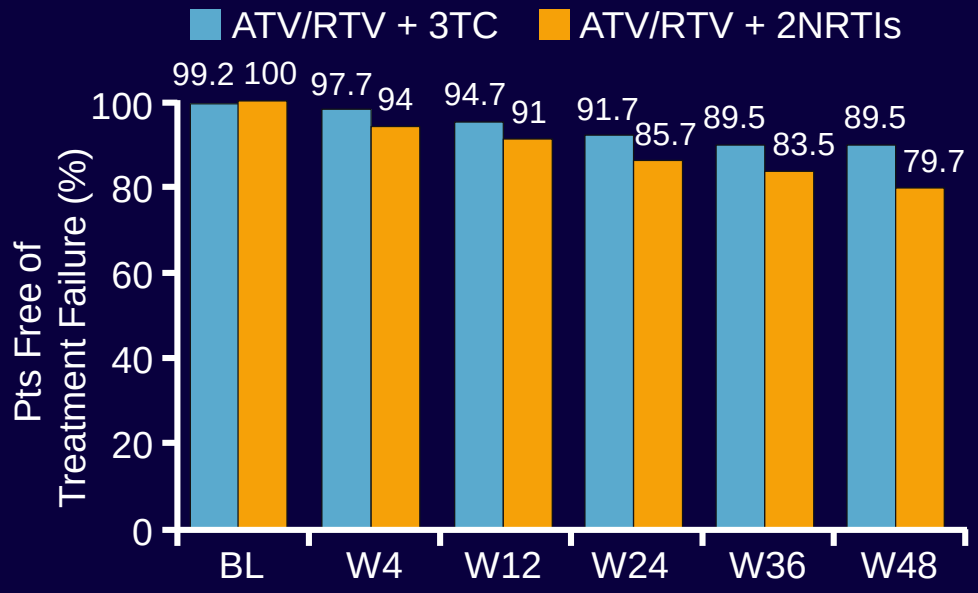
- Randomized, multicenter, open-label phase IV trial
  - Primary endpoint: absence of treatment failure at Wk 48, defined as ART modification for any reason and/or virologic failure

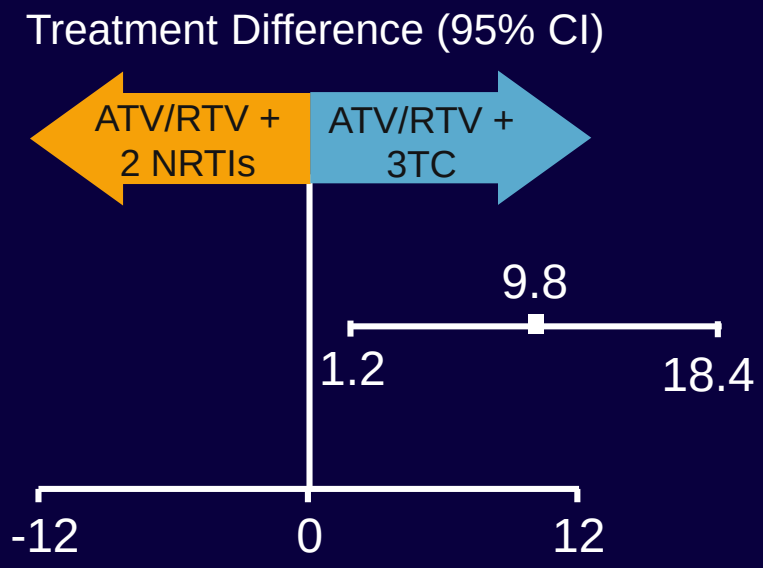


Di Giambenedetto S, et al. EACS 2015. Abstract 867.

ATLAS-M: Virologic Efficacy and Safety Through Wk 48

- Switch to ATV/RTV + 3TC noninferior and superior (post hoc) to continuing ATV/RTV + 2 NRTIs in ITT, S=F analysis



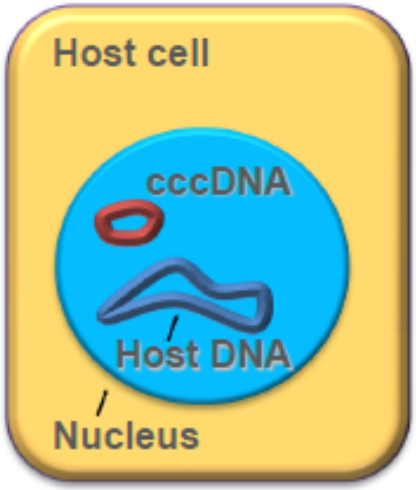


- Significantly greater increases in TC ($P < .01$), LDL ($P < .05$), and HDL ($P < .01$) with ATV/RTV + 3TC vs ATV/RTV + 2 NRTIs at Wk 48
- Mean change in eGFR at Wk 48: +2 mL/min with ATV/RTV + 3TC vs -4 mL/min with ATV/RTV + 2 NRTIs ($P < .001$)

Di Giambenedetto S, et al. EACS 2015. Abstract 867.

HBV

(Latent Reservoir)



Long-Term Reduction of Viral Replication to Lowest Possible Level

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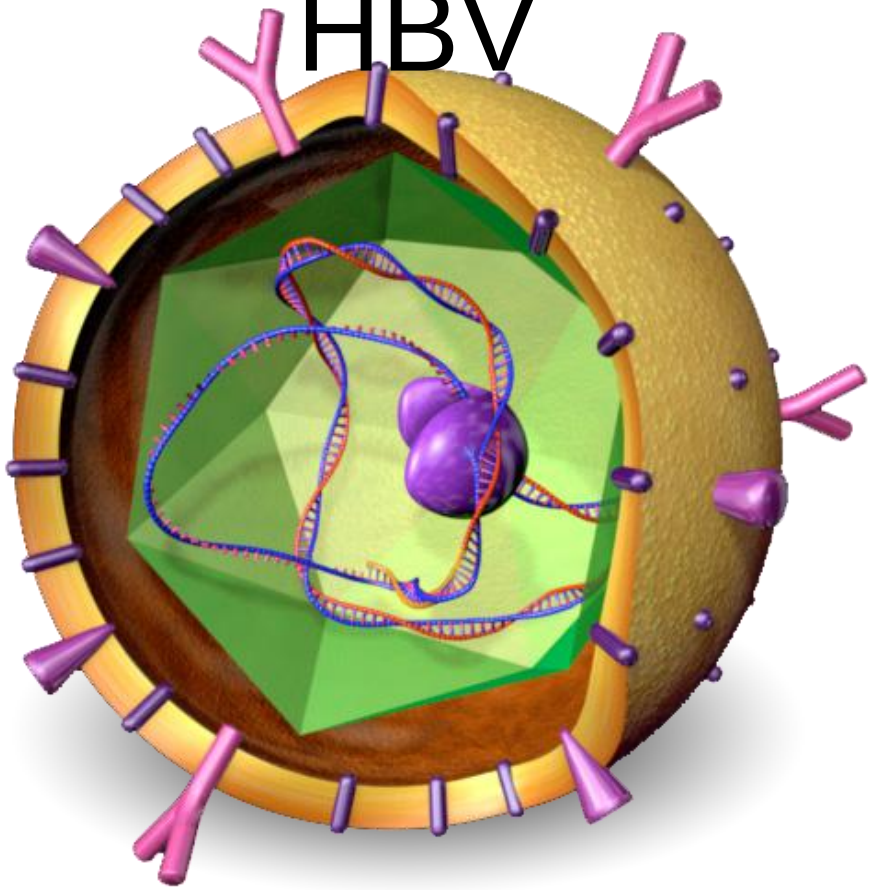
HBV



- Il genoma di HBV è costituito da una molecola di DNA circolare a doppia elica incompleta. Il doppio anello è formato da una catena lunga L di circa 3200 nucleotidi e una catena breve S di lunghezza tra il 50 e l'80% di quella lunga.

HBsAg positive patients in 2015

Chance finding of an HBsAg positive person
(blood donation, family screening, surgical intervention elevated ALT value).

NOW RARE

Symptomatic subjects with advanced liver disease (decompensated cirrhosis or cancer)

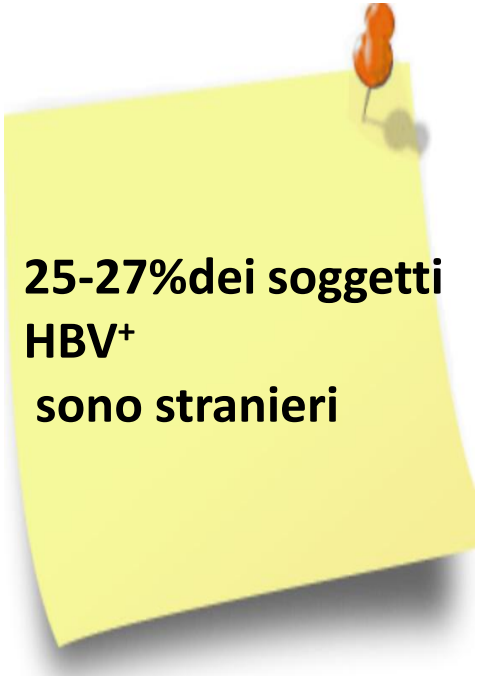
STILL HAPPENS

HBsAg positive non-Italian natives
(local screening campaigns, “integrated” subjects, delivery

INCREASING

CARATTERISTICHE

- ETA’
- RAZZA
- STORIA FAMILIARE
- NAZIONALITA’
- COMORBILITA’
- STILE DI VITA’



1. MASTER-B Cohort, AISF, Brancaccio et al, 2014; 2.SIMIT cohort, Fasano et al, Infection 2013

STADIAZIONE CLINICA

- HBeAg/anti-HBe
- HBV DNA
- ALT
- HBV genotipo
- qHBsAg
- stadio/grado malattia
- HDV, HIV, HCV
- Comorbilità

Genotipo HBV e dosaggio quantitativo di HBsAg sono estremamente importanti per un trattamento con Peg-IFN

J Hepatol 2009 & 2012

EASL Clinical Practice Guidelines: Management of chronic hepatitis B

2.2. Natural history

Chronic hepatitis B is a dynamic process. The natural history of CHB can be schematically divided into five phases, which are not necessarily sequential.

(1) The "immune tolerant" phase is characterized by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of aminotransferases, mild or no liver necroinflammation and no or slow progression of fibrosis [3,5].

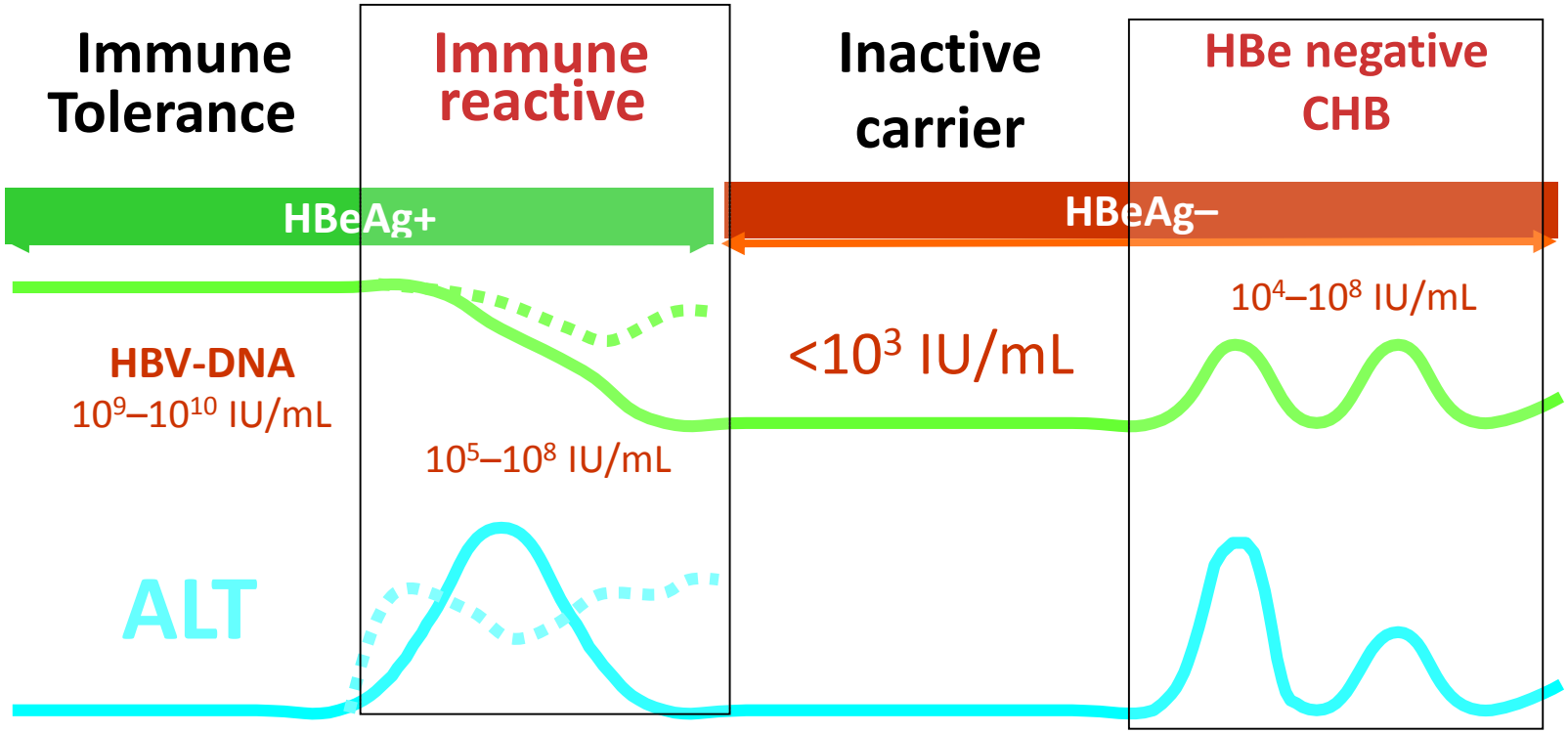
(2) The "immune reactive phase" is characterized by HBeAg positivity, a lower level of replication (as reflected by lower serum HBV DNA levels), increased or fluctuating levels of aminotransferases, moderate or severe liver necroinflammation and more rapid progression of fibrosis compared to the previous phase [3,5].

(3) The "inactive HBV carrier state" may follow seroconversion from HBeAg to anti-HBe antibodies. It is characterized by very low or undetectable serum HBV DNA levels and normal aminotransferases.

(4) "HBeAg-negative CHB" may follow seroconversion from HBeAg to anti-HBe antibodies during the immune reactive phase and represents a later phase in the natural history of CHB. It is characterized by periodic reactivation with a pattern of fluctuating levels of HBV DNA and aminotransferases and active hepatitis.

(5) In the "HBsAg-negative phase" after HBsAg loss, low-level HBV replication may persist with detectable HBV DNA in the liver [16]. Generally, HBV DNA is not detectable in the serum while anti-HBc antibodies with or without anti-HBs are detectable.

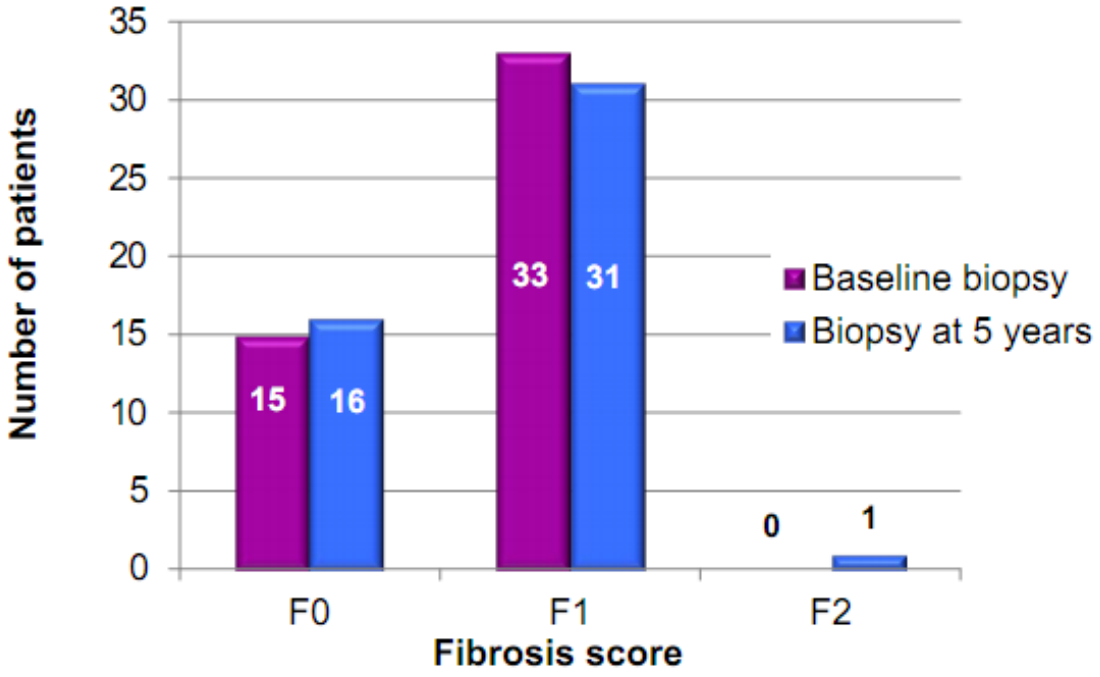
Chronic Hepatitis B



From: EASL Clinical Practice Guidelines

Immune tolerant : natural history

- **No significant disease progression** in the immunotolerant phase



Hui et al Hepatology 2007;46:395-401

No significant difference between initial and follow-up biopsy (p=0.58) in **48 Chinese** patients who remained in the immune-tolerant phase

- **No treatment**
- **Follow-up**

EASL Guidelines

>40 years
Family history of cirrhosis or HCC
CONSIDER LIVER BIOPSY

Immune tolerant: treatment in special patient groups (?!)

Heathcare workers[1]

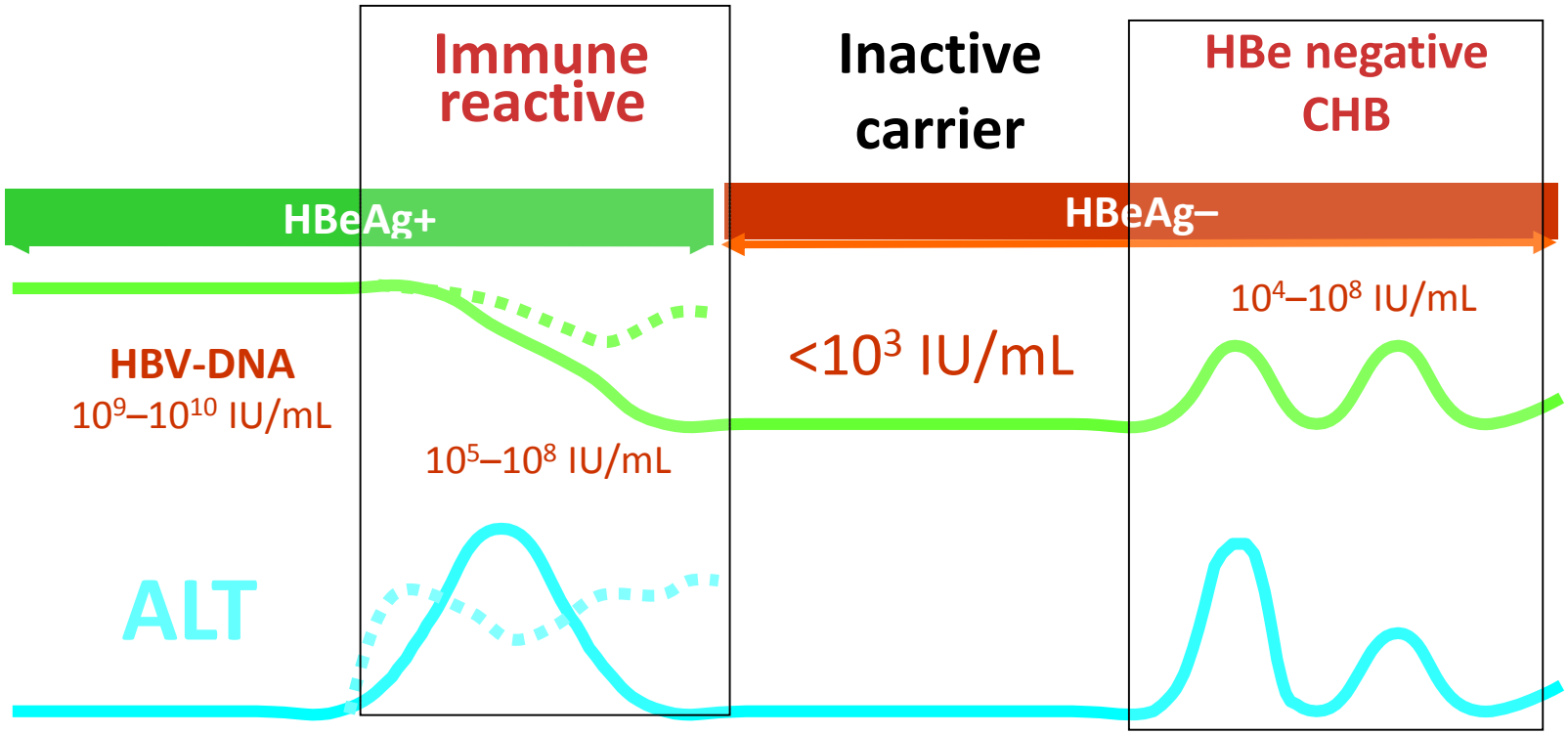
- May require antiviral therapy (ETV,TDF) even without typical indications for treatment to reduce direct transmission during exposure-prone procedures to patients

Pregnancy: prevention of vertical transmission[1,2]

- NA therapy may be used for prevention of perinatal and intra-uterine HBV transmission in the last trimester in HBsAg+ women with high viraemia (HBV DNA >10^{6-7} IU/ml), adding to the effectiveness of HBIg and vaccination. It may be discontinued within the first 3 months after delivery.

[1]EASL Guidelines J Hepatol 2012; [2] APASL 2012 update Hepatol Int 2012

Chronic Hepatitis B



From: EASL Clinical Practice Guidelines

Definition of inactive HBV carrier

Minimum follow-up: at least 1 year

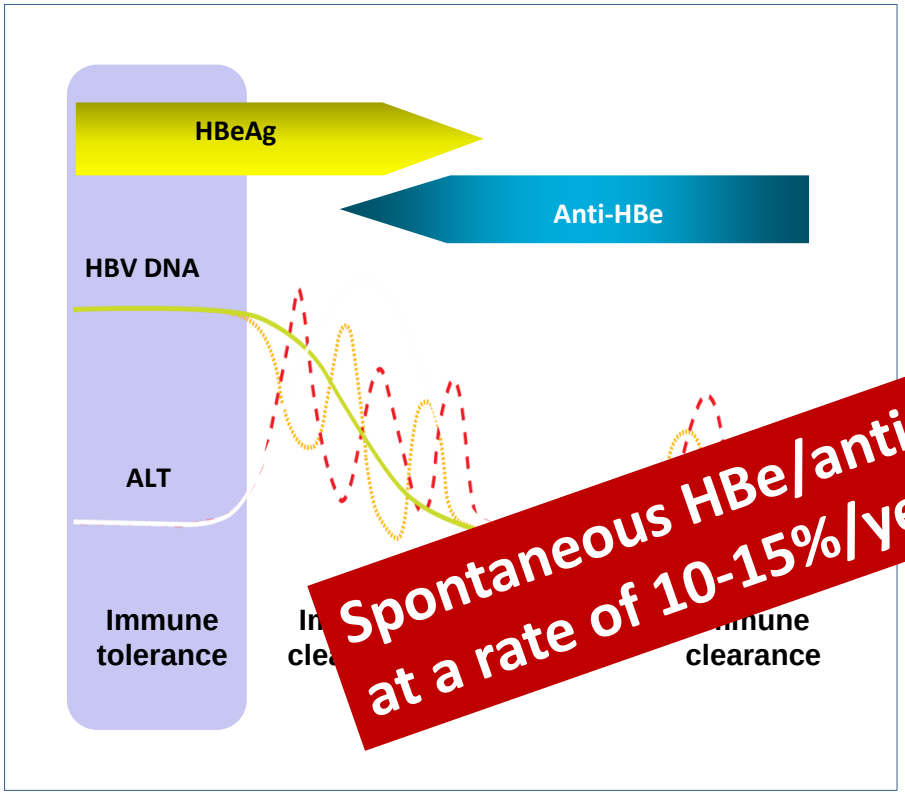
- ALT and HBV DNA
  - Every 3 months

Differential diagnosis between HBeAg-negative CHB and the inactive carrier state

- **ALT persistently normal**
- **HBV DNA <2,000 IU/mL**
- **Absence of significant liver disease**
- **Patients with >2,000<20,000**
- **Liver stiffness within normal range**
- **HBsAg <1000 U/mL**

Immune tolerant carrier

Phases of chronic HBV infection



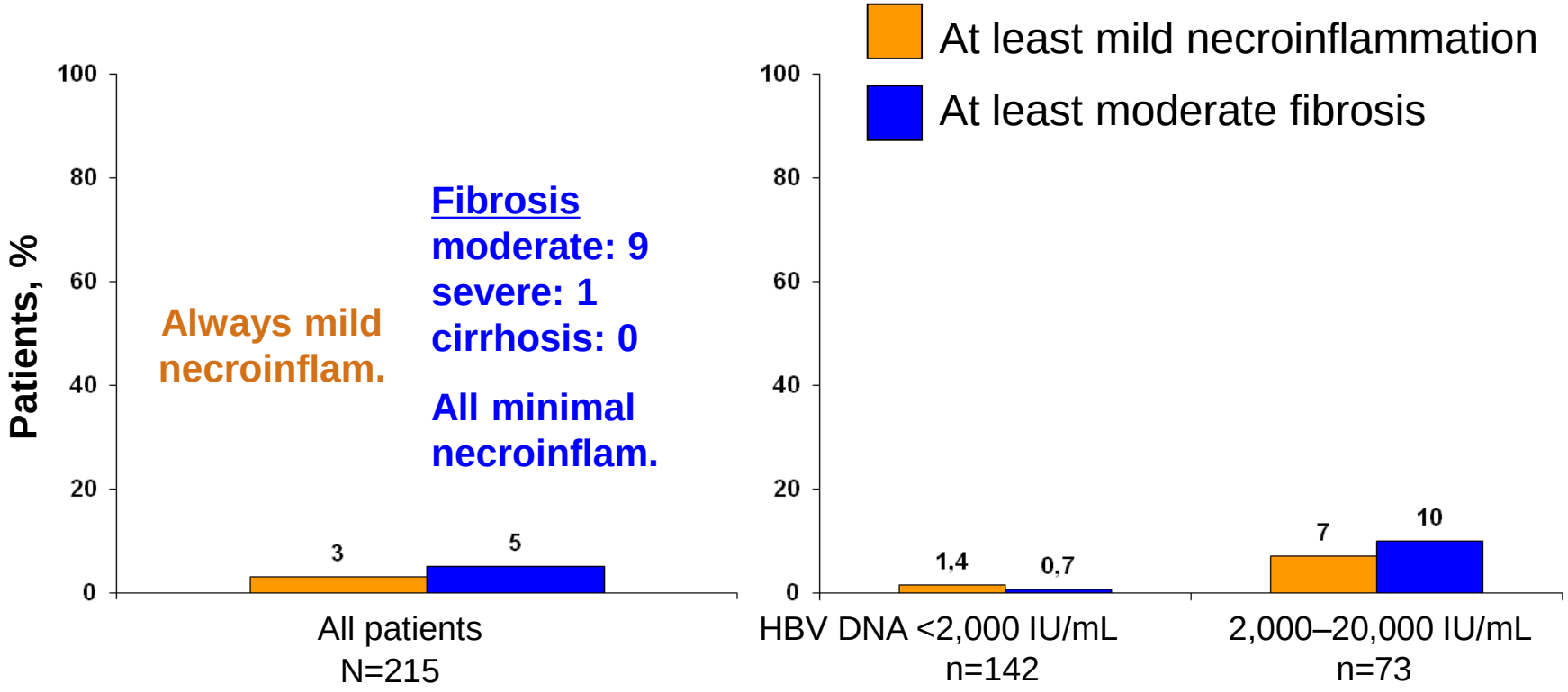
Yim HJ & Lok ASF. Hepatology 2006;43:S173-81

- **HOST**
  - Age <35 years
  - Often infected via perinatal transmission
  - Usually subiect… areas …mic
- **…iteria:**
- **…LOGIC**
  - HBeAg-positive
  - Anti-HBe-negative
  - High HBV DNA (>7 log IU/ml)
- **BIOCHEMICAL**
  - Normal ALT (3 times over 12 months)

Spontaneous HBe/anti-HBe seroconversion occurs at a rate of 10-15%/year

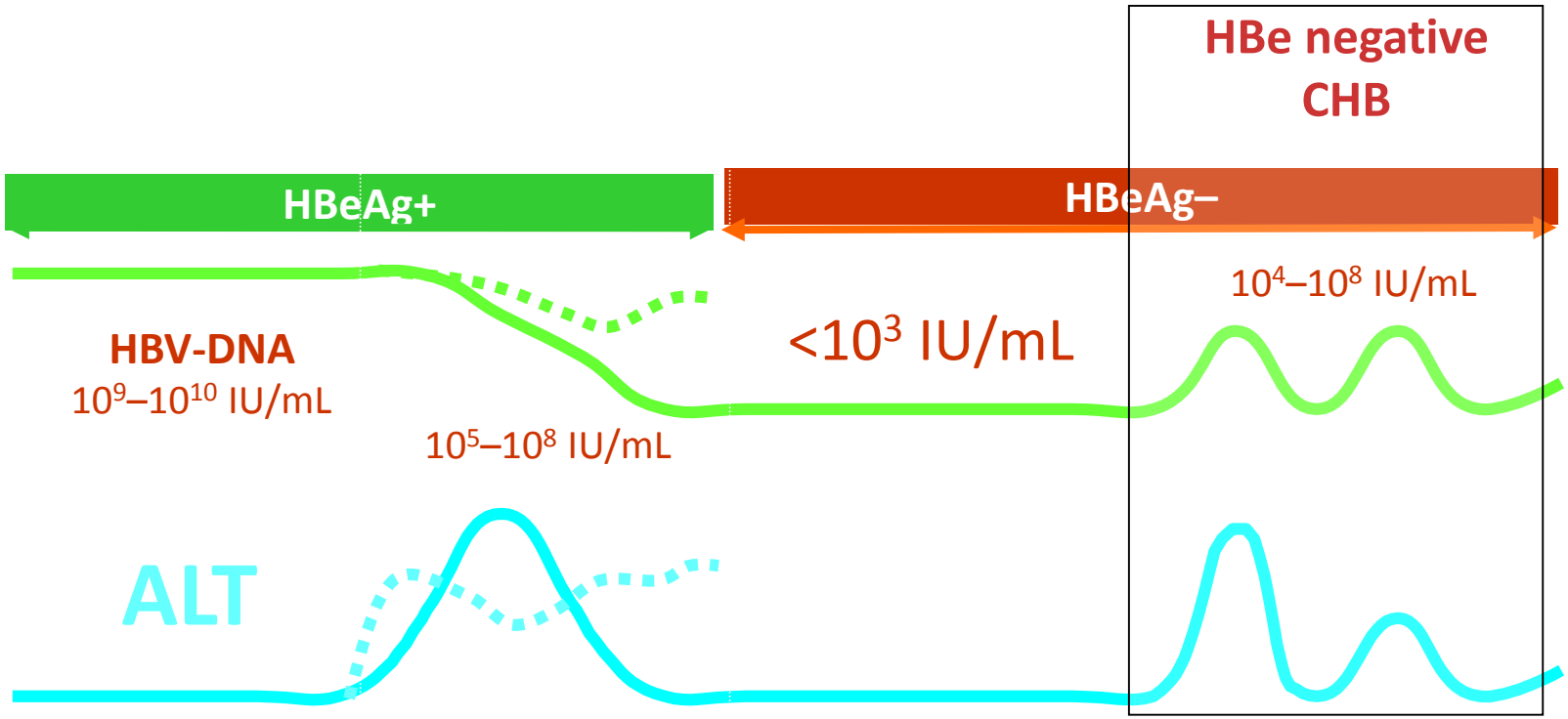
Cortesia prof. G. Gaeta.

Liver histology in HBeAg-ve patients with PNALT and HBV DNA <20,000 IU/mL



Papatheodoridis GV, et al. J Hepatol 2012;57:196-202

Chronic Hepatitis B



From: EASL Clinical Practice Guidelines

Chronic hepatitis B infection is not curable

Chronic HBV infection progresses through various phases determined by the host's immune response to the virus

HBsAg seroclearance, the ideal endpoint of Tx, but not equivalent to a cure

(In HBeAg-ve <1% after NUC and up 8% after Peg-IFN)

Goals of Therapy in chronic hepatitis B

- Prevent progression to cirrhosis and its complications
  - Liver failure
  - Hepatocellular carcinoma
  - Liver related death

- HBe - anti-HBe seroconversion
- Adequate ($<10^{4-5}$ copies/mL) and long-term durable HBV-DNA suppression with persistently normal ALT
- HBsAg clearance/anti-HBs seroconversion

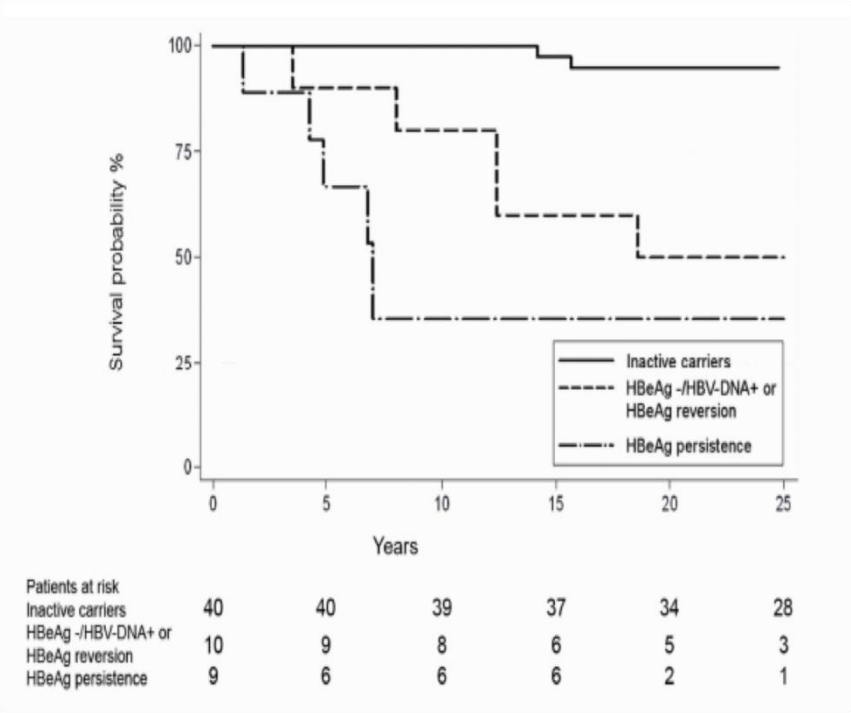
Preventing long term complications of HBV infection: the current goal of Tx

GUT ONLINE

Long-term outcome of chronic hepatitis B in caucasian patients: mortality after 25 years

Giovanna Fattovich, Nicola Olivari, Michela Pasino, Mirko D'Onofrio, Enrico Martone and Francesco Donato

Gut published online 22 Aug 2007;
doi:10.1136/gut.2007.128496



- Identify individuals at increased risk for:
  - cirrhosis
  - HCC
- Institute effective therapy

Chronic anti-HBe positive hepatitis B

Progression of **chronic hepatitis** to **cirrhosis** at 6 y in **45%** of pts

age, steatosis, absence of previous evidence of serum HBeAg, higher viremia levels

Progression of **cirrhosis to end stage complications** at 6 y in **24%** of pts

age, anti-HBc IgM flares as hallmark of recurrent hepatitis exacerbation

Brunetto MR, J Hepatol 2002

CHB: antiviral therapy

Peg-IFN used mainly in Chronic Hepatitis and early Cirrhosis

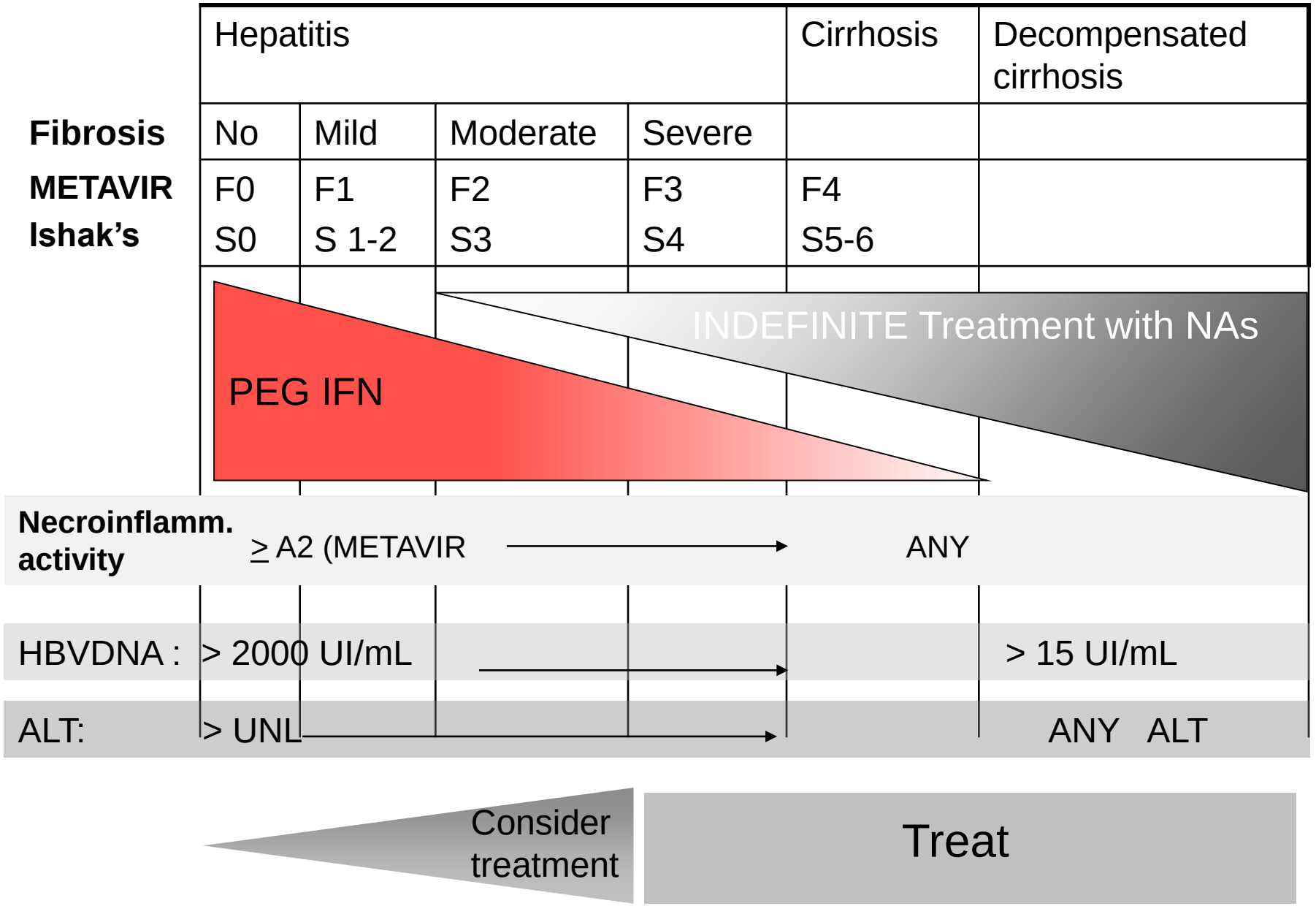
- transition from active to inactive infection in 20-40% of pts, with subsequent HBsAg clearance in about 50% of SVR
- reduction of liver disease progression rate (CHB to Cirrhosis, Cirrhosis to end stage liver disease and HCC)

NUCs used mainly in Cirrhosis

- HBV-DNA > 90% of pts after 3 years of treatment
- HBeAg to anti-HBe seroconversion in 40% of pts after 5 years
- HBsAg clearance in 3-10% of HBeAg pos cases, < 1%/year in HBeAg neg.
- histologic amelioration with regression of fibrosis
- reduction of liver disease progression to end stage complications

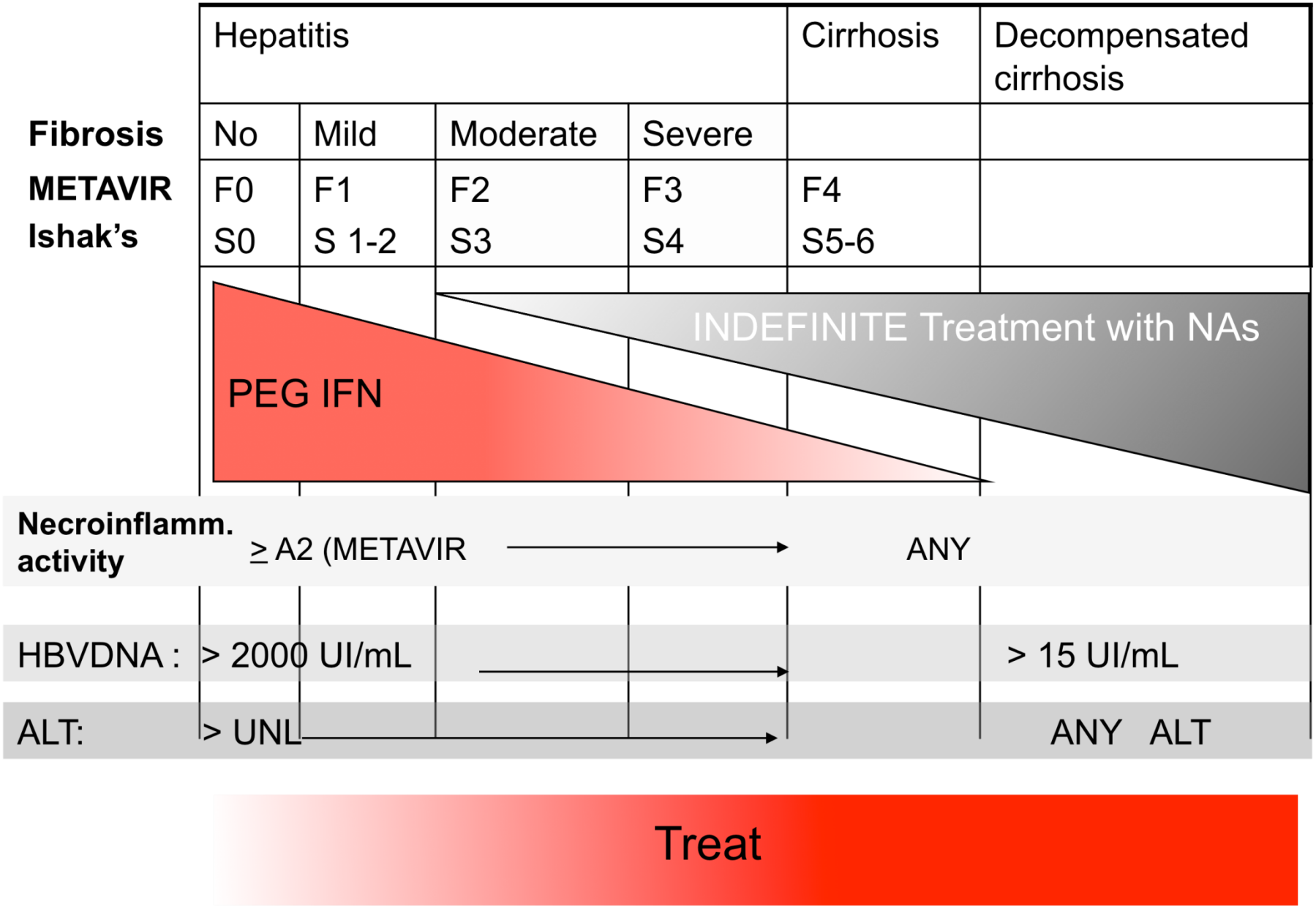
Lau et al. *AASLD* 2006; Buster E Gastro. 2008; Marcellin et al. EASL 2008; Brunetto MR, J Hep 2003; Sung et al. Ali Phl Ther 2008; Chang TT, et al. *N Engl J Med* 2006; Gish RG, et al. *Gastro.* 2007; Heathcote J, et al. AASLD 2010. Zoutendijk et al. J Infect Dis 2011; Wong et al, Hepatology 2013

HBeAg negative chronic hepatitis B



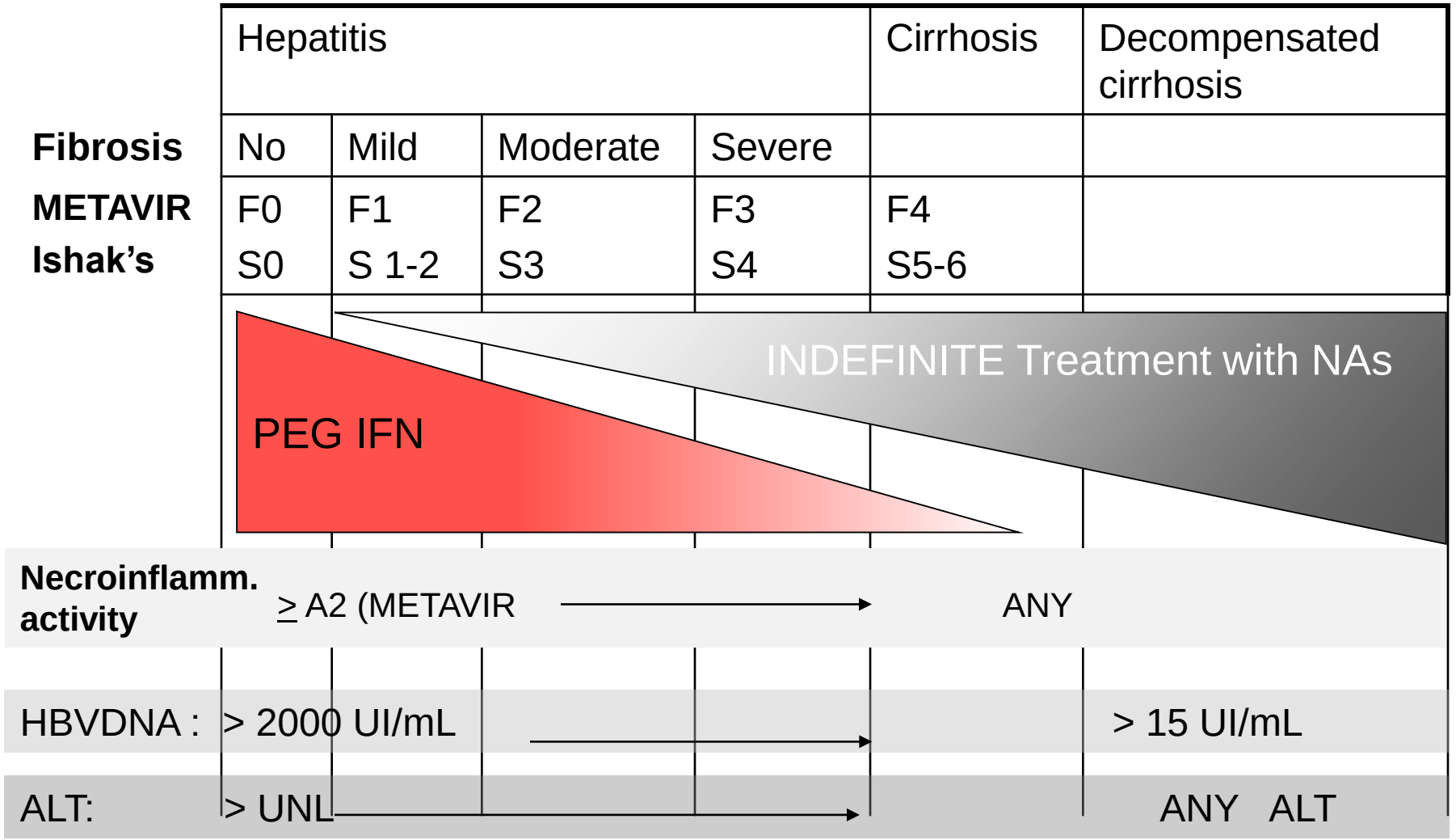
Carosi G, Rizzetto M et al, DLD 43 (2011) 259-265

HBeAg negative chronic hepatitis B



Carosi G, Rizzetto M et al, DLD 43 (2011) 259-265, *modified*

HBeAg negative chronic hepatitis B



Treat ?!

Carosi G, Rizzetto M et al, DLD 43 (2011) 259-265

Peg-IFN: still a place

Predictors of response

- Lower HBV-DNA (< 2 x 10^{7-8} IU/ml)
- High ALT (2 - 5 x ULN)
- HBV Genotype
- qHBsAg

Optimization of therapy, HBe-pos:

- 24 wk stopping rule:

HBsAg > 20.000 IU/ml (99 % for HBeAg loss with HBV-DNA < 2000 IU/ml and 100% NPV for HBsAg loss)

- Irrespective of HBV genotype

Optimization of therapy, HBe-neg:

- 12 wk stopping rule:

< 2 log10 HBV-DNA decline and no HBsAg decline

(95-100%, genotype A-D)

1. Sonneveld MJ, Hepatology 2013; 2. Rijckborst V, J Hepatol 2012

Achievable end-points with Peg-IFN

(cortesia prof. G.B.Gaeta)

HBeAg positive CHB		
HBeAg/anti-HBe seroconversion	EOT	**27-29%**
	1 y. Post-Treat.	**35-48%**

HBeAg negative CHB		
HBV-DNA < 2000 IU/ml + normal ALT	EOT	**36%**
	5 y. Post-Treat.	**25%**
HBsAg loss	EOT	**3%**
	5 y. Post-Treat.	**12%**

ETV or TDF therapy for CHB

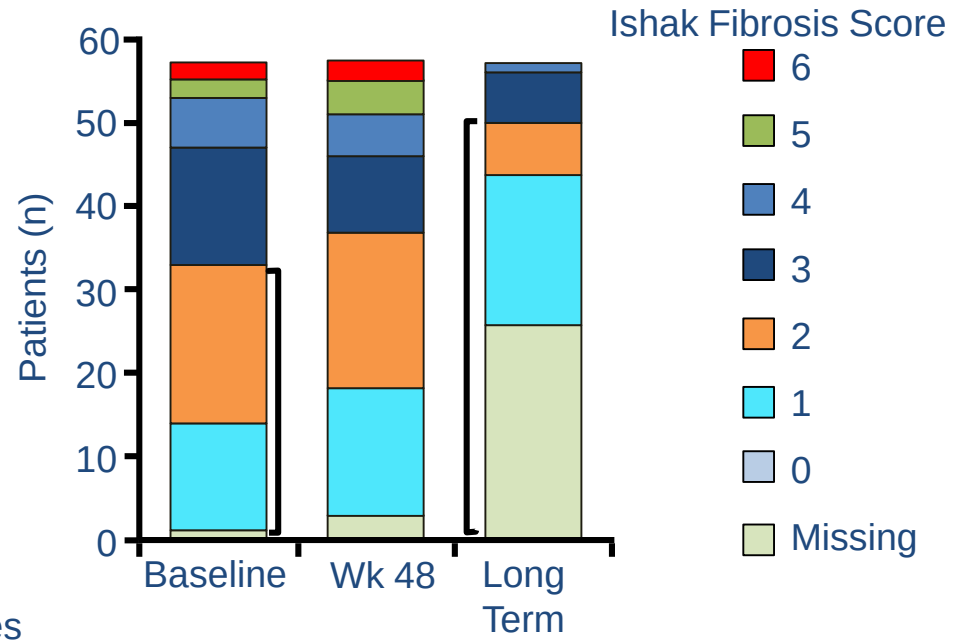
End-points after 5-8 year therapy

- **Viral suppression in >95% of patients**
- **HBeAg seroconversion in 40-50%**
- **HBsAg clearance in 1% (>in HBeAg positive patients). ALT normal in ~85%**
- **No major safety issues**
- **Regression of fibrosis/cirrhosis in 75-80%**
- **Reduced decompensation rate and improved survival**
- **Persistance of risk for HCC (?)**

Long-term Entecavir Study

Liver Histology

All patients with advanced fibrosis/cirrhosis (Ishak fibrosis score ≥ 4) at baseline demonstrated at least a 1-point reduction (median change: -1.5)

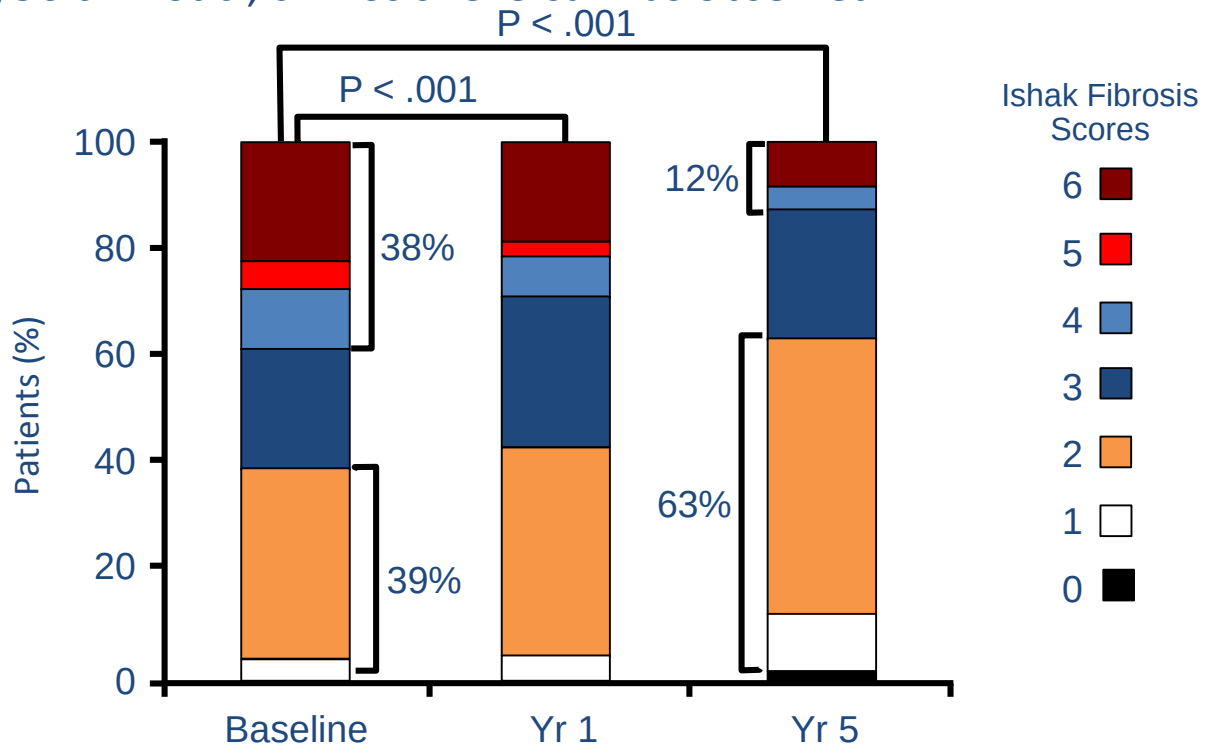


N = 57 matched biopsies

Chang TT, et al. Hepatology. 2010;52:886-893.

Most pts treated with tenofovir had stable or improved fibrosis at Yr 5

- Pts with Ishak score ≥ 4: 38% at baseline, 12% at Yr 5
- Pts with cirrhosis (Ishak score ≥ 5): 28% at baseline, 8% at Yr 5 (n=96)
- In 71/96 cirrhotic , chirrosis reversal was observed



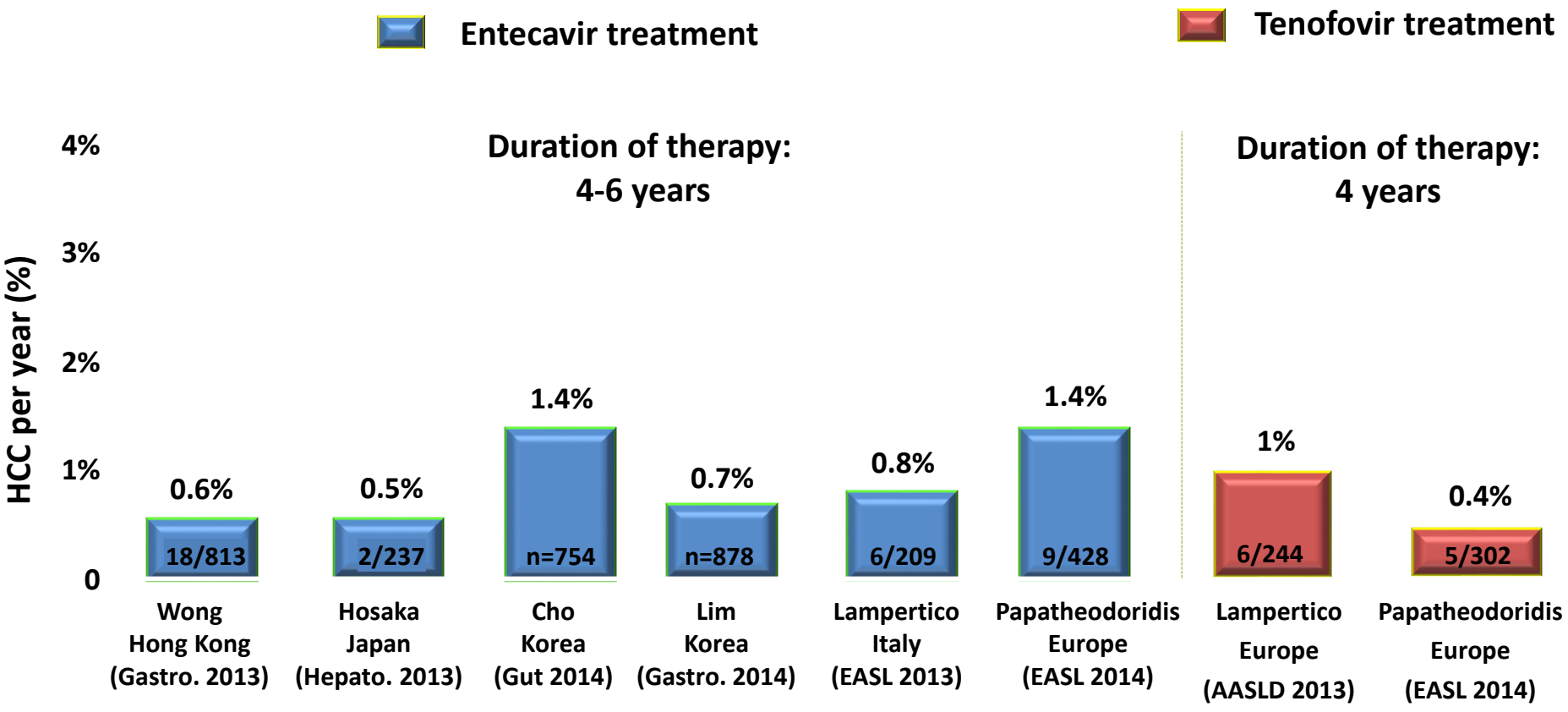
N = 348 matched biopsies

Marcellin P, et al. Lancet. 2013;381:468-475.

HCC in HBV: a challenging issue

- Complex pathogenesis (single cell event)
- Multiple risk factors (host, virus, interactions)
- 20-75% of HCC HBV-related
- Early clinical diagnosis effective but multifocal pattern possible (latency period)
- Poor prognosis, no curative therapy (OLT)
- Competitive causes of liver-related death

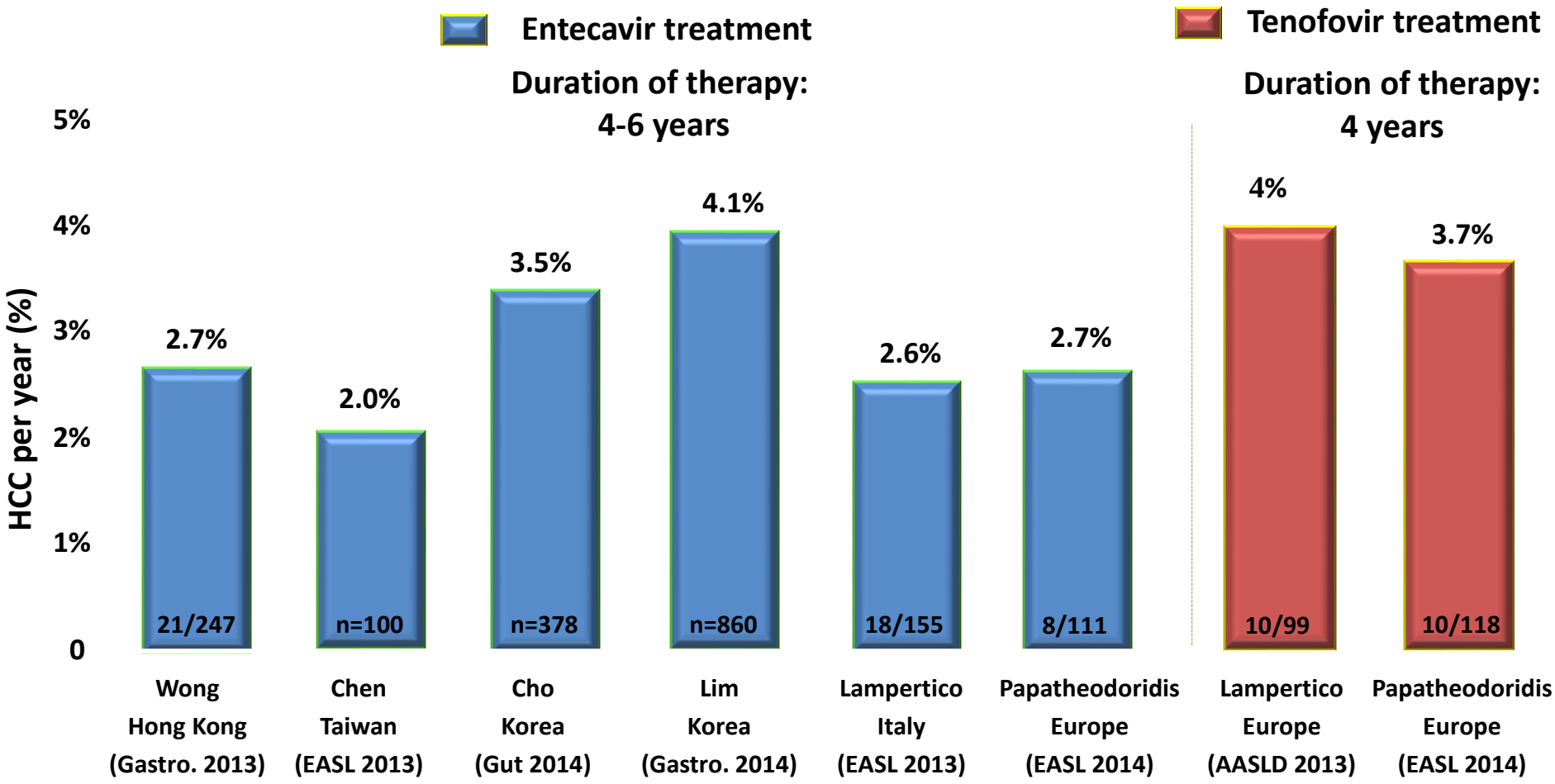
HCC in NUC-naïve CHB non-cirrhotic patients treated with ETV and TDF



HCC/yr in untreated CHB patients: 0.6% (Asia) and 0.3% (Europe)*

*Viganò M et al. Liv Int 2015; *Fattovich G et al, J Hepatol 2008*

HCC rates in NUC-naïve CHB cirrhotic patients treated with ETV and TDF



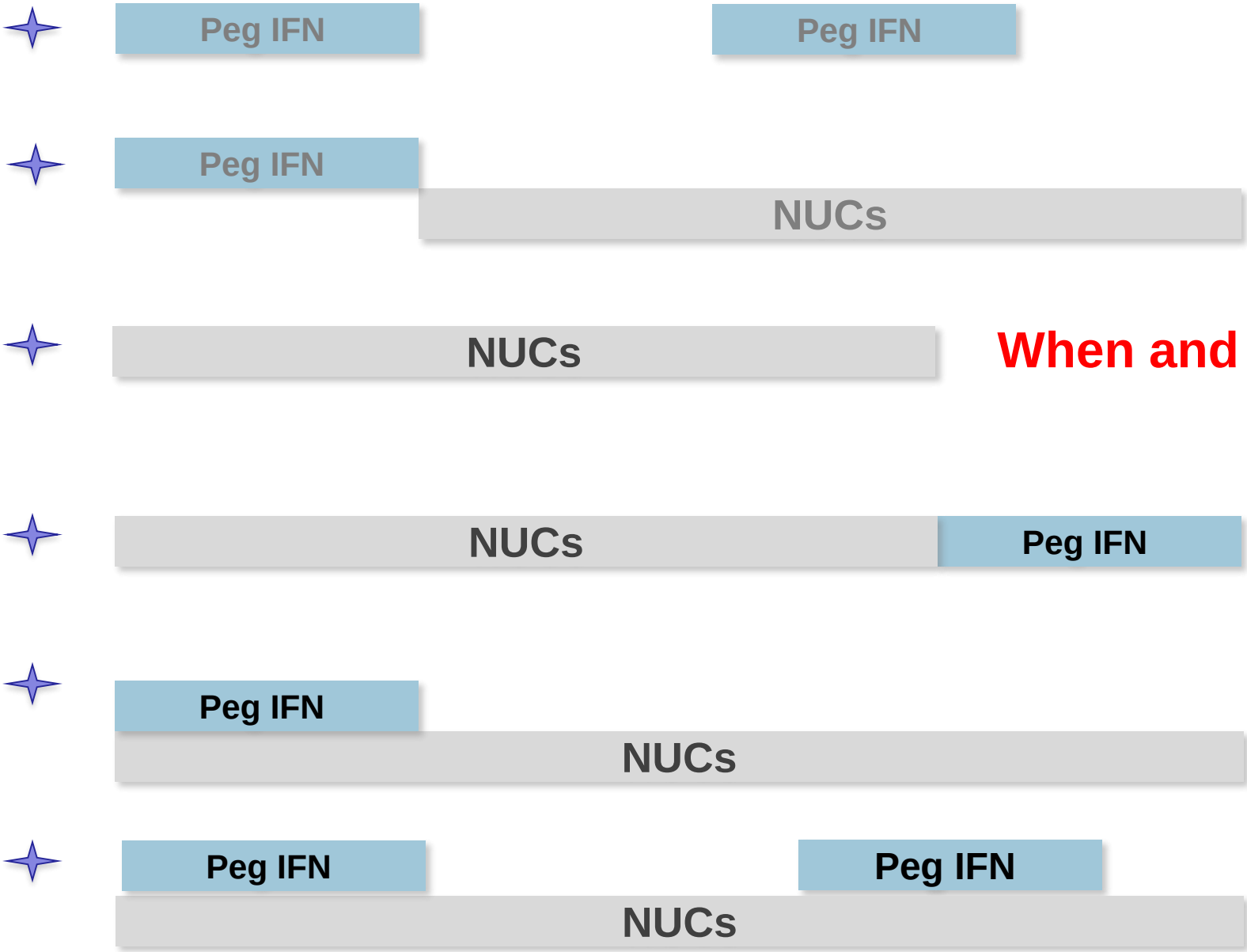
HCC/yr in untreated cirrhotics: 3.7% (Asia) and 2.2% (Europe)*

*Viganò M et al. Liv Int 2015; *Fattovich G et al, J Hepatol 2008*

Can with improve response rates by combining NUCs and Peg-IFN ?

IFN and NUCs: possible synergy

cortesia prof. M.Brunetto



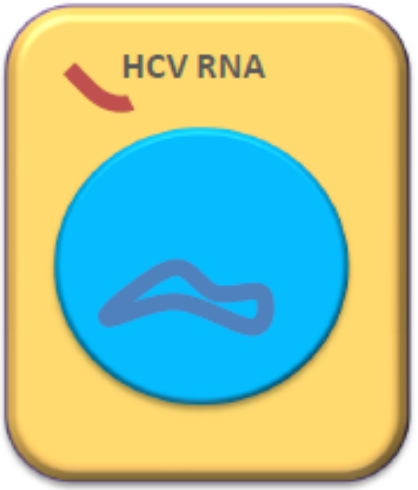
Emerging drugs against HBV

	Targets	Compounds	Stage of development	References or ClinicalTrials.gov Identifier
DAAs	HBV capsid	Phenylpropenamide derivatives	Preclinical and early clinical phase	119, 120
		Heteroaryldihydropyrimidines	Morphothiadine mesilate (GLS4) in phase II	123, 124, 128
	rcDNA-cccDNA conversion	Disubstituted sulfonamide	Preclinical	133
	cccDNA	DNA cleavage enzymes	Preclinical	114, 134, 135, 136
	HBV RNA	siRNA	ARC-520 in phase II	NCT02065336
		antisense	ISIS-HBVRx in phase I	170, 171
HTAs	NTCP	HBV preS1-derived lipopeptide	Myrcludex-B in phase II	149
		cyclosporine A, ezetimibe	FDA approved but not tested for HBV	146, 147, 148
	Host factors involved in HBV secretion and budding	Iminosugar derivatives of butyldeoxynojirimycin and related glycolipids	Preclinical	145
		α-glucosidase inhibitors	Preclinical	145
		triazol-o-pyrimidine derivatives	Preclinical	150
		benzimidazole derivative	Preclinical	151
		phosphorothioate oligonucleotides	REP 9 AC in phase II	152
	Innate immune responses	LTβR agonists	Preclinical	153
		TLR7 agonists	Phase II	NCT02166047
		thymosin α1	Phase IV	NCT00291616
		Nitazoxanide	Phase I	156, 157
		interleukin-7	Phase I/II	NCT01027065
		IFN-λ	Phase II	NCT01204762
	Adaptive immune responses	PD1 blockade	Phase I/II for HCC	NCT01658878
				172, 173
		X-S-Core proteins (antigen-based vaccine)	GS-4774 in phase II,	159, 160
		HBV DNA (DNA-based vaccine)	DV-601 in phase I	
			DNA vaccine pCMVS2.S in phase I/II	NCT00536627
				161, 162, 164

Zeisel MB et al, Gut 2015

HCV

(No Latent Reservoir)

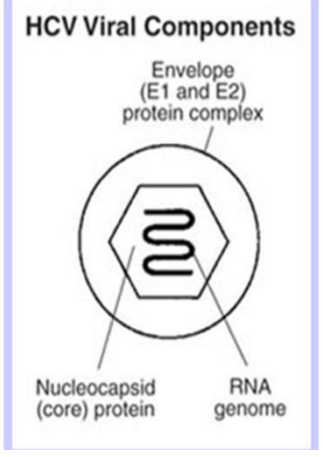


Definitive Viral Clearance:
Cure is possible for HCV

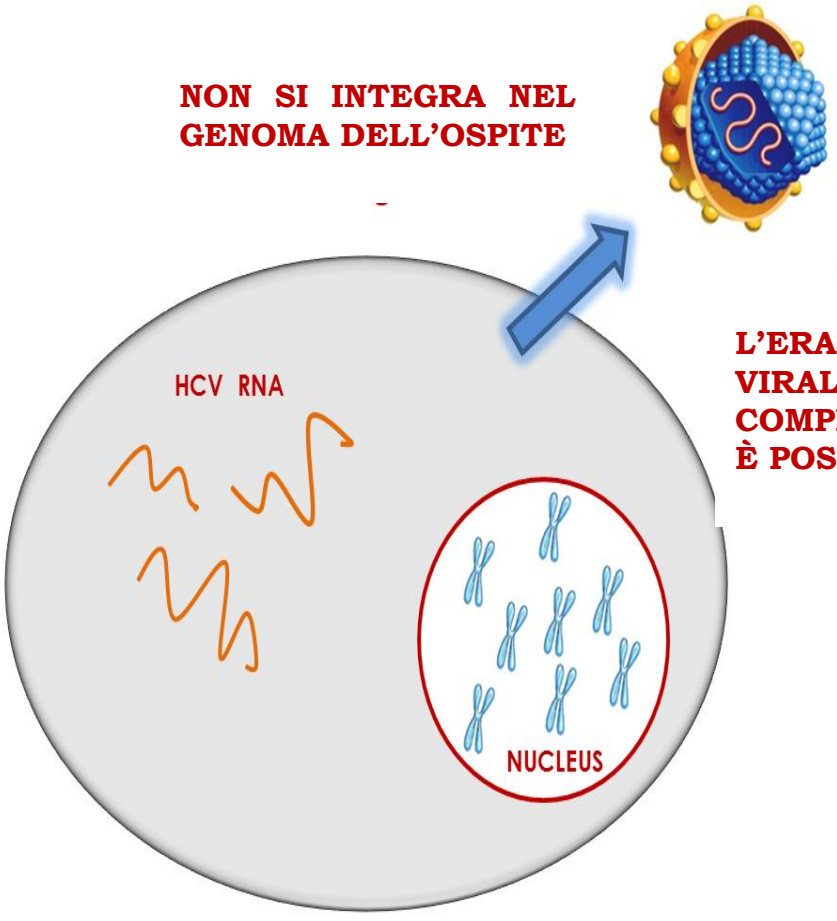
Kieffer TL, et al. *J Antimicrob Chemother*. 2010;65:202-212.

HCV

- Membro della famiglia Flaviviridae
- virus a RNA
- alto tasso di mutazione
- HCV RNA: 10,000-bp, singo filamento a polarità positiva



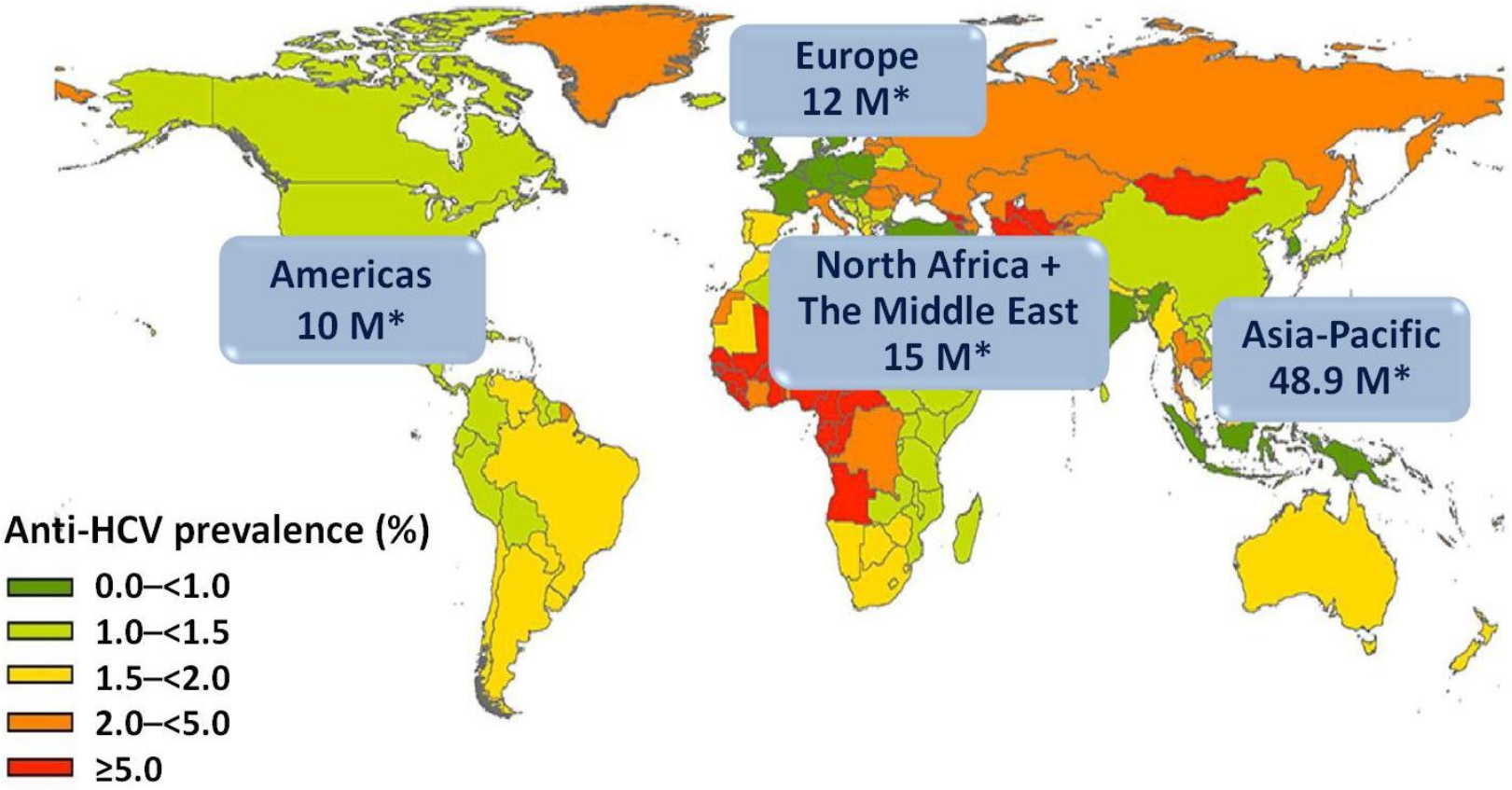
NON SI INTEGRA NEL GENOMA DELL'OSPITE



L'ERADICAZIONE VIRALE COMPLETA È POSSIBILE

Epidemiologia mondiale

LA PREVALENZA TOTALE DI ANTI HCV è STIMATA A 115 MILIONI (92-149)

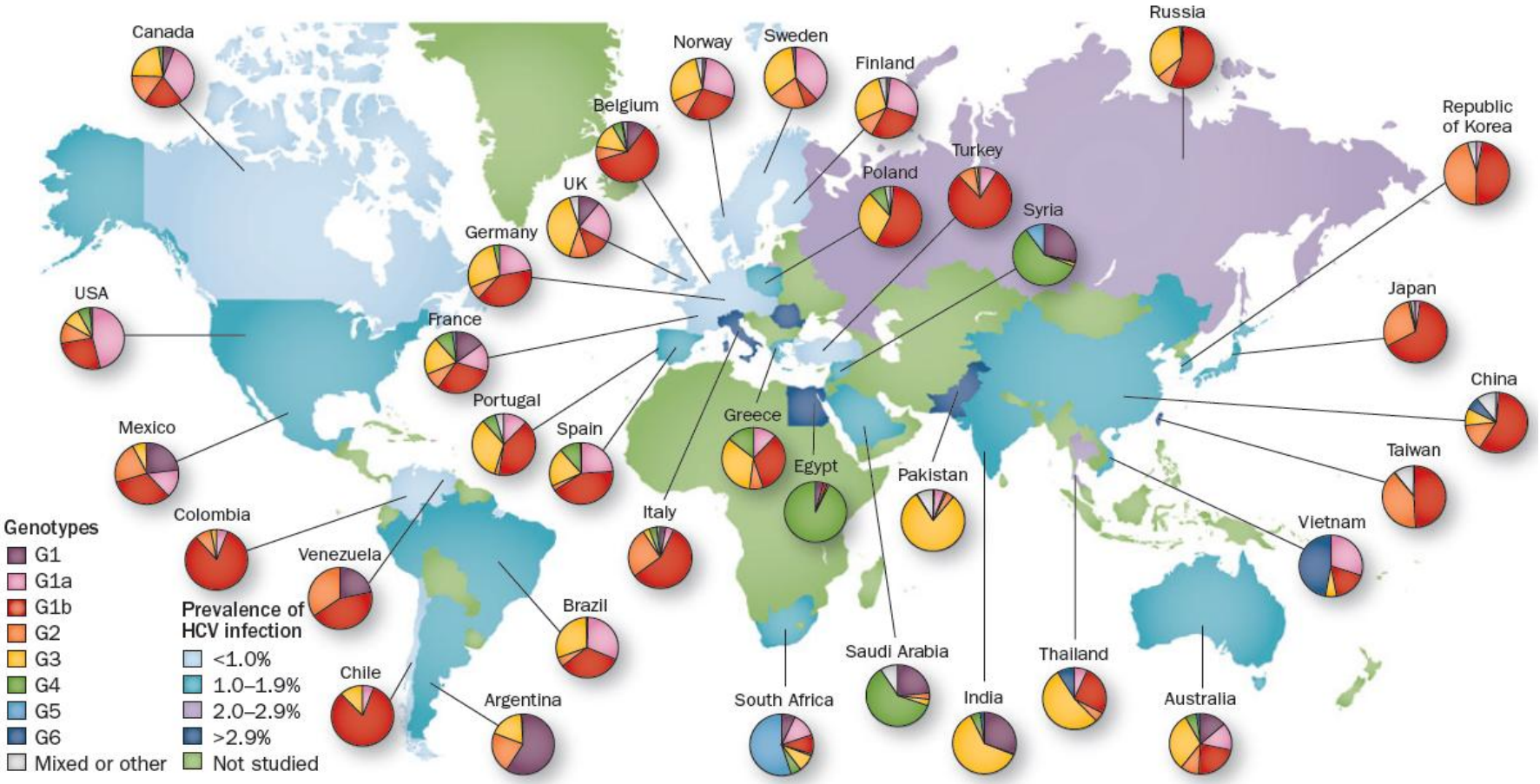


* Estimated number of anti-HCV infected individuals.

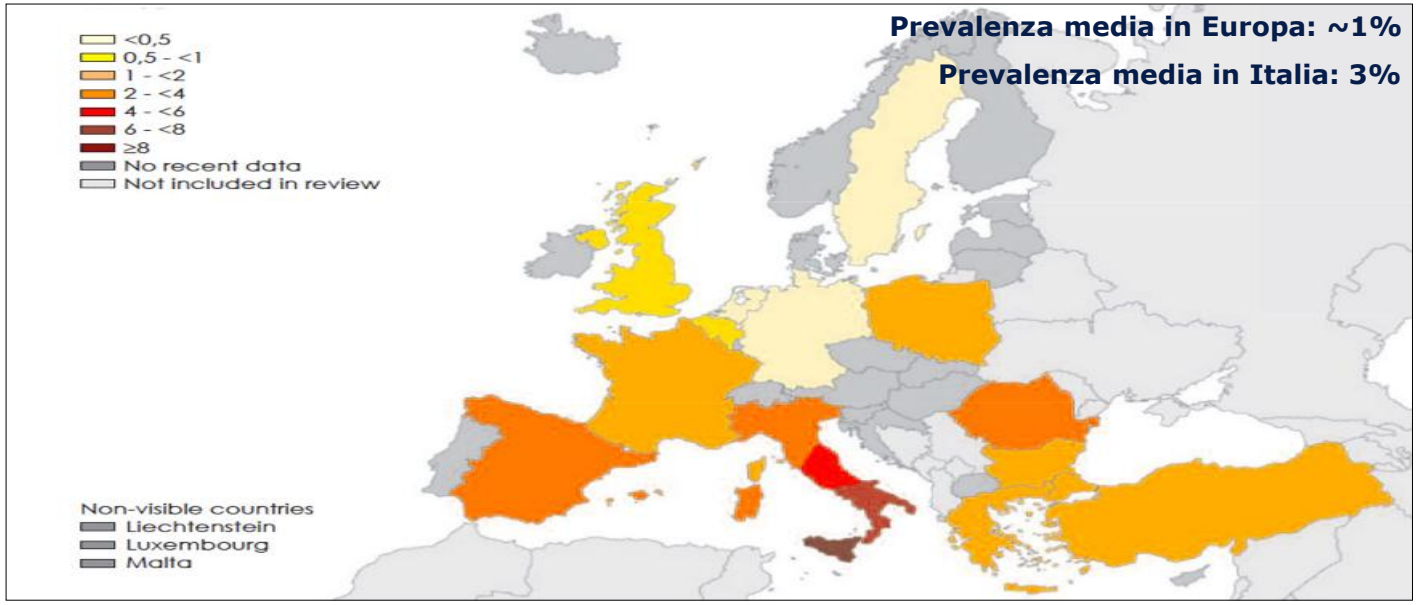
Gower E, *et al. J Hepatol* 2014; **61:**S45–S57.

Genotipo di HCV	Area geografica
1a	Europa e USA
1b	USA, Europa, Giappone
2	Italia, Paesi in via di sviluppo
3	Paesi occidentali (tossicodipendenti)
4	Medio Oriente, Africa del Nord
5	Africa del Sud
6	Asia

distribuzione dei genotipi



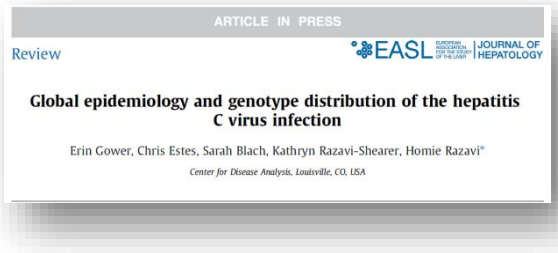
Epidemiologia in europa



- **La prevalenza di HCV stimata in Europa è di circa 9-12 milioni di individui**
- **La più bassa prevalenza di HCV (≤ 0.5%) è stata riscontrata nelle regioni del nord Europa**
- **La prevalenza è alta in Italia (~3%), Spagna (2,6%) e Romania (3,5%)**
- **La prevalenza è età-specifica e correlata all'area geografica**

Epidemiologia in italia

- In Italia i dati di sieroprevalenza sono particolarmente disomogenei :
  - **1-2% al Nord**
  - **≥3% al Centro**
  - **>10% in alcuni distretti del Sud ed Isole**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Review

EASL | JOURNAL OF HEPATOLOGY

Global epidemiology and genotype distribution of the hepatitis C virus infection

Erin Gower, Chris Estes, Sarah Blach, Kathryn Razavi-Shearer, Homie Razavi*

Center for Disease Analysis, Louisville, CO, USA

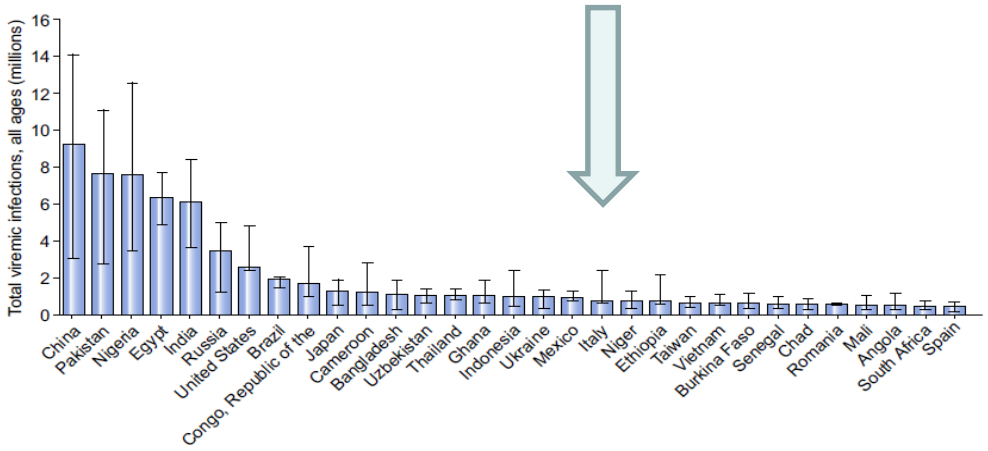
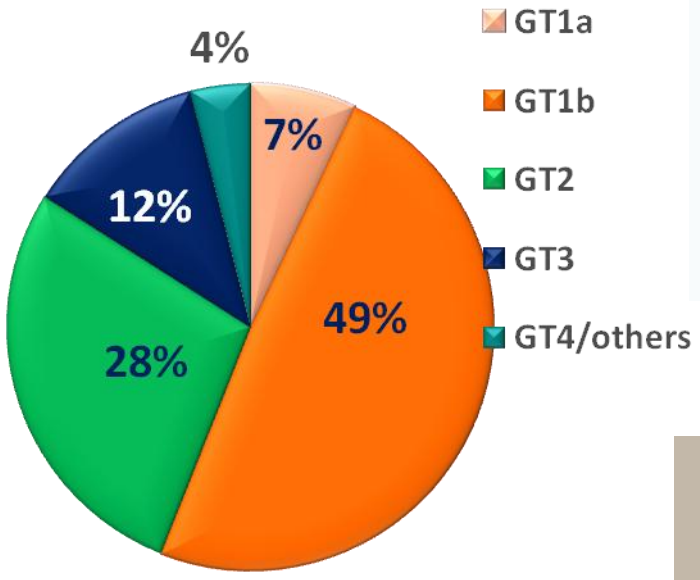


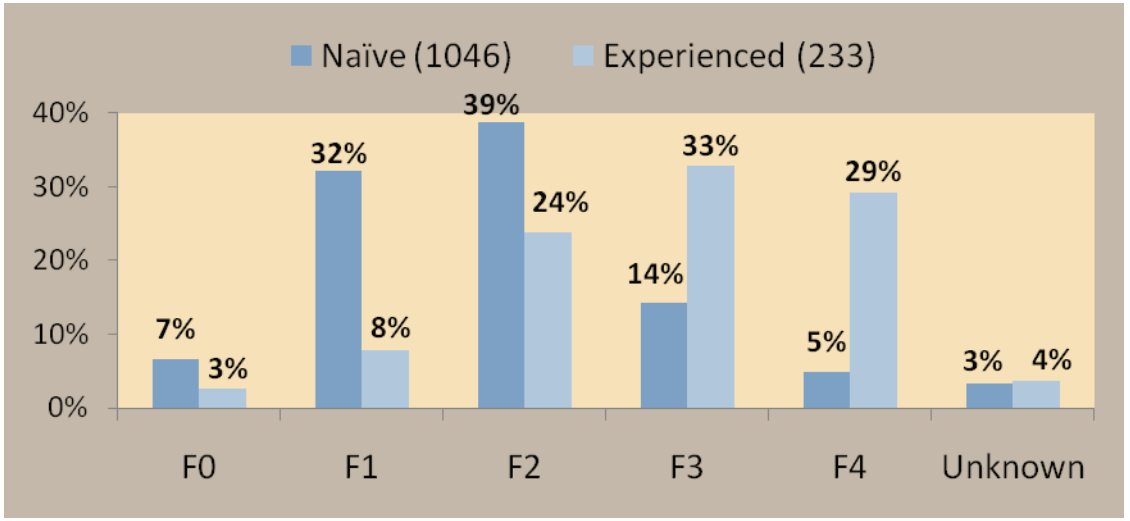
Fig. 4. Countries accounting for 80% of the total viraemic HCV infections.

Diffusione dei genotipi in italia



- **I genotipi 1b e 2 sono più frequenti nelle persone anziane**
- **il 3 e 4 sono più frequenti nei giovani**
- **Il 4 negli immigrati**
- **Ciascun genotipo risponde in modo diverso al trattamento**

% dei pazienti naive ed experienced per livello di fibrosi



Major Sources: ISTAT; Decision Resources ; EPAC; IMS Consulting Group xpertise

Prevalenza dei marker di HCV nei gruppi ad alto rischio:

42-83% Talassemici
50-95% Emofilici
10-45% Emodializzati
0-10% Esposizione professionale
48-90% Tossicodipendenti
11% Soggetti tatuati
21% Pz trasfusi o sottoposti ad interventi chirurgici
15-46% Detenuti
18% Pz in PS
15-25% Alcolisti
9% Pz sottoposti ad interventi di chirurgia dentaria
62% Pz trapiantati con organi di donatori anti-HCV positivi
4-7% Handicappati o pazienti istituzionalizzati
0-18% Partner eterosessuali di pazienti anti-HCV positivi
0.7-6% Prostitute
3-18% Omosessuali
0-11% Contatti domestici con pz anti-HCV positivi
0-6% Bambini nati da madri anti-HCV positive

EVOLUZIONE DELL'INFEZIONE DEL VIRUS C

Lauer et al., N Engl J Med 2001; 345: 41-52

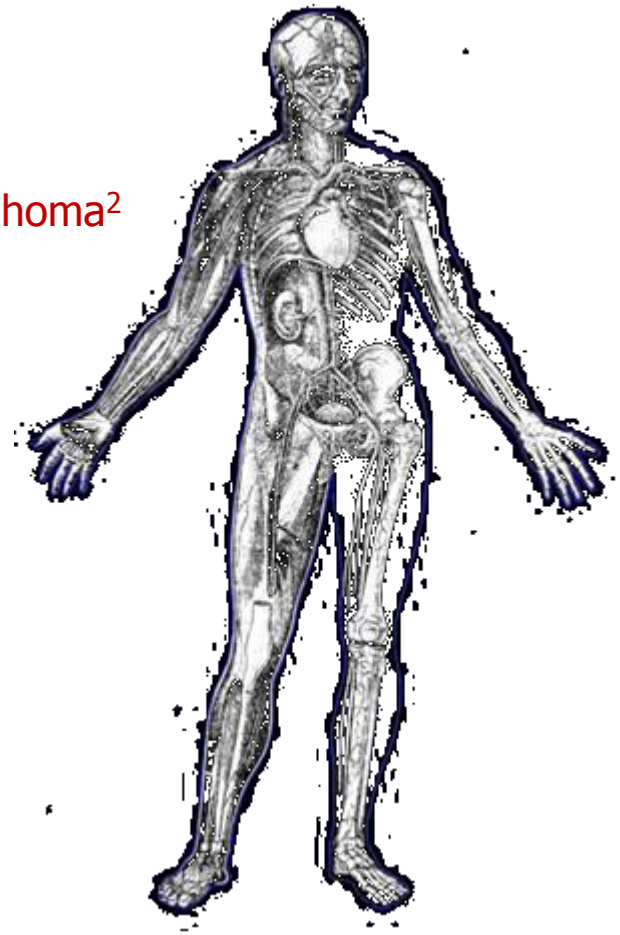
Extrahepatic Manifestations Associated with HCV

Hematologic
- Mixed cryoglobulinemia[1]
- Aplastic anemia[2]
- Thrombocytopenia[2]
- Non-Hodgkin's b-cell lymphoma[2]

Dermatologic
- Porphyria cutanea tarda[1]
- Lichen planus[2]
- Cutaneous necrotizing
- vasculitis2

Renal
- Glomerulonephritis[1]
- Nephrotic syndrome[2]

Endocrine
- Hypothyroidism[2]
- Diabetes mellitus[2]



Ocular
- Corneal ulcer[2]
- Uveitis[2]

Vascular
- Necrotizing vasculitis[2]
- Polyarteritis nodosa[2]

Neuromuscular[2]
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

Autoimmune Phenomena[2]
- CREST syndrome

Neuropsychiatric
- Depression[1]

[1]NIH. *NIH Consens State Sci Statements*. 2002;19(3):1-46.
[2]Sene D et al. *Metab Brain Dis*. 2004;19(3-4):357-381.

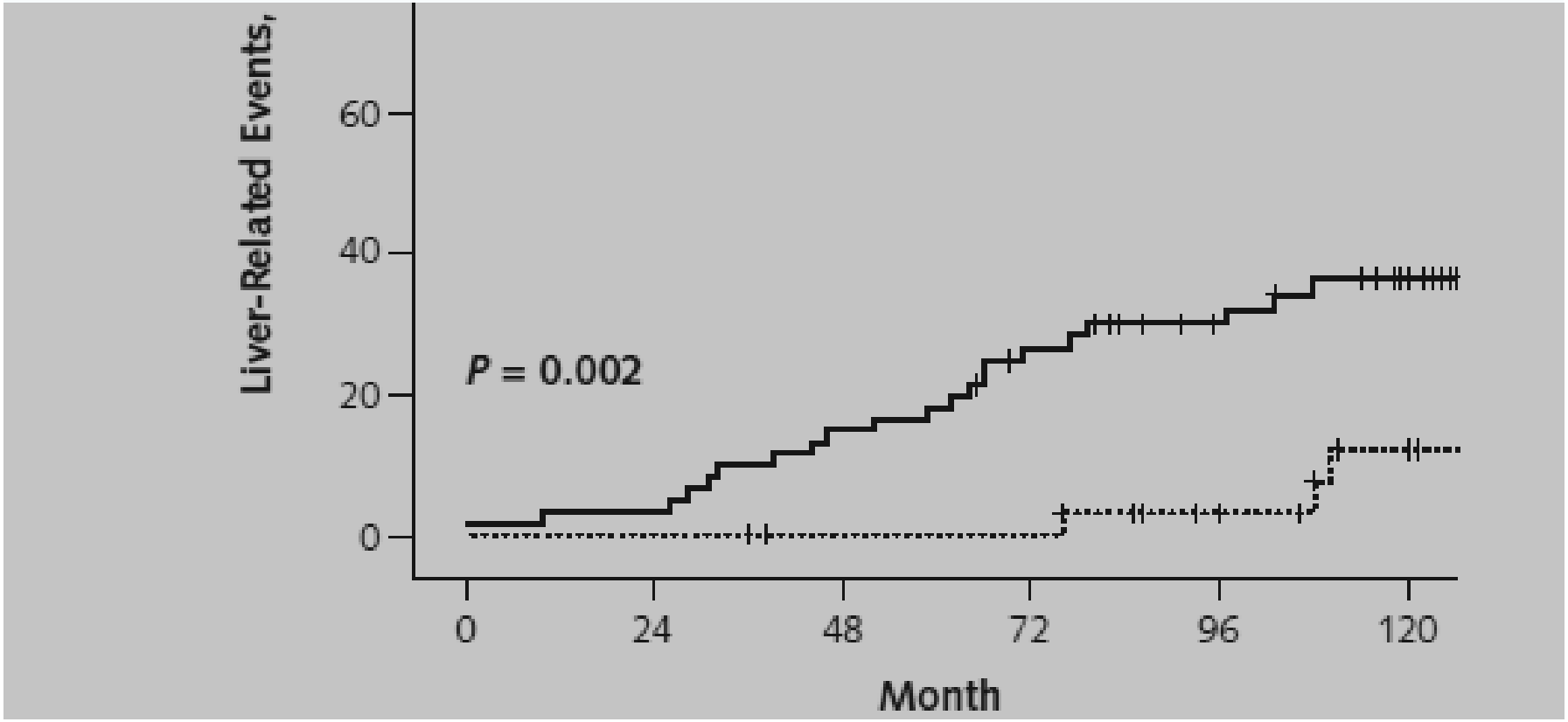
OBIETTIVO DELLA TERAPIA EFFICACE

- ✓**Bloccare la progressione della malattia**
- ✓**Ridurre le complicazioni HCV relate**
- ✓**Migliorare la sopravvivenza**

Questi obiettivi possono essere raggiunti solo se “eradichiamo” il virus !

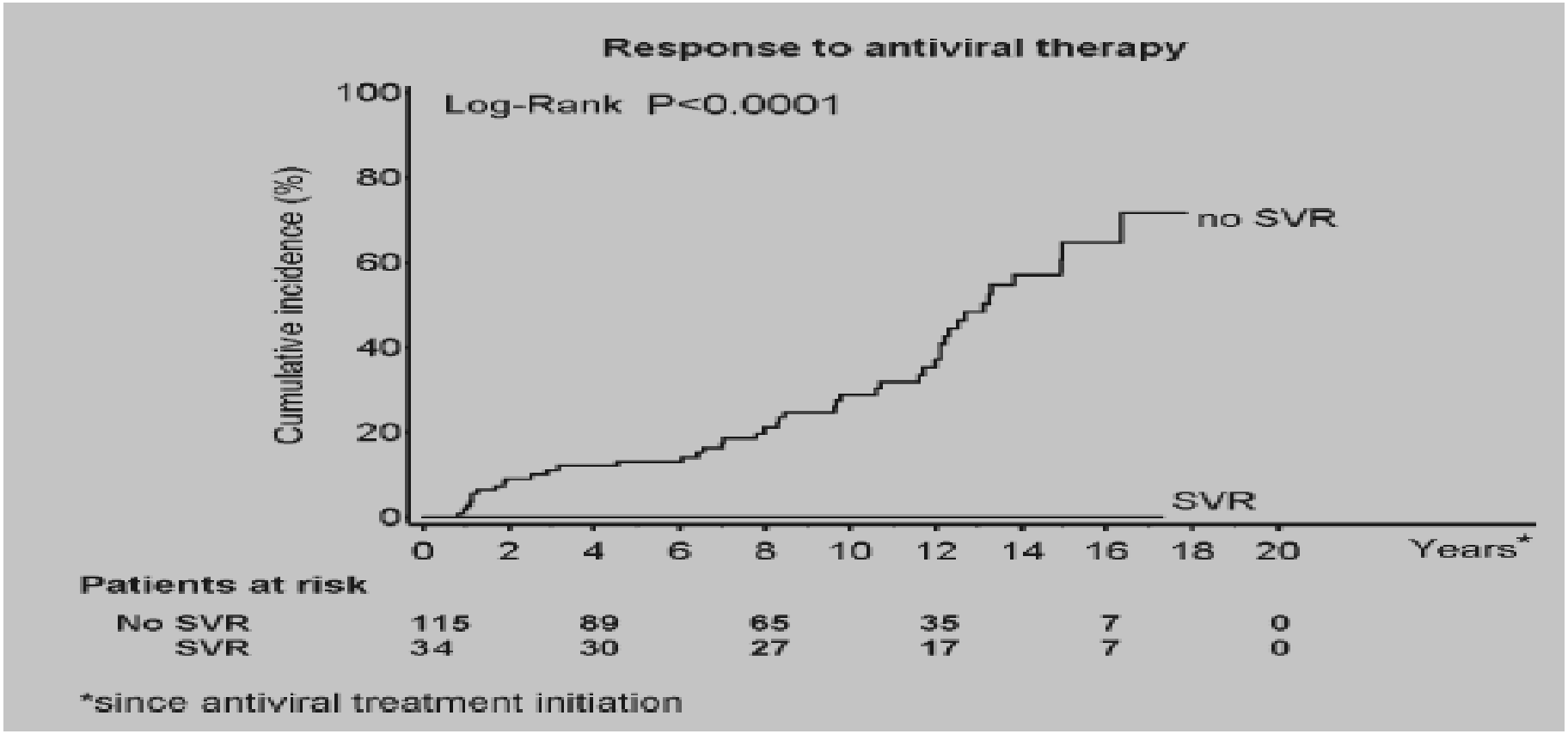
REGRESSIONE DELLA CIRROSI DOPO SVR

Biopsia epatica dopo 11 mesi dopo SVR: regressione della cirrosi in 17/39 (44%)



Mallet v et al., Ann Intern Med 2008; 149:399-403

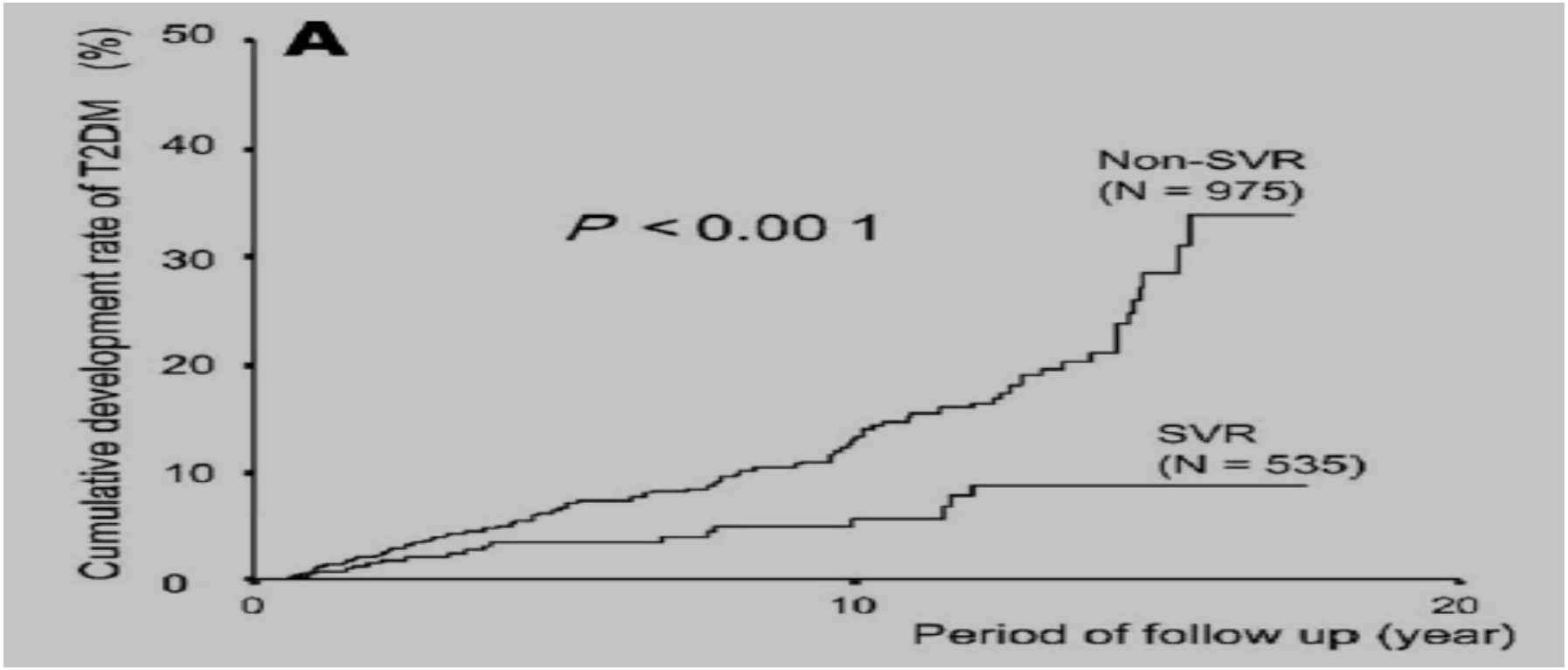
IMPATTO DELLA SVR SULLO SVILUPPO DELLE VARICI



Bruno S. et al., Hepatology 2010:51; 2069-2076

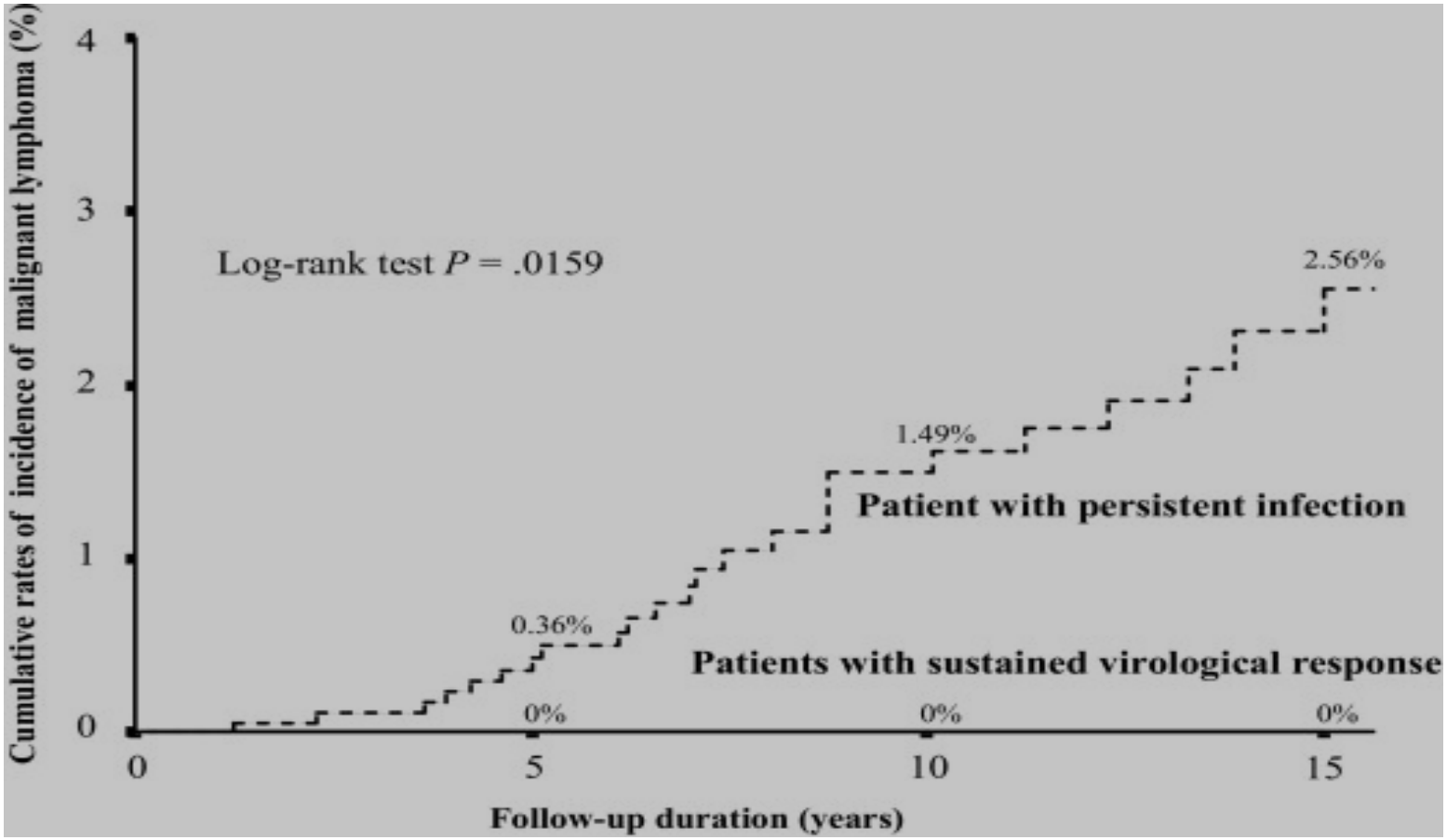
INFLUENZA DELLA SVR SULL'INCIDENZA DEL DIABETE

Analisi retrospettiva di 2842 pazienti HCV trattati



Arase Y. Et al., Hepatology 2009; 49:739-744

INFLUENZA DELLA SVR SULL'INCIDENZA DEL LINFOMA



Kawamura Y et al., Am J Med 2007; 120: 1034-1041

INCIDENZA ANNUALE DELL'HCC

Fibrosi (Metavir)	Non Trattati (n=490)	Trattati (n= 2400)	SVR (n= 789)	Non SVR (n= 1568)
F0-F1	0,45 (3/160)	0,08 (2/710)	0,11 (1/257)	0,07 (1/443)
F 2	1,99 (11/164)	0,54 (16/896)	0,10 (1/316)	0,78 (15/568)
F 3	5,34 (13/59)	1,95 (38/564)	1,29 (7/163)	2,20 (30/389)
F 4	7,88 (32/107)	4,16 (33/230)	0,49 (1/53)	5,32 (30/168)
Totali	3,17 (59/490)	1,10 (89/2400)	0,38 (10/789)	1,41 (76/1568)

Yoshida H. et al. Ann Intern Med 1999; 131: 174-81

QUINDI …..

ESTREMA IMPORTANZA DELLA SVR

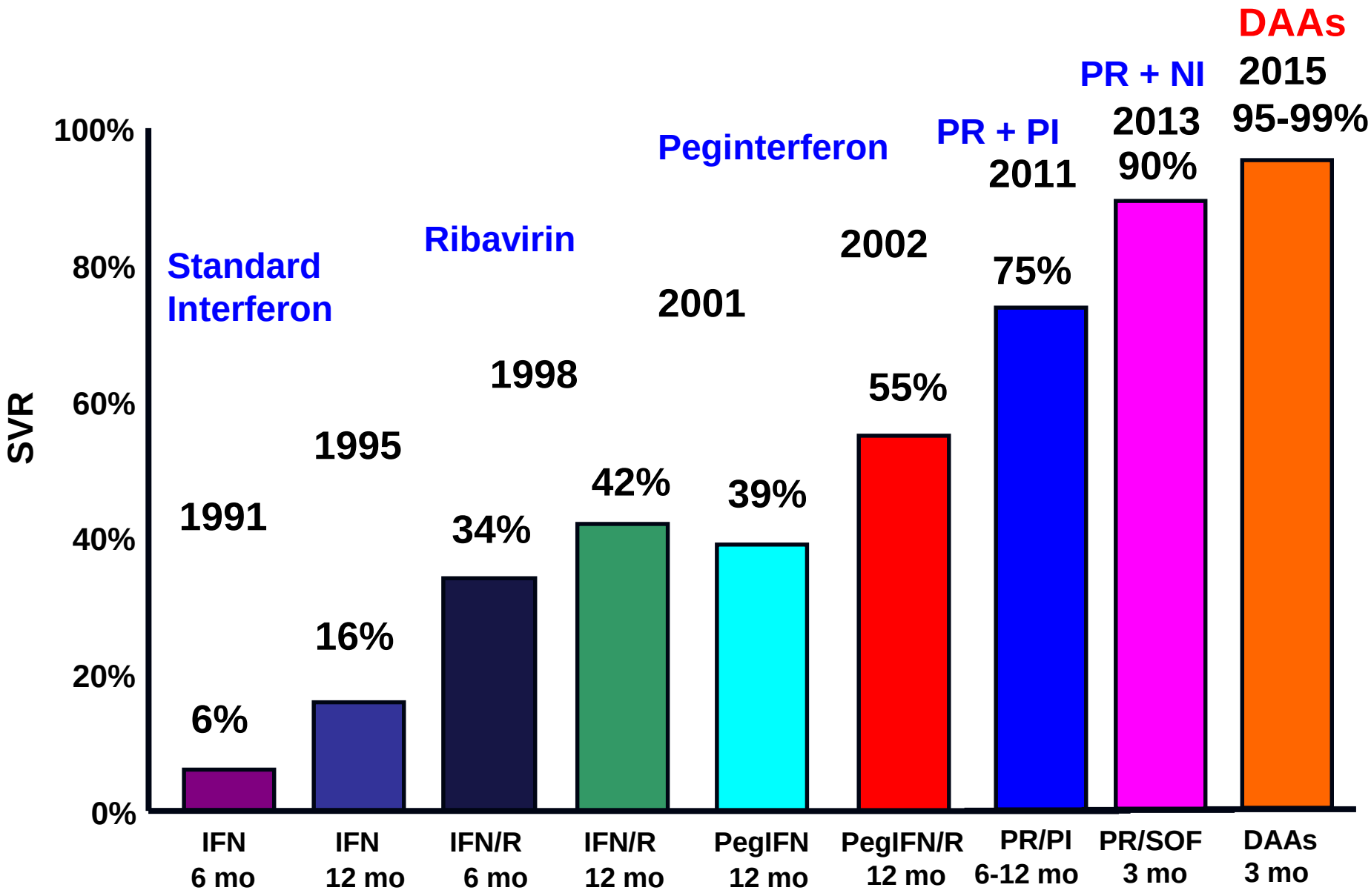
Certamente l'SVR:

- **riduce la mortalità nella cirrosi**
- **riduce le complicanze cliniche della cirrosi**
- **produce un miglioramento istologico della cirrosi**
- **previene la ricorrenza dell'infezione da HCV nell'OLT**

Quindi gli studi hanno confermato che probabilmente la SVR:

- **riduce la mortalità nei pz HCV**
- **riduce la progressione della fibrosi**
- **riduce le manifestazioni extraepatiche dell'HCV**

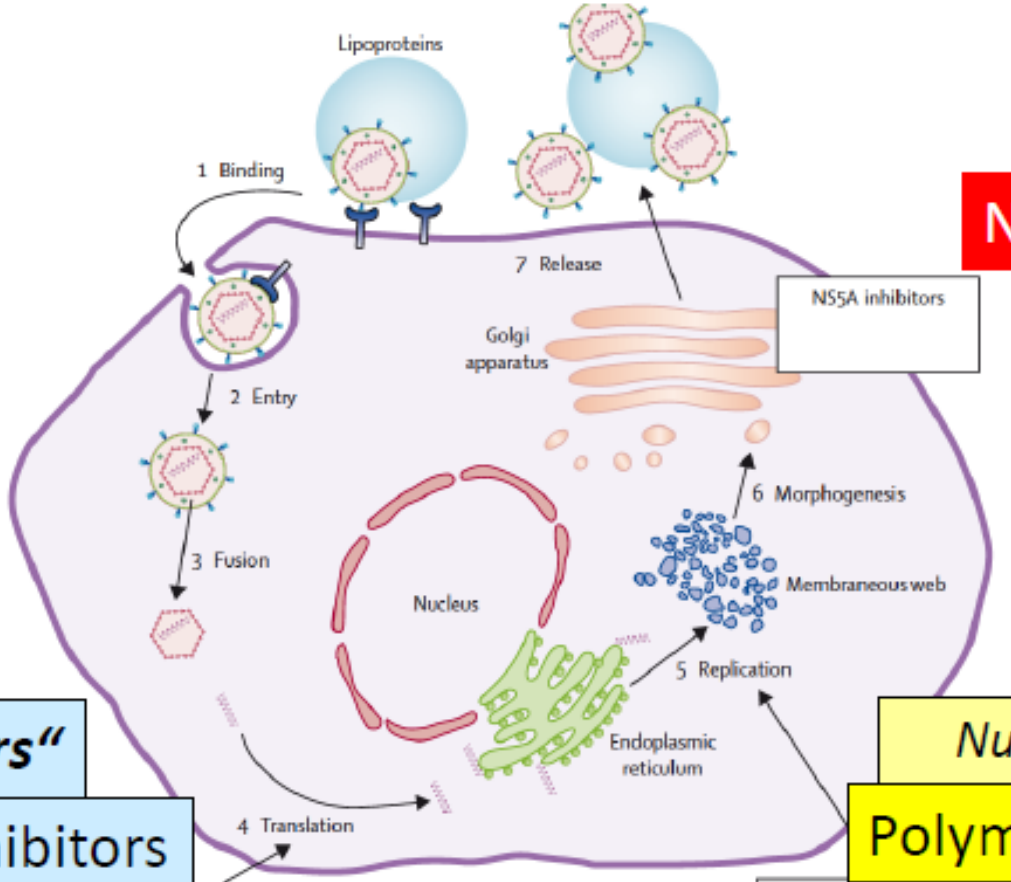
Treatment improvement : The real reason



Armamentario terapeutico anti-HCV

- Peginterferone
- Ribavirina
- DAAs di I generazione
  - inibitori della proteasi NS3/4A boceprevir e telaprevir
- DAAs di II generazione
  - inibitori della proteasi NS3/4A
  - inibitori dell'NS5A
  - inibitori della polimerasi NS5B

Direct Acting Antivirals against HCV



"...asvirs"

NS5A Inhibitors

"...previrs"

Protease Inhibitors

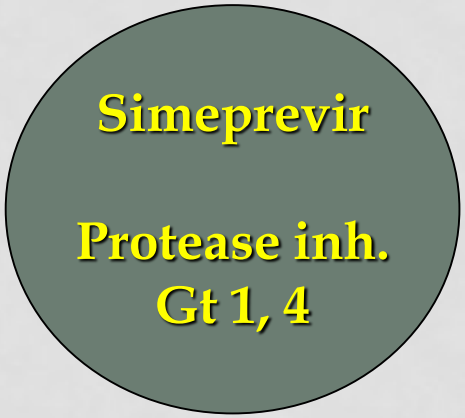
Nucs | **Non-Nucs**

Polymerase Inhibitors

"...buvirs"

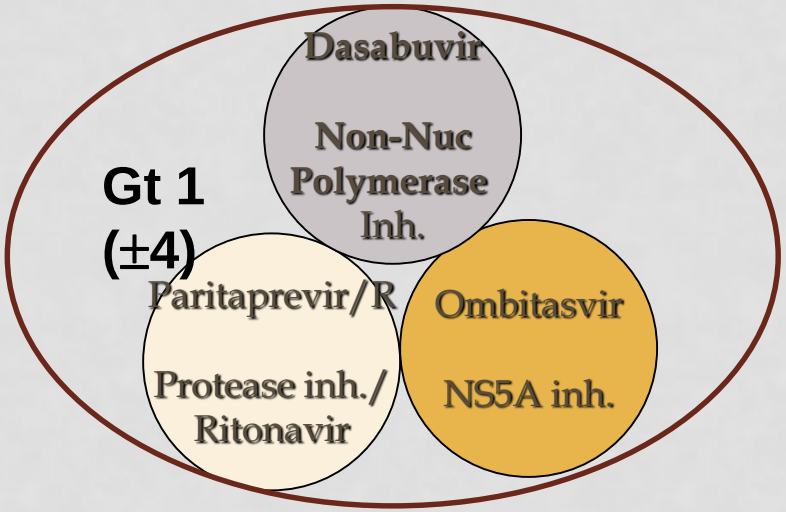
Manns, von Hahn, Nat Rev Drug Discov 2013

I FARMACI DISPONIBILI OGGI

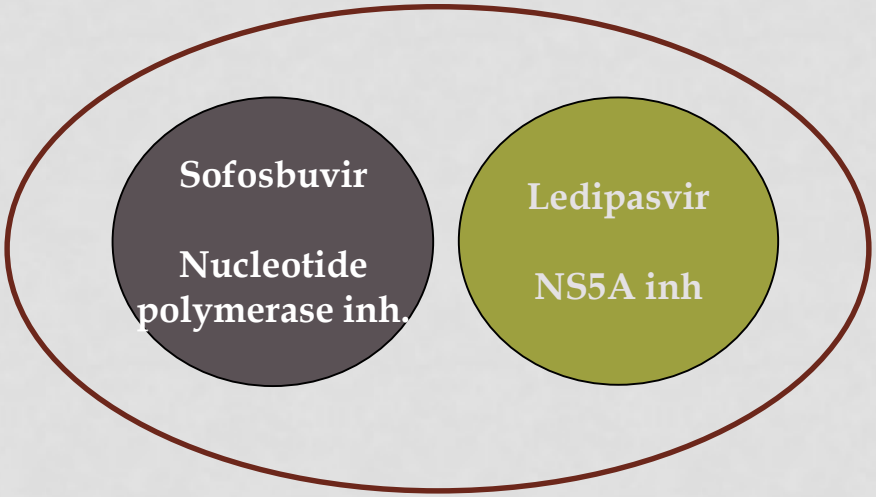


Combination of one DAA and ribavirin

Combination of two DAAs ± ribavirin

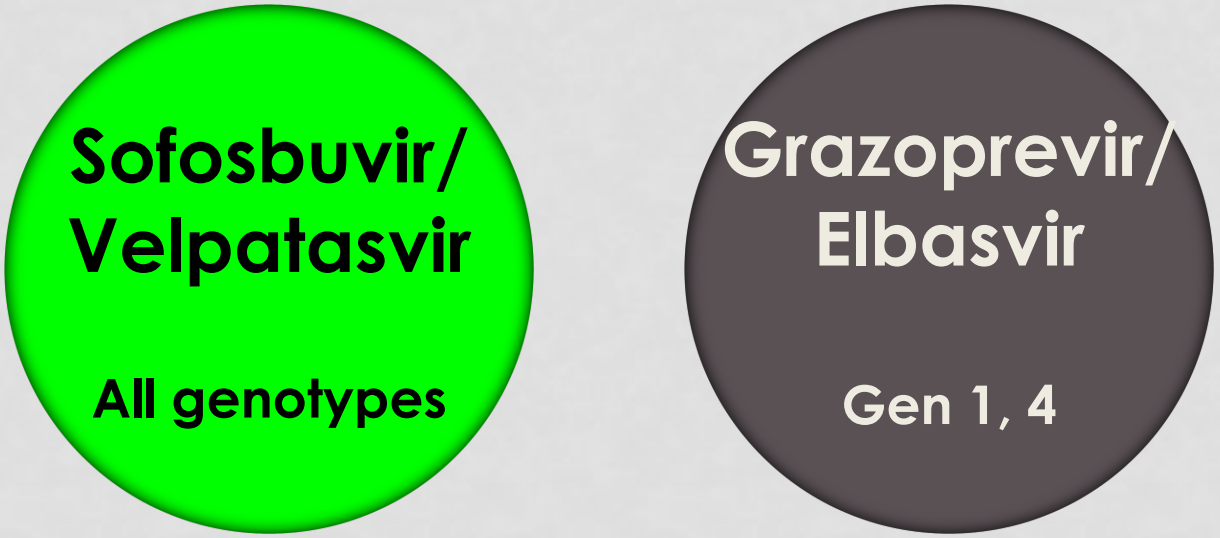


Fixed dose combination (3D) of three DAAs ± ribavirin.



Fixed dose combination of two DAAs ± ribavirin.

DAAS APPROVED IN 2016



I farmaci

Classe	Farmaco	Dose
NS3/4A protease inhibitor	**Paritaprevir/RTV**	150/100 mg
NS3 protease inhibitor	**Asunaprevir**	100 mg BID
NS3/4A protease inhibitor	**Grazoprevir**	100 mg QD
NS3/4A protease inhibitor	**Simeprevir**	150 mg QD
NS5B nonnucleoside polymerase inhibitor	**Dasabuvir**	250 mg BID
NS5B nucleotide polymerase inhibitor	**Sofosbuvir**	400 mg QD
NS5A inhibitor	**Daclatasvir**	60 mg QD
NS5A inhibitor	**GS-5816**	25 or 100 mg QD
NS5A inhibitor	**Ledipasvir**	90 mg QD
NS5A inhibitor	**Elbasvir**	20 or 50 mg QD
NS5A inhibitor	**Ombitasvir**	25 mg QD

LE INCONGRUENZE

(per i pazienti)

Individual Health Criteria for Prioritization

Criteria	Subcriteria	EASL	WHO	AISF/AIFA
Advanced liver disease	Cirrhosis Child B & C	**Treated urgently**	**Yes**	**Yes**
	Cirrhosis Child A	**Prioritized**		
Hepatic	F3			
	F2	**Justified**	**No indication**	**Yes in post-transplant**
	F0-1	**Individualized**		**No indication**
Risk of fibrosis progression	HIV coinfection	**Prioritized**	**Yes**	**No specific indication**
	HBV coinfection			
	Pre & post liver transplant		**No**	**yes (MELD<25)**
Extra-hepatic	Metabolic syndrome	**No specific indication**	**Yes**	**No specific indication**
Extra-hepatic disease	Cryoglobulinemia & LPDs	**Prioritized**		**Yes**
	Renal Disease Debilitating fatigue			**No specific indication**
Significant psychosocial morbidity	Stigma, discrimination and fear of transmision to others	**No specific indication**		**No specific indication**

Public Health Criteria for Prioritization

Criteria	Subcriteria	EASL	WHO	AISF/AIFA
Increased Risk of Transmission	PWID	**Yes**	**Yes**	**No indication**
	MSM	**With high risk practices**		
	Prisoners	**Yes**		
	Women with childbearing potential			
	Sex workers	**No indication**		
	Health care workers			
	Haemodialysis patients	**Yes**	**No indication**	

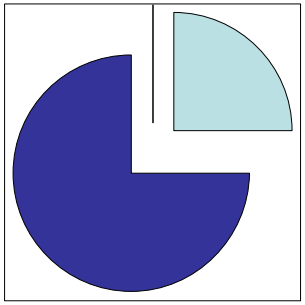
:

Categoria I	TERAPIA DEL PAZIENTE CON CIRROSI IN CLASSE DI CHILD-PUGH A o B e/o CON HCC CON RISPOSTA COMPLETA A TERAPIE RESETTIVE CHIRURGICHE O LOCO-REGIONALI, NON CANDIDABILI A TRAPIANTO EPATICO, NEI QUALI LA MALATTIA EPATICA SIA DETERMINANTE PER LA PROGNOSI
Categoria II	TERAPIA DEL PAZIENTE CON RECIDIVA DI EPATITE DOPO TRAPIANTO DI FEGATO CON FIBROSI METAVIR ≥2 (O S3 ISHAK) O CON VARIANTE FIBROSANTE COLESTATICA
Categoria III	TERAPIA DEL PAZIENTE CON EPATITE CRONICA CON GRAVI MANIFESTAZIONI EXTRA-EPATICHE HCV-CORRELATE (SINDROME CRIOGLOBULINEMICA CON DANNO D'ORGANO, SINDROMI LINFOPROLIFERATIVE A CELLULE B)
Categoria IV	TERAPIA DEL PAZIENTE CON EPATITE CRONICA CON FIBROSI METAVIR F3 (O CORRISPONDENTE ISHAK)
Categoria V	TERAPIA DEL PAZIENTE IN LISTA PER TRAPIANTO EPATICO CON CIRROSI MELD <25 e/o CON HCC ALL'INTERNO DEI CRITERI DI MILANO CON LA POSSIBILITA' DI ATTESA IN LISTA DI ALMENO 2 MESI
Categoria VI	TERAPIA DEL PAZIENTE CON EPATITE CRONICA DOPO TRAPIANTO DI ORGANO SOLIDO (NON FEGATO) O DI MIDOLLO CON FIBROSI METAVIR ≥2 (O CORRISPONDENTE ISHAK)
Categoria VII	TERAPIA DEL PAZIENTE CON EPATITE CRONICA CON FIBROSI METAVIR F0-F2 (O CORRISPONDENTE ISHAK)

IFN-free

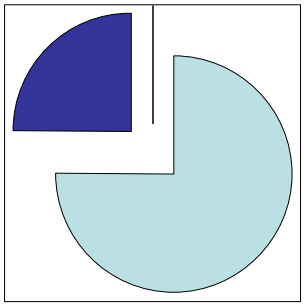
diverse politiche

Economy class



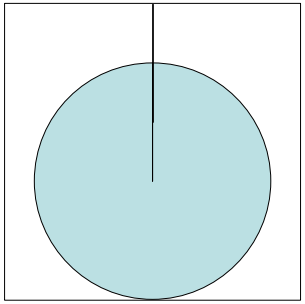
Trattamento solo per i soggetti con malattia significativa o progressiva

Business class



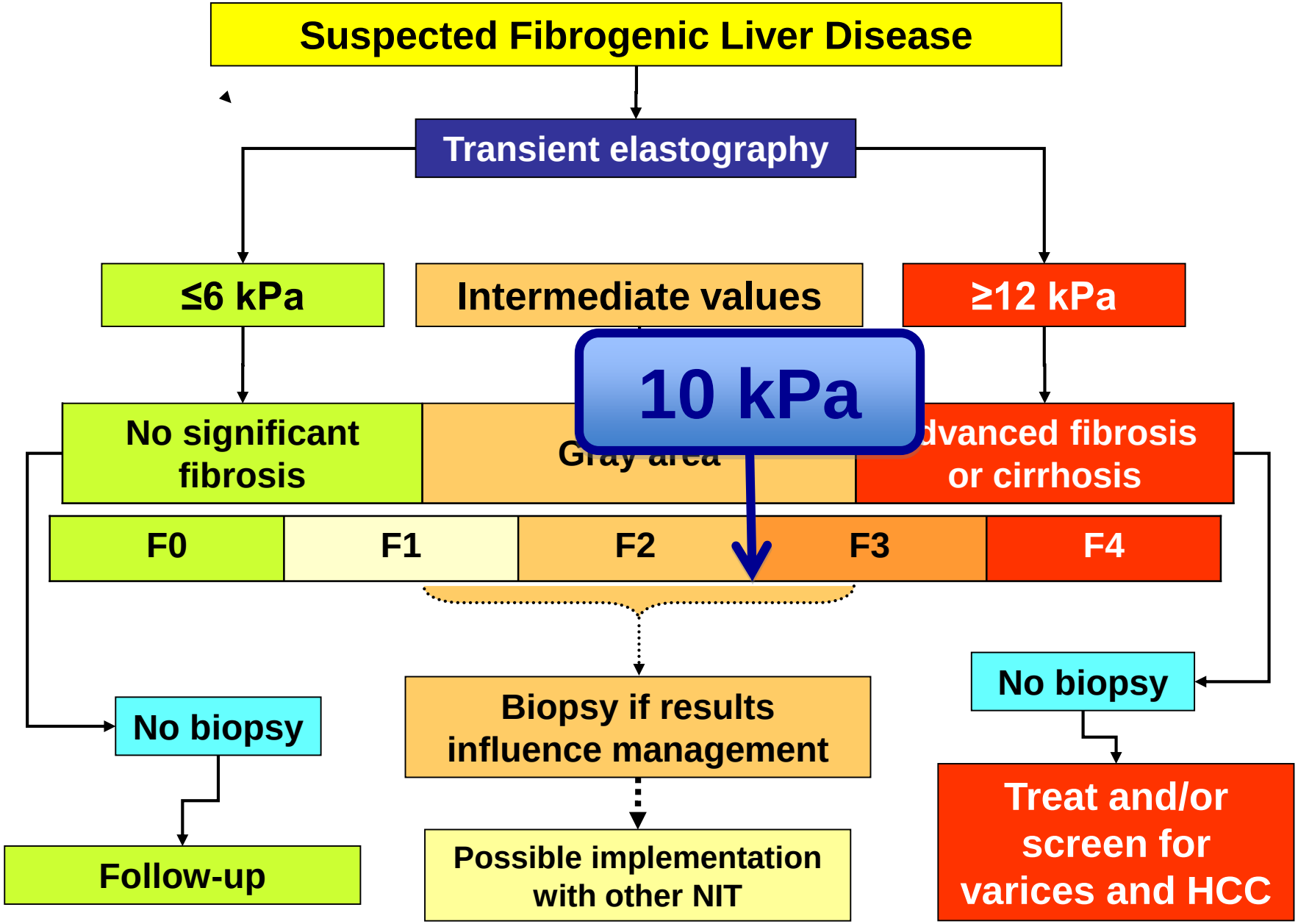
Trattamento allargato a particolari setting

First class



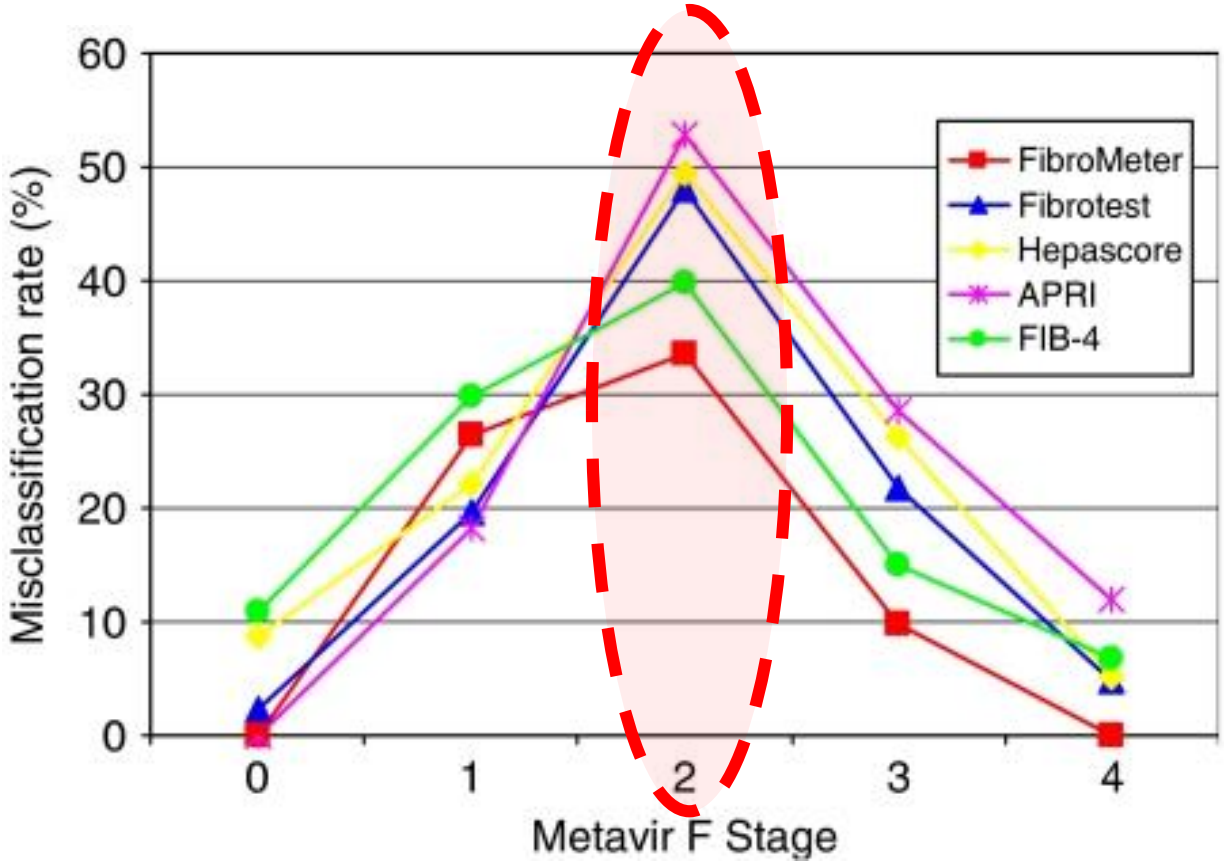
Trattamento per tutti i soggetti con infezione da HCV

E DI CONSEGUENZA



Modified from Vizzutti et al., Gut 2009;58:157

Poor classification of intermediate stages by non-invasive tests



Cales et al., Liver Int 2008;28:1352

LE INCONGRUENZE

(per i medici)

IL RUOLO DEL CLINICO

Definire come realizzare il percorso diagnostico terapeutico più appropriato per il singolo soggetto in considerazione delle variabili che ha a disposizione.

Caratteristiche del paziente

Costo efficacia del trattamento

Beneficio atteso/ottenuto

Complicanze dovute alla malattia epatica di base

Sicurezza efficacia delle terapie

Volontà del paziente

Risorse disponibili

Cortesia Dr. G. Rizzardini

FNOMCeO

Codice di deontologia medica (2014)

Art. 13 - Prescrizione a fini di prevenzione, diagnosi, cura e riabilitazione

- Diretta, specifica, esclusiva e non delegabile competenza del medico,
- impegna la sua autonomia e responsabilità e deve far seguito a una diagnosi circostanziata o a un fondato sospetto diagnostico.
- Deve fondarsi sulle **evidenze scientifiche disponibili, sull'uso ottimale delle risorse e sul rispetto dei principi di efficacia clinica, di sicurezza e di appropriatezza**.
- Il medico **tiene conto delle linee guida diagnostico-terapeutiche accreditate da fonti autorevoli e indipendenti** quali raccomandazioni e ne valuta l'applicabilità al caso specifico.

Cortesia Dr. G. Rizzardini

FNOMCeO

Codice di deontologia medica (2014)

Art. 13 - Prescrizione a fini di prevenzione, diagnosi, cura e riabilitazione

- **L'adozione di protocolli diagnostico-terapeutici o di percorsi clinico-assistenziali** impegna la diretta responsabilità del medico nella verifica della tollerabilità e dell'efficacia sui soggetti coinvolti.
- Il medico è tenuto a un'adeguata conoscenza della natura e degli effetti dei farmaci prescritti, delle loro indicazioni, controindicazioni, interazioni e reazioni individuali prevedibili e delle modalità di impiego appropriato, efficace e sicuro dei mezzi diagnostico-terapeutici.
- Il medico segnala tempestivamente all'Autorità competente le reazioni avverse o sospette da farmaci e gli eventi sfavorevoli o sospetti derivanti dall'utilizzo di presidi biomedicali.

FNOMCeO

Codice di deontologia medica (2014)

Art. 13 - Prescrizione a fini di prevenzione, diagnosi, cura e riabilitazione

- Il medico non acconsente alla richiesta di una prescrizione da parte dell'assistito al solo scopo di compiacerlo.
- Il medico non adotta né diffonde pratiche diagnostiche o terapeutiche delle quali non è resa disponibile idonea documentazione scientifica e clinica valutabile dalla comunità professionale e dall'Autorità competente
- Il medico non deve adottare né diffondere terapie segrete.

Parere pro veritate sulla potenziale responsabilità del Medico Infettivologo in quanto prescrittore di nuovi farmaci antivirali attivi per il trattamento dell'epatite "C". (Prof. Avv. Piermaria Corso)

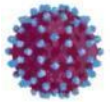
- … il Medico deve prescrivere la cura più adeguata alla fattispecie concreta, ma non assume alcuna responsabilità in merito alla sostenibilità economica del trattamento sanitario prescritto: il Centro, l'Azienda Ospedaliera o il SSN possono o no farsi carico dei costi, possono o no chiedere al paziente di farsi carico (in tutto o in parte) dei relativi oneri, ma certamente questa è una attività inter alios acta che non coinvolge minimamente la responsabilità del Medico.

Parere pro veritate sulla potenziale responsabilità del Medico Infettivologo in quanto prescrittore di nuovi farmaci antivirali attivi per il trattamento dell'epatite "C". (Prof. Avv. Piermaria Corso)

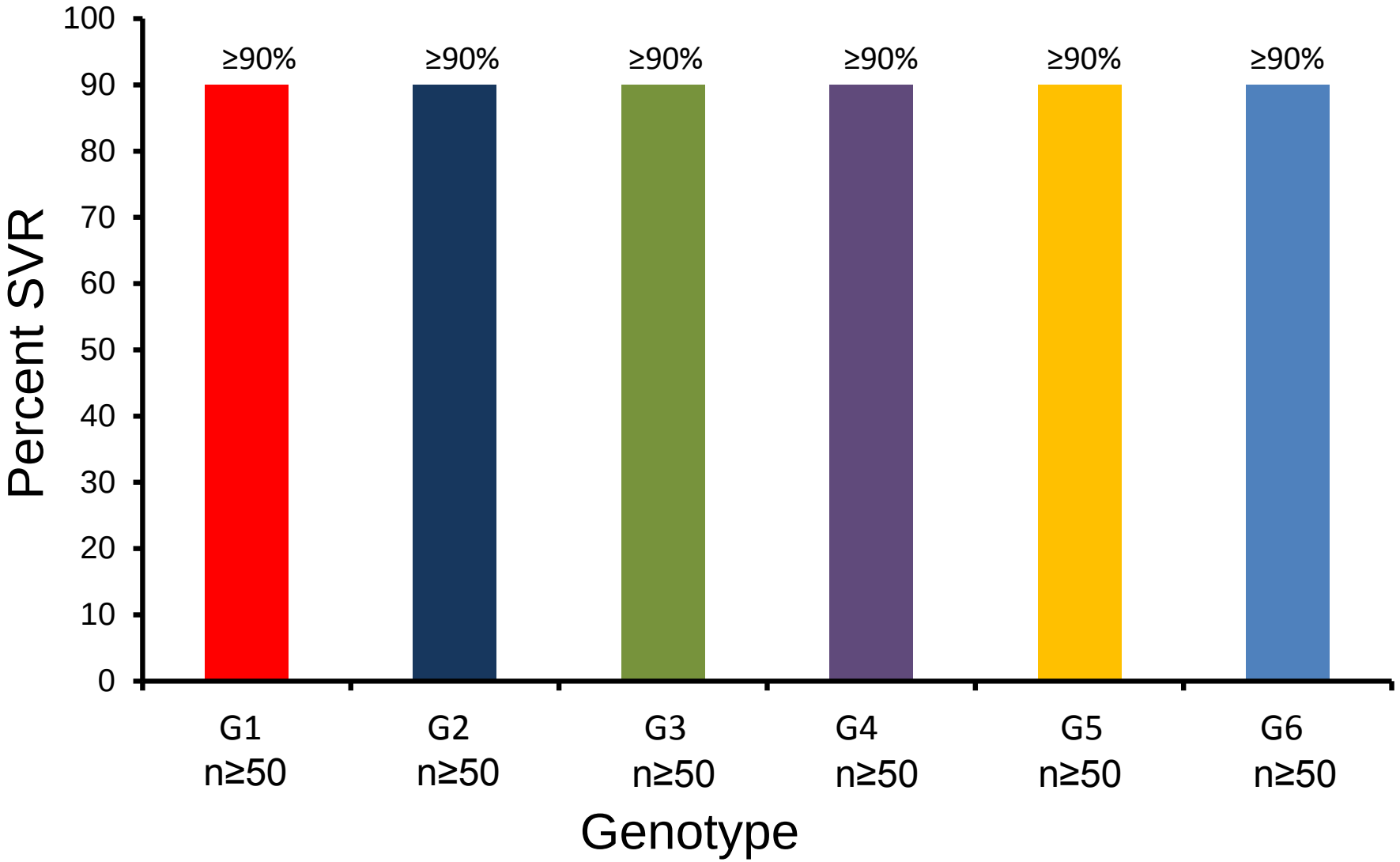
Il Medico Infettivologo – sotto sua responsabilità anche penale – visita il paziente e indica quali farmaci antivirali possano costituire la migliore risposta terapeutica alla "infezione cronica da virus dell'epatite C" e assicurare "risultati clinici eccellenti". Nella indicazione dei farmaci migliori, il Medico non deve farsi condizionare da altro che l'interesse clinico del paziente: in particolare, deve prescrivere il farmaco più efficace e, a parità di risultati clinici, deve prescrivere il farmaco meno costoso, a prescindere dal fatto che il costo finale dell'acquisto del farmaco ricada sull'utente finale o sul SSN.

ESEMPI DI EFFICACIA DEI DAAs

NEGLI STUDI REGISTRATIVI



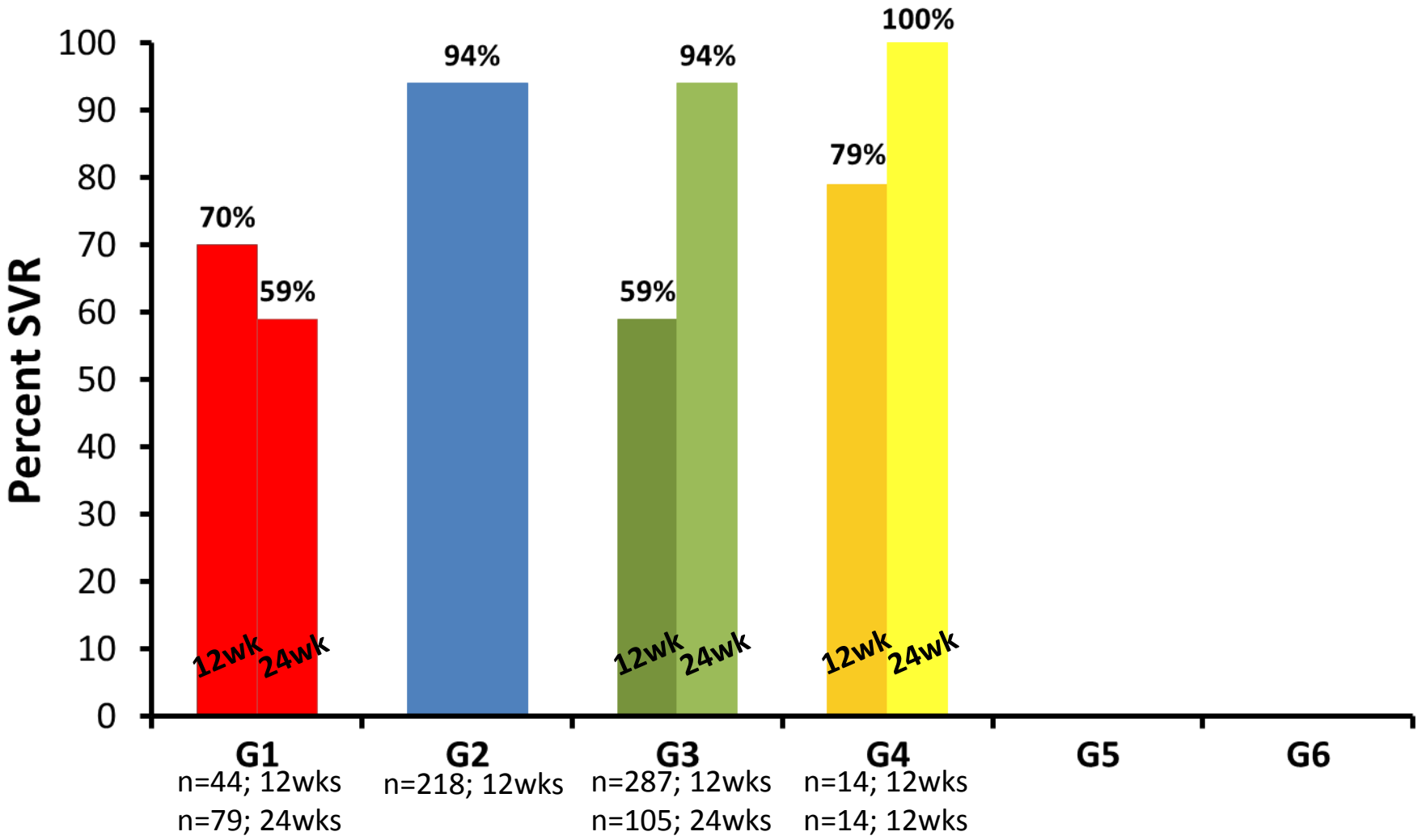
IL TRATTAMENTO IDEALE: BASSO COSTO, > 90% DI SVR, PANGENOTIPICO, BREVE DURATA, BEN TOLLERATO



Raccomandazioni EASL sulla durata

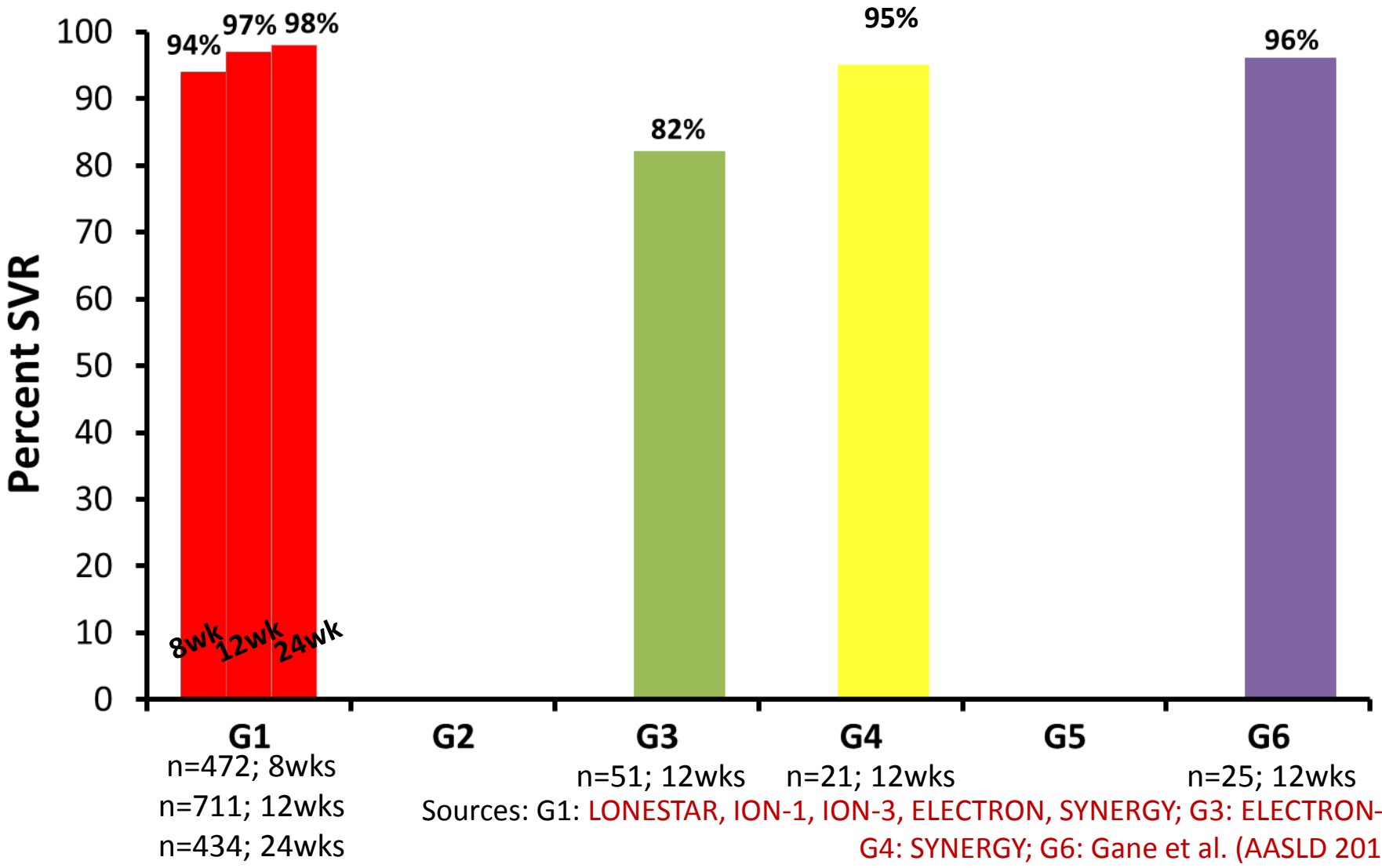
- Regimi contenenti interferone
  - 12 settimane
  - 24 settimane
  - 48 settimane
- Regimi interferon-free
  - 8 settimane (solo pz. naïve, non cirrotici, genotipo 1, viremia basale <6,8 $\log_{10}$ UI/ml trattati con sofosbuvir + ledipasvir)
  - 12 settimane
  - 24 settimane

SOFOSBUVIR + RBV



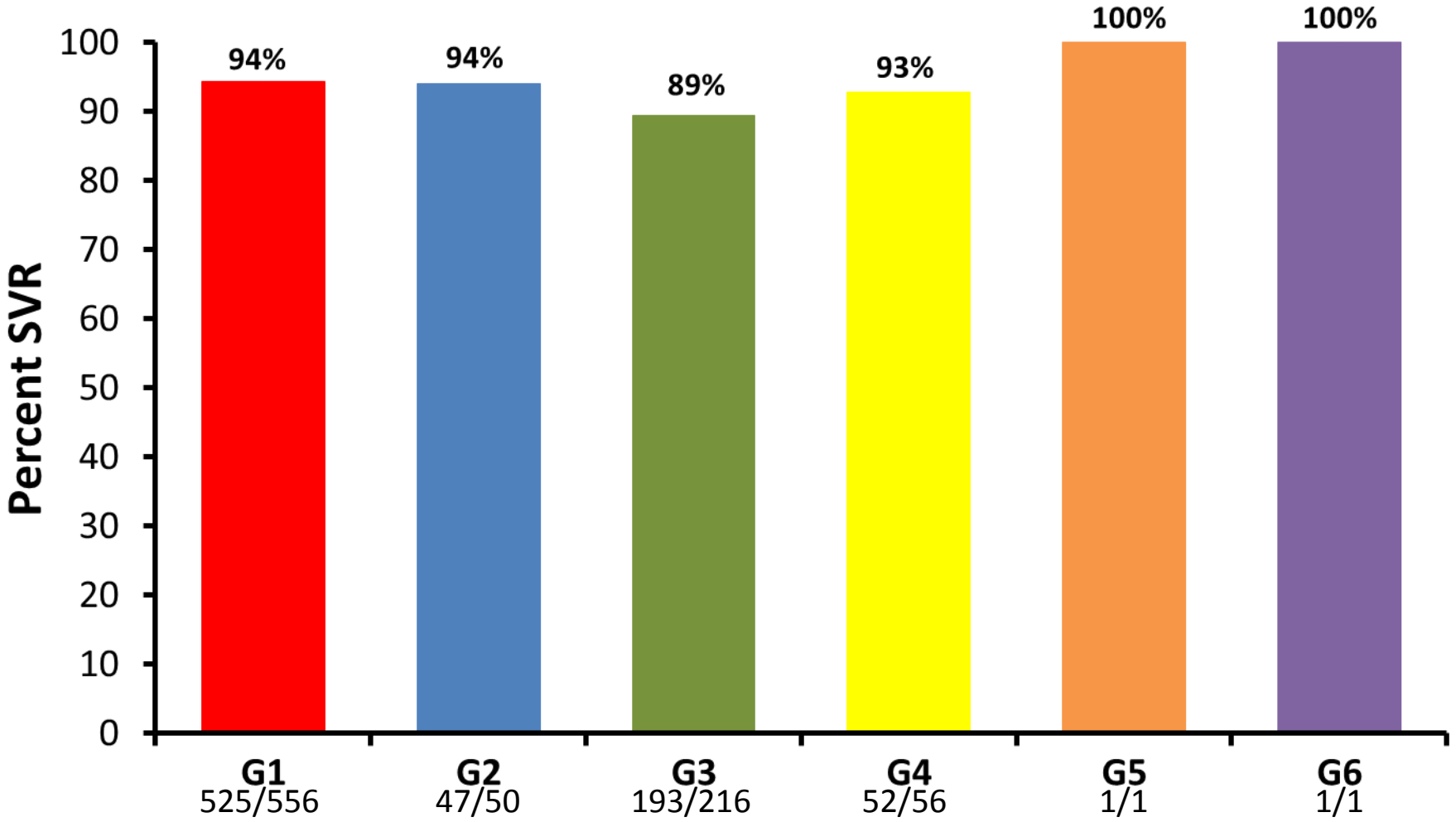
Sources: G1: SPARE, QUANTUM, VALENCE; G2: POSITRON, VALENCE, FISSION; G3: VALENCE; G4: Ruane et al.

SOFOSBUVIR + LEDIPASVIR +/- RBV



Sources: G1: LONESTAR, ION-1, ION-3, ELECTRON, SYNERGY; G3: ELECTRON-2; G4: SYNERGY; G6: Gane et al. (AASLD 2014)

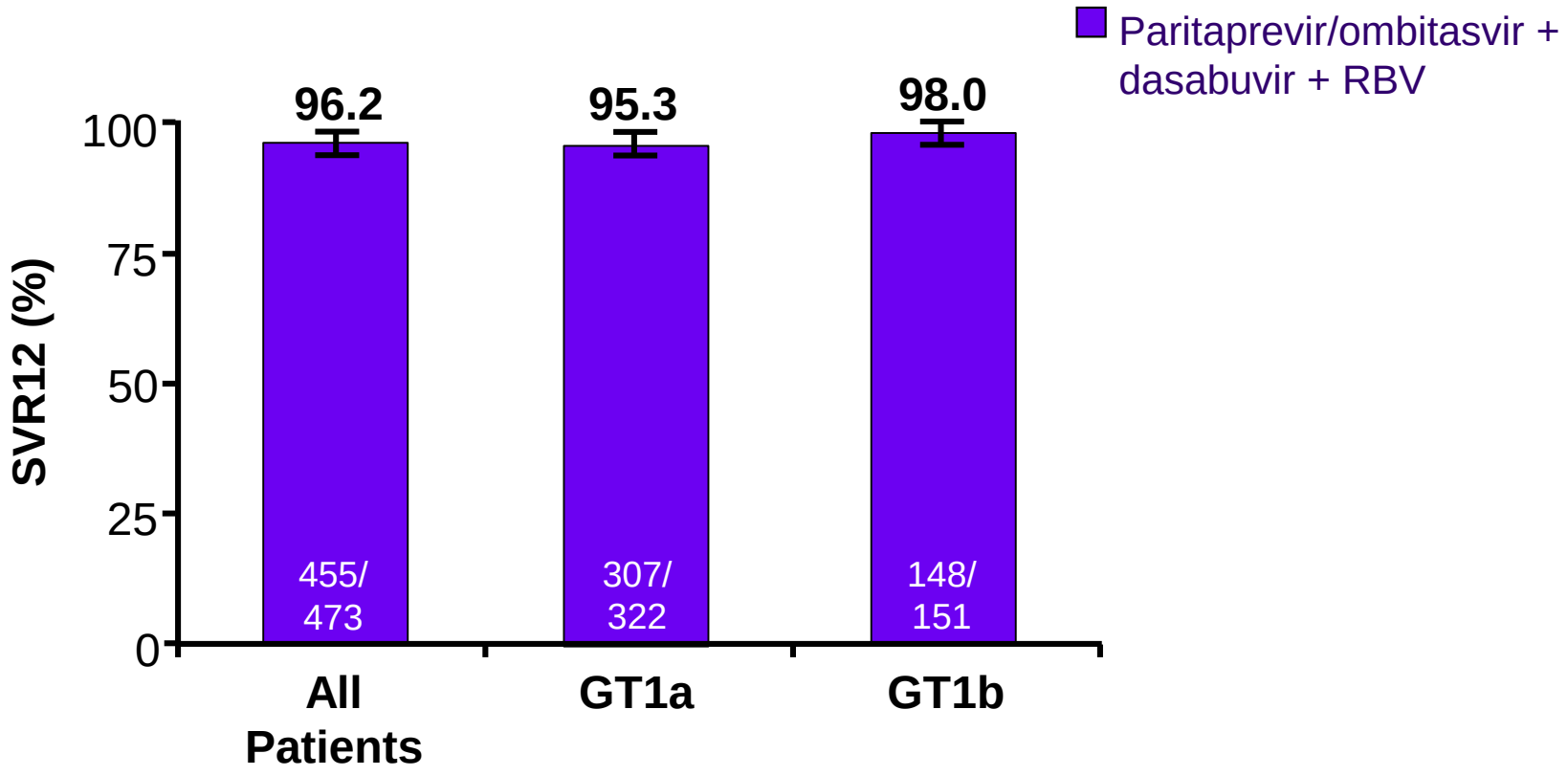
SOFOSBUVIR + DACLATASVIR +/- RBV (12 -24 W)



Sources: A1444040 trial; ALLY-1; ALLY-2; ALLY-3; 3 French EAPs

SAPPHIRE I: SVR12 CON 3DAA$_S$ +RBV IN NAIVE

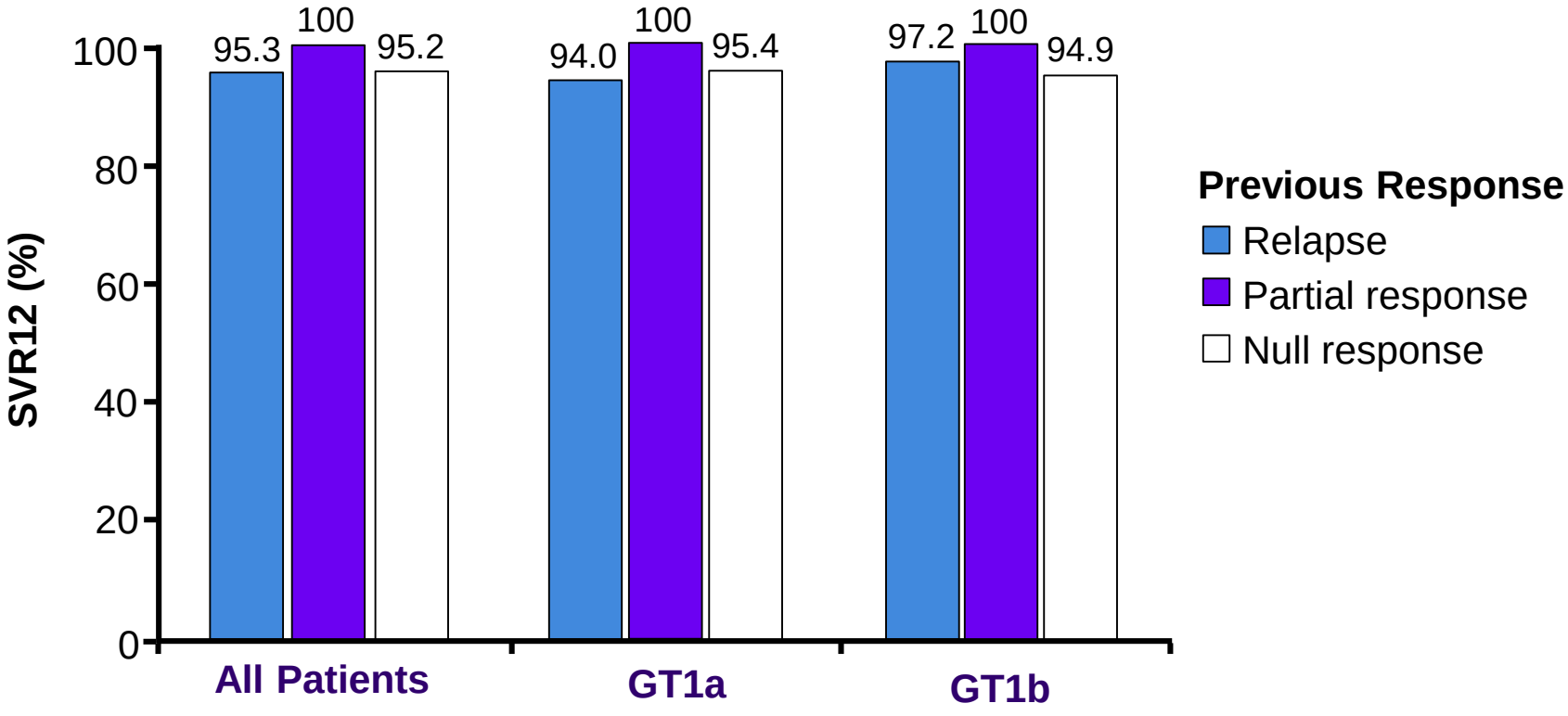
- High response rates in treatment-naive patients across subgenotypes



1. Feld JJ, et al. EASL 2014. Abstract O60.. 2. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.

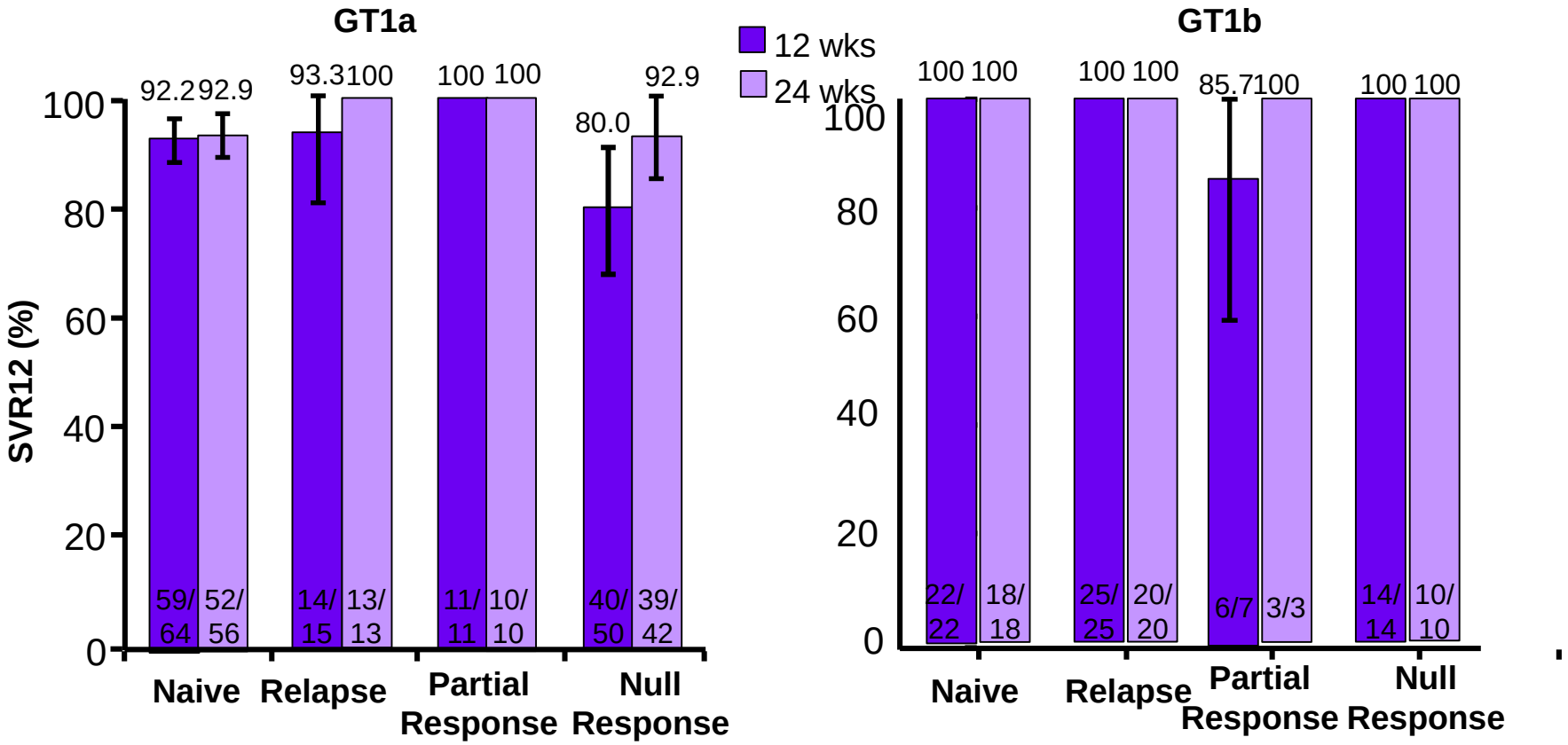
SAPPHIRE II: SVR12 CON 3DAA$_S$ +RBV IN EXPERIENCED

- High response rates in treatment-experienced patients, across subgenotypes, and regardless of previous response to peginterferon/ribavirin



Zeuzem S, et al. EASL 2014. Abstract O1. Zeuzem S, et al. N Engl J Med. 2014;370:1604-1614.

TORQUOISE II: SVR12 CON 3 DAAS + RBV IN CIRROTICI



- Virologic **failure** in 17/380 pts (4.5%); relapse more frequent with 12-wk vs 24-wk treatment (12 vs 1 pt), 7/12 relapsers by posttreatment Wk 12 were GT1a null responders

Poordad F, et al. EASL 2014. Abstract O163..

… ED IN QUELLI OSSERVAZIONALI

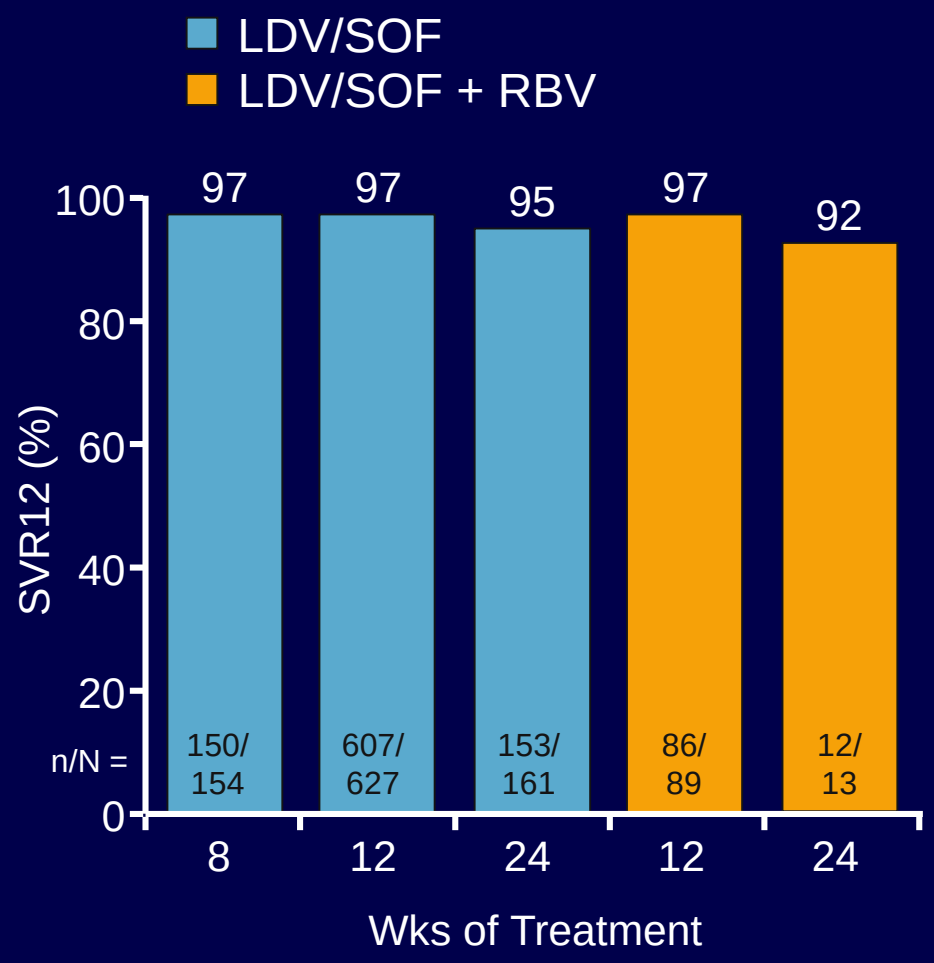
HCV-TARGET: Multicenter, Prospective, Observational Cohort Study

- 44 academic/17 community medical centers in North America/Europe
- Current analysis includes medical record data from sequential pts with GT1 HCV treated with LDV/SOF regimens

Baseline Characteristic, %	LDV/SOF 8 Wks (n = 154)	LDV/SOF 12 Wks (n = 627)	LDV/SOF 24 Wks (n = 161)	LDV/SOF Other (n = 27)	LDV/SOF + RBV 12 Wks (n = 89)	LDV/SOF + RBV 24 Wks (n = 13)	LDV/SOF + RBV Other (n = 3)
Treatment status							
▪ Exp'd	4	40	97	48	67	92	67
▪ DAA exp'd	1	10	32	19	16	39	33
Subgenotype							
▪ 1a	66	65	68	78	57	62	67
▪ 1b	29	28	21	15	34	23	33
Cirrhosis	2	29	78	41	61	85	67
▪ Decompensated	2	9	27	19	19	31	33
PPI use	20	26	34	30	35	46	33

Terrault N, et al. AASLD 2015. Abstract 94.

HCV-TARGET: SVR12 With 8-, 12-, or 24-Wk Ledipasvir/Sofosbuvir ± Ribavirin



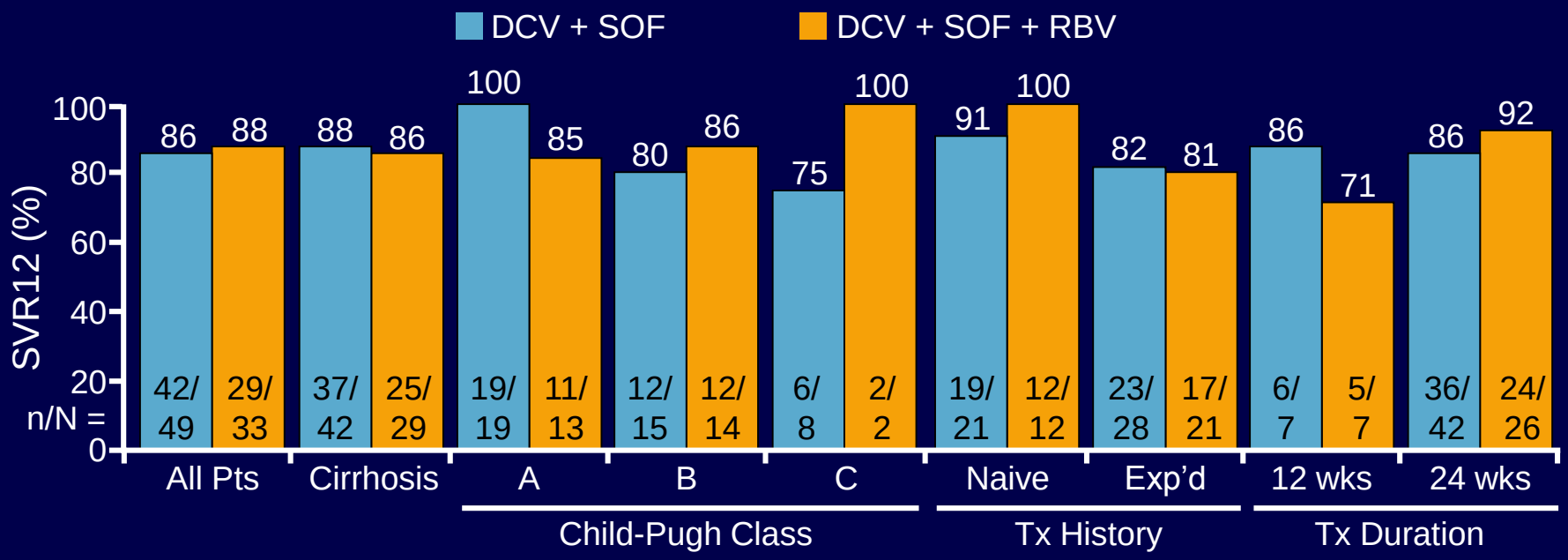
- Only 131 out of 323 pts who qualified for 8-wk treatment (treatment naive, no cirrhosis, and baseline HCV RNA ≤ 6 million IU/mL) received 8-wk regimen

Tx Outcome in Pts Qualifying for 8-Wk Regimen	LDV/SOF 8 Wks (n = 131)	LDV/SOF 12 Wks (n = 192)
SVR12, %	97	97
Failure, %	3	3
SVR12 according to Wk 4 HCV RNA, % (n/N)	(n = 99)	(n = 133)
▪ Below limit of quantification	97 (89/92)	97 (114/117)
▪ Quantifiable	100 (7/7)	94 (15/16)

Terrault N, et al. AASLD 2015. Abstract 94. Reproduced with permission.

Interim Analysis: Daclatasvir + Sofosbuvir ± RBV in GT3 HCV in European CUP

- Pts treated with DCV 60 mg + SOF 400 mg QD for 24 wks; RBV added or duration shortened to 12 wks per physician discretion
- Most common AEs: fatigue, nausea, anemia
  - Tx-related serious AEs (n = 1 each): pancytopenia, HE, HCC, circulatory collapse



Welzel TM, et al. AASLD 2015. Abstract 37. Reproduced with permission.

Real-World Efficacy and Safety of OBV/PTV/RTV ± DSV ± RBV

- German Hepatitis C Registry cohort[1]:
  - Efficacy population (complete follow-up): n = 543
  - Safety population (initiated treatment): n = 1017
    - GT1: 88%; GT4: 12%; cirrhosis: 22%; CP B/C: 7%; tx exp'd: 59%
- Israeli cohort (12 treatment centers in Israel)[2]:
  - Efficacy population (complete follow-up): n = 432
  - Safety population (initiated treatment): n = 661
    - GT1: 100%; cirrhosis: 62%; tx exp'd: 62%; post LT: n = 22
    - Of 410 pts with cirrhosis, 404 CP A, 6 CP B

1. Hinrichsen H, et al. EASL 2016. Abstract GS07.
2. Zuckerman E, et al. EASL 2016. Abstract PS004.

Real-World Use of OBV/PTV/RTV ± DSV ± RBV: Efficacy

- German cohort[1]: SVR12/24 rates ≥ 93% across sub-groups except for pts not treated according to guidelines
  - SVR12/24 99% if treated according to guidelines (eg, duration, RBV use) vs 92% if not
  - SVR12/24 rates 96% to 100% across GFR strata
- Israeli cohort[2]: SVR12 rate 99%, regardless of cirrhosis in mITT analysis (pts without SVR12 for reasons other than VF excluded)
  - ITT SVR12 rate in 22 pts post–liver transplantation: 82%
    - Another pt who discontinued early achieved SVR12 for overall SVR12 rate of 86%

1. Hinrichsen H, et al. EASL 2016. Abstract GS07.
2. Zuckerman E, et al. EASL 2016. Abstract PS004.

Real-World Use of OBV/PTV/RTV ± DSV ± RBV: Safety

- Most common AEs across both cohorts[1,2]: fatigue, pruritus, headache, insomnia, nausea, anemia
  - Serious AE: 2.1% to 3.8%
  - Discont. for AE: 1.5% to 3%
  - 3 deaths deemed unrelated to HCV therapy: stroke, MI, multiple organ failure
- In Israeli cohort,[2] 20 pts discontinued for AEs
  - Serious AE: n = 12
  - Decompensation: n = 8
- In Israeli cohort,[2] several factors identified as significant predictors of hepatic decompensation

Factor	*P* Value
Age older than 75 yrs	.005
Platelets < 90,000/mL	.03
Albumin < 3.5 g/dL	.048
CPT score ≥ 7	.07
MELD score > 10	.01
Previous decompensation	< .001

1. Hinrichsen H, et al. EASL 2016. Abstract GS07. 2. Zuckerman E, et al. EASL 2016. Abstract PS004. Reproduced with permission.

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IFN-free regimens: SVR12 in HCV/HIV coinfected patients

Patient, % (n)		DCV + SOF 12 week ALLY 2 Phase 3	LDV/SOF 12 week ION-4 Phase 3	SOF + RBV 24 week PHOTON 1	SOF + RBV 12 week PHOTON 1	SOF + RBV 12 or 24 week PHOTON 2	AbbV 3D 12–24 week TURQUOISE1 Phase 3	GZR + EBV 12 weeks C-EDGE Phase 3
GT-1	TN	**96%** (83)	96% (n = 335)[e]	76% (87/114)	-	85% (112)	93.5% (31)[c] 90.6% (32)[d] GT-1 overall	1a: 94.4% (136) 1b: 95.5% (42)
	TE	**98%** (44)	-	-	-	-		
GT-2	TN	**100%** (11)	-	-	88% (23/26)	88% (25) GT-2 overall	-	-
	TE	**100%** (2)	-	92% (24)	-		-	-
GT-3	TN	**100%** (6)	-		67% (42)	89% (106) GT-3 overall	-	-
	TE	**100%** (4)	-	94% (17)	-		-	-
GT-4	TN	**100%** (1)	-	-	-	84% (31)	-	96.4% (27)
	TE	**100%** (2)	-	-	-	-	-	-

IFN-free regimens:SVR12 in HCV/HIV coinfected patients with GT-1

Patient		**DCV + SOF 12 week** ALLY2 Phase 3	**GPV+EBV 12 weeks** C-EDGE Phase 3	**Harvoni 12 week** ION-4 Phase 3	**SOF + RBV 24 week** Pooled Data of PHOTON 1&2 Phase 3	**Viekira Pak 12–24 week** TURQUOISE-1 Phase 3
TN + TE	Overall	**97**% (n = 127)	NA	96% (n = 335)[f]		93.5% (n = 31)[d] 90.6% (n = 32)[e]
	GT-1a	96%(n = 104)	94.4% (136)			91% (n = 56)
	GT-1b	100% (n = 23)	95.5% (42)			100% (n = 7)
TN	Overall	**96**% (n = 83)	NA	95% (n = 150)[f]	**81%** (n = 226)	
	Cirrhotic	89% (n = 9) [c]	NA		**64%** (n = 22)	
	Non-cirrhotic	98% (n = 90)[c]	NA		82% (n = 204)	
TE	Overall	**98**% (n = 44)	NA	97% (n = 185)[f]		
	Cirrhotic	93% (n = 15)[c]	NA			
	Non-cirrhotic	100% (n = 34)[c]	NA			

SAT-188

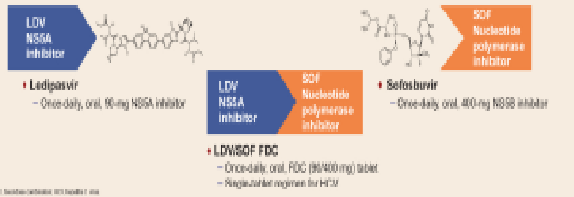
An Integrated Safety and Efficacy Analysis of Sofosbuvir-Based Regimens in Patients With Hereditary Bleeding Disorders

K. Rajender Reddy,[1] Catherine Stedman,[2] Kimberly Workowski,[3] Jenny C. Yang,[4] Luisa M. Stamm,[4] Ming Lin,[4] Diana M. Brainard,[4] John G. McHutchinson,[4] Gayle P. Balba,[5] Edward J. Gane,[6] Christopher Walsh[7]

[1]University of Pennsylvania, Philadelphia, USA; [2]Christchurch Clinical Studies Trust, Christchurch, New Zealand; [3]Emory University, Atlanta, Georgia, USA; [4]Gilead Sciences, Inc., Foster City, California, USA; [5]MedStar Georgetown University Hospital, Washington, DC, USA; [6]Auckland Clinical Studies, Auckland, New Zealand; [7]Mount Sinai Hospital, New York, New York, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction



- Patients with hereditary bleeding disorders have high rates of HCV infection due to exposure to contaminated blood products prior to 1992[1]
- This patient population has historically been excluded from HCV clinical trials due to concern for unique adverse events (AEs), comorbidities, and their underlying diagnosis
- Patients with hereditary bleeding disorders were included in the Phase 2 and 3 clinical trials of SOF and LDV/SOF, as well as in a dedicated study in this patient population

Objectives

- To evaluate the safety and efficacy of SOF-based regimens in HCV-infected patients with hereditary bleeding disorders

Methods

- Integrated analysis of patients with hereditary bleeding disorders who participated in a SOF or LDV/SOF Phase 2 or 3 study
  - Patients identified by search of medical history for:
    - Reported terms include "hemophilia" or "haemophilia," "factor" and "deficiency," "hemophi" or "haemophi," "willebrand" or "wilebrand," "VWD" or "VWF," "vw" and "disease"
    - Coded terms (if available) include "haemophilia" or "Von Willebrand's disease," or "factor" and "deficiency"

Patients With Bleeding Disorders, n (%)	SOF+PEG/RBV 12 wk (n=3)	SOF+RBV (n=45) 12 wk (n=17)	SOF+RBV 16 wk (n=6)	SOF+RBV 24 wk (n=22)	LDV/SOF (n=119) 12 wk (n=111)	LDV/SOF 24 wk (n=8)	LDV/SOF+RBV (n=17) 12 wk (n=16)	LDV/SOF+RBV 24 wk (n=1)	Total N=184
FISSION (P7977-1231)	—	1 (6)	—	—	—	—	—	—	1 (<1)
POSITRON (GS-US-334-0107)	—	0	—	—	—	—	—	—	0
FUSION (GS-US-334-0108)	—	0	3 (50)	—	—	—	—	—	3 (2)
NEUTRINO (GS-US-334-0110)	1 (33)								1 (<1)
VALENCE (GS-US-334-0133)	—	4 (24)	—	5 (23)	—	—	—	—	9 (5)
BOSON (GS-US-334-0153)	2 (67)	—	3 (50)	2 (9)	—	—	—	—	7 (4)
Bleeding disorders study (GS-US-334-1274)	—	10 (59)	—	6 (27)	99 (89)	5 (63)	—	—	120 (65)
ELECTRON (P7977-0523 Part 8)	—	—	—	—	1 (<1)	—	14 (88)	—	15 (8)
ION-1 (GS-US-337-0102)	—	—	—	—	1 (<1)	2 (25)	0	1 (100)	4 (2)
ION-2 (GS-US-337-0109)	—	—	—	—	0	1 (13)	2 (13)	0	3 (2)
ION-3 (GS-US-337-0108)	—	—	—	—	0	—	—	—	0
ION-4 (GS-US-337-0115)	—	—	—	—	10 (9)	—	—	0	10 (5)
PHOTON-1 (GS-US-334-0123)	—	1 (6)	—	1 (5)	—	—	—	—	2 (1)
PHOTON-2 (GS-US-334-0124)	—	1 (6)	—	8 (36)	—	—	—	—	9 (5)

PEG, pegylated interferon; RBV, ribavirin.

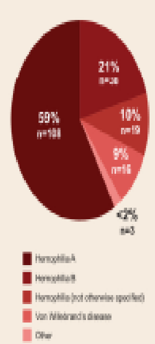
- Efficacy: proportion of patients with sustained virologic response 12 weeks after treatment end (SVR12)
- Safety
  - AEs and discontinuations
  - Laboratory abnormalities
  - Bleeding events

Results

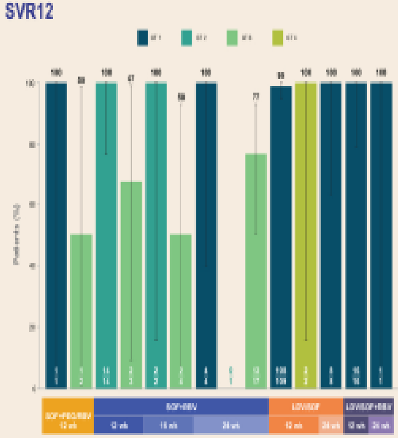
Baseline Characteristics

	SOF+PEG/RBV 12 wk n=3	SOF+RBV (n=45) 12 wk n=17	SOF+RBV 16 wk n=6	SOF+RBV 24 wk n=22	LDV/SOF (n=119) 12 wk n=111	LDV/SOF 24 wk n=8	LDV/SOF+RBV (n=17) 12 wk n=16	LDV/SOF+RBV 24 wk n=1	Total N=184
Demographics									
Mean age, y (range)	56 (48–66)	48 (30–75)	49 (38–58)	48 (21–67)	48 (22–68)	45 (32–63)	53 (29–73)	58	48 (22–73)
Male, n (%)	2 (67)	15 (88)	6 (100)	21 (96)	100 (90)	8 (100)	14 (88)	1 (100)	171 (93)
White, n (%)	3 (100)	15 (88)	6 (100)	21 (96)	83 (75)	6 (75)	14 (88)	1 (100)	148 (81)
Mean BMI, kg/m² (SD)	30.2 (3.3)	26.4 (3.6)	28.2 (2.3)	24.8 (2.3)	26.9 (4.7)	26.2 (7.6)	27.6 (4.6)	26.1	26.7 (4.5)
HCV									
HCV GT, n (%)									
1a	1 (33)	0	0	—*	74 (67)	6 (75)	12 (75)	1 (100)	94 (51)
1b	0	0	0	—*	34 (31)	2 (25)	4 (25)	0	40 (22)
2	0	14 (82)	2 (33)	1 (5)	0	0	0	0	17 (9)
3	2 (67)	3 (18)	4 (67)	17 (77)	0	0	0	0	26 (14)
4	0	0	0	0	2 (2)	0	0	0	2 (1)
IL28B non-CC, n (%)	2 (67)	5 (29)	3 (50)	11 (50)	87 (78)	5 (63)	12 (75)	1 (100)	126 (69)
Mean baseline HCV RNA, log_{10} IU/mL (SD)	6.6 (0.5)	6.2 (0.6)	6.6 (0.4)	6.5 (0.7)	6.2 (0.7)	6.0 (0.7)	6.3 (0.7)	6.4	6.3 (0.7)
Cirrhosis, n (%)	1 (33)	3 (18)	3 (50)	6 (27)	32 (29)	5 (63)	1 (6)	0	51 (28)
Prior HCV treatment, n (%)	1 (33)	4 (24)	6 (100)	12 (55)	47 (42)	6 (75)	5 (31)	0	82 (45)
HIV									
HIV positive status, n (%)	0	6 (35)	0	12 (55)	29 (26)	0	0	0	47 (26)

Type of Inherited Bleeding Disorders at Baseline (N=184)



SVR12



Overall Safety Summary

Patients, n (%)	SOF+PEG/RBV 12 wk n=3	SOF+RBV (n=45) 12 wk n=17	SOF+RBV 16 wk n=6	SOF+RBV 24 wk n=22	LDV/SOF (n=119) 12 wk n=111	LDV/SOF 24 wk n=8	LDV/SOF+RBV (n=17) 12 wk n=16	LDV/SOF+RBV 24 wk n=1
Overall safety								
Any AE	3 (100)	14 (82)	6 (100)	18 (82)	89 (82)	5 (63)	15 (94)	1 (100)
Grade 3/4 AE	0	0	0	2 (9)	7 (6)	1 (13)	1 (6)	0
Serious AE	1 (33)	0	0	2 (9)	5 (5)	1 (13)	2 (13)	0
Laboratory abnormalities								
Grade 3/4	1 (33)	3 (18)	1 (17)	2 (9)	9 (8)	1 (13)	8 (50)	0
Hemoglobin								
<10 g/dL	1 (33)	0	0	0	0	0	4 (25)	0
<8.5 g/dL	0	0	0	0	0	0	0	0
AEs in ≥5% of patients in LDV/SOF 12 wk treatment arm								
Fatigue	3 (100)	7 (41)	3 (50)	6 (27)	31 (28)	2 (25)	7 (44)	0
Headache	1 (33)	5 (30)	1 (17)	4 (18)	18 (16)	1 (13)	6 (38)	0
Diarrhea	0	1 (6)	0	5 (23)	10 (9)	0	0	0
Insomnia	1 (33)	1 (6)	3 (50)	3 (14)	6 (5)	0	2 (13)	0
Hemarthrosis	0	1 (6)	0	1 (5)	10 (9)	0	0	0
Nausea	0	2 (12)	1 (17)	1 (5)	8 (7)	0	4 (25)	0
Disturbance in attention	0	1 (6)	1 (17)	1 (5)	6 (5)	0	0	0
Bleeding AEs in >1 patient								
Hemarthrosis	0	1 (6)	0	1 (5)	10 (9)	0	0	0
Muscle hemorrhage	0	0	0	0	5 (5)	0	0	0
Epistaxis	0	0	0	1 (5)	3 (3)	0	0	0

Conclusions

- SOF + RBV and LDV/SOF ± RBV led to high rates of SVR12 in HCV GT 1–4-infected patients with bleeding disorders
- SOF-based regimens were safe and well tolerated, with no new toxicity specific to patients with bleeding disorders

Reference

1. AASLD/IDSA HCV Guidance Panel. Hepatology 2015;62:932-54.

Acknowledgements

The authors thank the patients who participated in these studies. These studies were funded by Gilead Sciences, Inc.

Presented at EASL–The International Liver Congress™, 13–17 April 2016, Barcelona, Spain

Presented at The International Liver Congress™ 2016; April 13-17, 2016; Barcelona, Spain

C-EDGE IBLD: Efficacy and Safety of Elbasvir/Grazoprevir in Patients With Chronic Hepatitis C Virus Infection and Inherited Blood Disorders

Background

- Almost all patients who received blood-derived clotting factors or red blood cell transfusions prior to the early 1990s were infected with the hepatitis C virus (HCV)[1]
  - Patients with blood factor deficiencies, such as hemophilia and von Willebrand disease, as well as hemoglobinopathies, such as sickle cell anemia and β-thalassemia, are therefore at risk for the significant morbidity (such as end-stage liver disease and hepatocellular carcinoma) and mortality associated with HCV infection[2]
- Treatment of HCV infection in patients with inherited blood disorders (IBLDs) is complex
  - Historically, the use of ribavirin has been restricted due to the risk of hemolytic anemia,[3] and frequent comorbidities mean that many patients with IBLDs are not eligible for interferon-based HCV therapy
- Interferon- and ribavirin-free direct-acting antiviral regimens offer new treatment opportunities for patients with IBLDs and HCV infection
  - Elbasvir (EBR) is a once-daily NS5A inhibitor and grazoprevir (GZR) is a once-daily HCV NS3/4A protease inhibitor; the combination (**Figure 1**) has been approved by the US Food and Drug Administration for the treatment of patients with HCV genotype (GT)1 or 4 infection[4]
    - Combination has broad in vitro genotypic activity[5-7]
    - Rates of sustained virologic response (SVR) >90% have been achieved in phase 3 studies of EBR/GZR, with a safety profile that does not differ markedly from that of placebo[8-10]

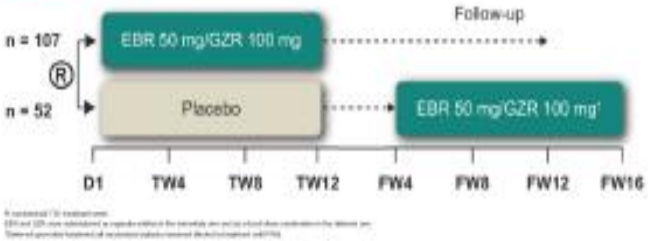
Figure 1. EBR/GZR

Aim

- To assess the safety and efficacy of EBR/GZR in patients with HCV infection and sickle cell anemia, β-thalassemia, or hemophilia von Willebrand disease

Patients and Methods

Figure 2. Study design



Study Design

- Randomized, parallel-group, multisite, placebo-controlled trial (**Figure 2**)
  - Stratification by cirrhosis (yes/no) and disease status (sickle cell anemia vs. β-thalassemia vs. hemophilia/von Willebrand disease)
- 159 patients randomized to immediate treatment with EBR/GZR or deferred treatment where patients received placebo for 12 weeks and then open-label EBR/GZR starting at follow-up week (FW)4

Key Inclusion/Exclusion Criteria

- HCV GT1, 4, or 6 infection
- Patients could be treatment-naïve or treatment-experienced
- IBLD
  - Sickle cell anemia
  - β-thalassemia
  - Hemophilia A/B
  - von Willebrand disease
- Patients with sickle cell anemia and β-thalassemia were required to have hemoglobin levels >7.0 g/dL
- Compensated cirrhosis allowed
  - Liver staging was based on biopsy, FibroScan >12.5kPa within 12 months of enrollment, or a combination of FibroTest score >0.75 and an aspartate aminotransferase/platelet ratio index of >2
  - Patients with a presence or history of ascites, gastric or variceal bleeding, hepatic encephalopathy, or other signs/symptoms of advanced liver disease were excluded
- Patients with HIV/HCV co-infection were enrolled, provided they were receiving stable antiretroviral therapy using tenofovir or abacavir and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine for ≥8 weeks prior to study entry, and had a CD4+ T-cell count >200 cells/mm³ and undetectable plasma HIV-1 RNA

Endpoints

- Primary efficacy endpoint was SVR12
  - HCV RNA <15 IU/mL at FW12 visit
    - HCV RNA analyzed by COBAS® TaqMan® test v2.0 (lower limit of quantification 15 IU/mL)
- Efficacy analysis population
  - The full analysis set included all patients who received ≥1 dose of study drug
- Safety analysis
  - Adverse events (AEs) and discontinuations
  - Laboratory abnormalities
  - Key comparisons between randomized arms (immediate and deferred) during blinded period
- Emergence of viral resistance was assessed in patients who met criteria for virologic failure with HCV RNA >1000 IU/mL
  - Resistance analysis population: patients who achieved SVR12 or did not achieve SVR12 due to meeting virologic failure criteria and had sequencing data available
- Population sequencing sensitivity threshold <20%
  - NS5A: any variant at amino acid positions 28, 30, 31, or 93
  - NS3: any variant at the following amino acid positions: 036, 054, 055, 056, 080, 107, 122, 132, 156, 166, 168, 169, 170, 175

Results

Demographics

- Approximately 50% of patients were treatment-experienced, 24% were cirrhotic, and 6% were HIV co-infected (**Table 1**)
  - In the immediate-treatment group (ITG), 44% had hemophilia A/B or von Willebrand disease, 28% had β-thalassemia, and 19% had sickle cell anemia

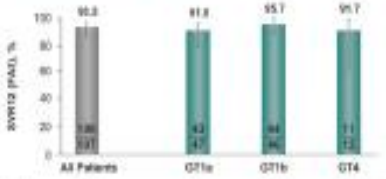
Table 1. Patient demographics

	EBR/GZR (immediate) 12 weeks n = 107	Placebo (deferred) 12 weeks (n = 52)
Sex, n (%)		
Male	80 (74.8)	39 (75.0)
Female	27 (25.2)	13 (25.0)
Race, n (%)		
White	81 (75.7)	40 (76.9)
Black/African American	19 (17.8)	9 (17.3)
Asian	6 (5.6)	3 (5.8)
Other	1 (0.9)	0 (0)
HCV genotype, n (%)		
GT1a	47 (43.9)	19 (36.5)
GT1b	46 (43.0)	23 (51.9)
GT1 other	2 (1.9)	0 (0)
GT4	12 (11.2)	6 (11.5)
GT6	0 (0)	1 (1.9)
Prior treatment history, n (%)		
Naive	53 (49.5)	27 (51.9)
Experienced	54 (50.5)	25 (48.1)
Cirrhosis, n (%)	20 (24.3)	12 (23.1)
HIV co-infected, n (%)	9 (8.6)	4 (7.7)
IL28B CC, n (%)	27 (25.2)	9 (17.3)
Blood disorder, n (%)		
Sickle cell anemia	19 (17.8)	10 (19.2)
β-thalassemia	41 (38.3)	20 (38.5)
von Willebrand disease/hemophilia A/B	47 (43.9)	22 (42.3)

Virologic Response

- SVR12 was 93.8% in the ITG (**Figure 3**)

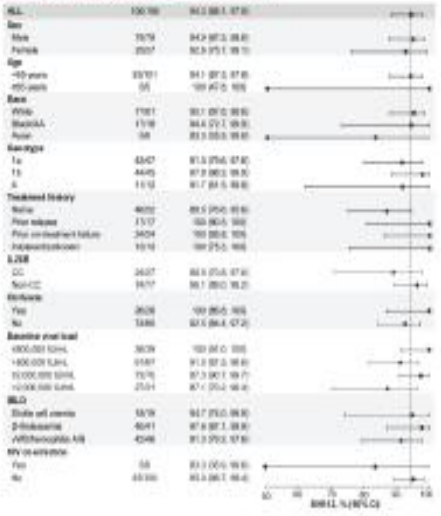
Figure 3. SVR12 primary efficacy analysis (ITG; FAS)



Breakthrough	0	0	0	0
Relapse	3	4	1	1
LTFU/early DC	1*	0	1	0
SVR12 (n/N)	100/107 (93.5%)	45/49 (91.8%)	44/46 (95.7%)	11/12 (91.7%)

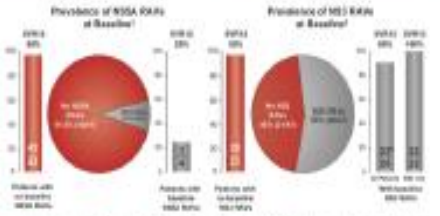
- Subgroup analyses are shown in **Figure 4**

Figure 4. SVR12 subgroup analyses (ITG; mFAS*)



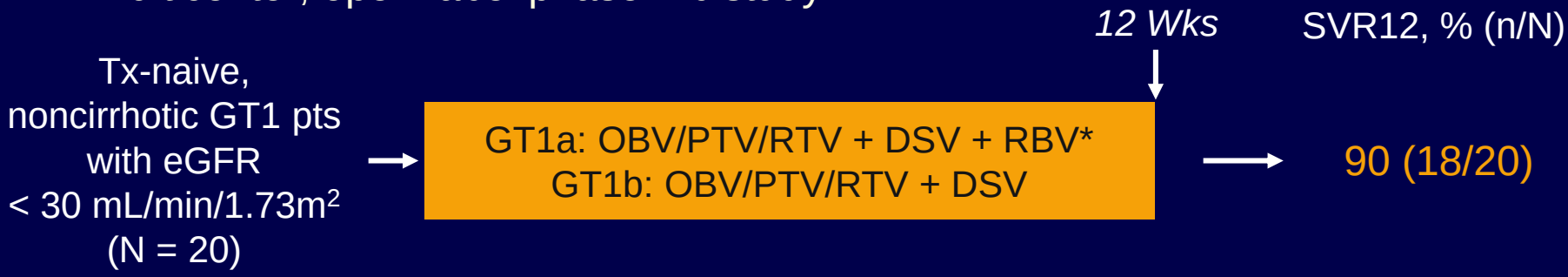
- Among patients with HCV GT1a infection, 43/49 (88%) patients without baseline NS5A resistance-associated variants (RAVs) achieved SVR12 (**Figure 5**)
- NS3 RAVS had no impact on SVR12 in patients with HCV GT1a infection
  - A pooled analysis of the phase 2/3 EBR/GZR clinical program demonstrated that 149/147 (99%) of treatment-naïve patients with GT1a infection and baseline NS3 RAVs but without baseline NS5A RAVs achieved an SVR12, while univariate logistic regression models of treatment-experienced patients with GT1a infection failed to show an association between baseline NS3 RAVs and lower treatment response rates[11]

Figure 5. Impact of baseline NS5A RAVs (panel A) and NS3 RAVs (panel B) on SVR12 in patients with HCV GT1a infection[11]



RUBY-1: OBV/PTV/RTV + DSV ± RBV in Tx-naive, Noncirrhotic GT1 Pts With CKD

- Multicenter, open-label phase IIIb study



*RBV dosed at 200 mg QD and managed as follows: RBV dosed 4 hrs before hemodialysis in hemodialysis pts; wkly Hb assessment in Mo 1 and then Wks 6, 8, 12; RBV suspended in pts with > 2 g/dL decline in Hb in < 4 wks or Hb < 10 g/dL; RBV dosing resumed at clinician's discretion if Hb normalized.

- Key baseline characteristics
  - F3 fibrosis: 20%; eGFR 15-30: 30%; eGFR < 15 or on dialysis: 70%
- 2 pts without SVR12: 1 relapsed, 1 died of LV systolic dysfunction, cardiac arrest after treatment completion
- 69% of pts with GT1a required RBV dose reduction for anemia
  - No discontinuations for anemia
- No cases of grade 3 or higher ALT elevations

Pockros P, et al. AASLD 2015. Abstract 1039.

E DALL’ EASL ALCUNE CONFERME CLINICHE

Hepa-C Registry: Treating HCV in Advanced Liver Disease

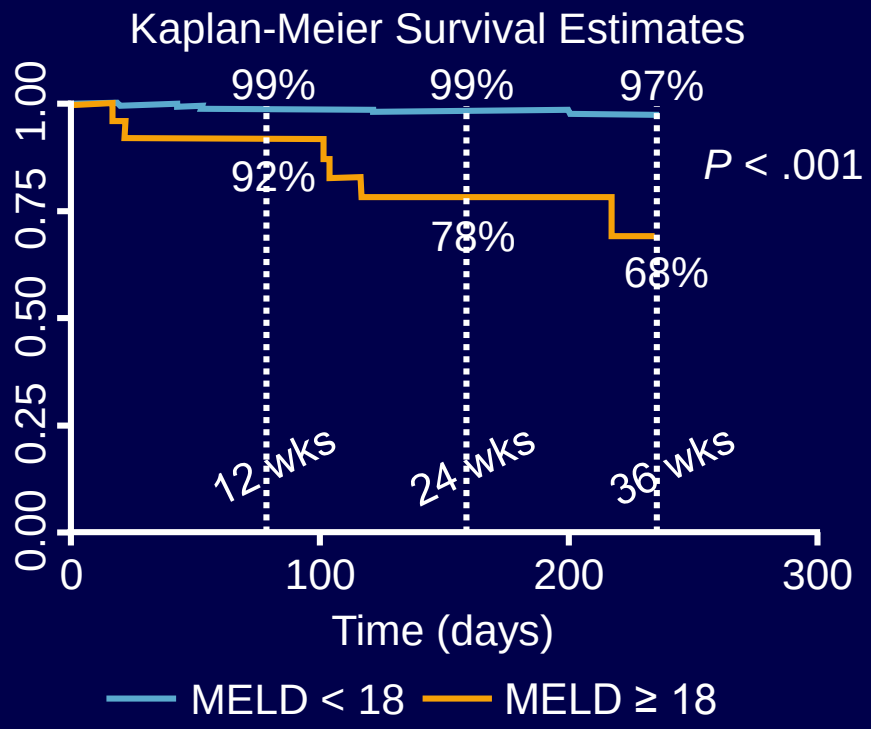
- Retrospective, observational analysis of pts with cirrhosis who were not LT candidates or who were listed for LT but did not receive LT during or for 12 wks after HCV treatment
  - CP A (n = 564; 7% with HCC)
  - CP B/C (n = 175; 10% with HCC)
- Pts treated for 12 or 24 wks with IFN-free regimens, with or without RBV:
  - SMV + SOF (45%)
  - DCV + SOF (22%)
  - LDV/SOF (16%)
  - OBV/PTV/RTV + DSV (10%)
  - SOF (3%)
  - DCV + SMV (2%)
  - OBV/PTV/RTV (2%)

Fernández-Carrillo C, et al. EASL 2016. Abstract GS01.

Hepa-C Registry: SVR, Safety, and Deaths With HCV Tx in Advanced Liver Disease

- SVR12 rate lower for CP B/C vs CP A (78% vs 94%; *P* < .001)
  - SAE incidence higher for CP B/C vs CP A (50% vs 11.7%; *P* < .001)
  - Death rate higher for CP B/C vs CP A (6.4 % vs 0.9%; *P* < .001)

Predictor	SAE		Death (On Study)	
	OR (95% CI)	Multiv. *P* Value	OR (95% CI)	Multiv. *P* Value
CP A vs B/C	**2.16 (1.29-3.64)**	**.004**	**1.73 (0.39-7.64)**	**.034**
MELD	**1.31 (1.2-1.43)**	**< .001**	**1.34 (1.16-1.53)**	**< .001**
MELD ≥ 18	NR	.171	NR	**< .001**
Platelets	0.99 (0.98-0.99)	.008	1.002 (0.99-1.02)	.151
Platelets < 100,000	2.94 (1.8-4.8)	< .001	NR	.711



Fernández-Carrillo C, et al. EASL 2016. Abstract GS01.
Reproduced with permission.

UK Expanded Access: SOF + (DCV or LDV) ± RBV in Decompensated Cirrhosis

- HCV Research UK Database of pts with decompensated cirrhosis
  - Enrolled at/after EAP start and treated: n = 409
    - SVR12: 80.4% (329/409)
  - Enrolled 6 mos before EAP start: n = 261
    - Subsequently treated after EAP start: n = 177

- Lower rate of liver events in treated vs untreated pts

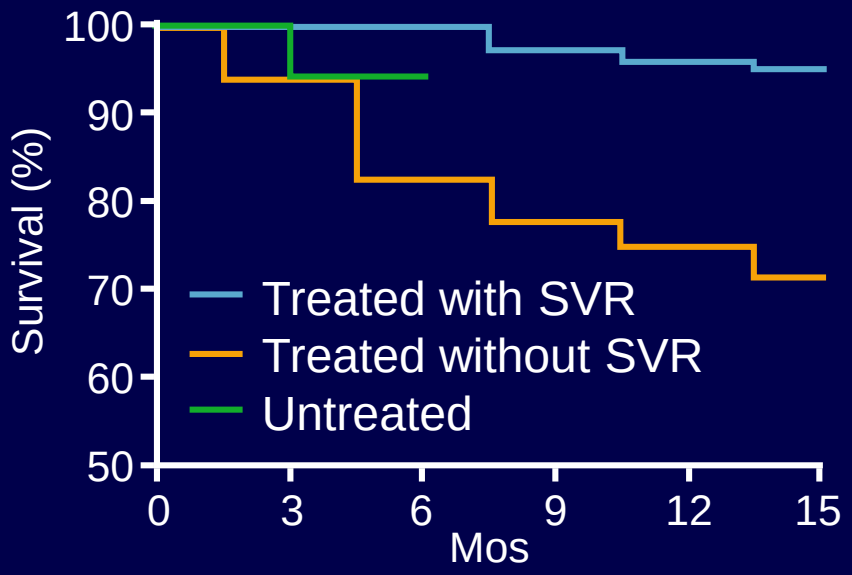
Adverse Events in First 6 Mos, %	Treated (n = 409)	Untreated (n = 261)
Total	52.1	63.6*
Death	3.2	5.7
Decompensation	**17.6**	**28.0***
New HCC	4.6	8.0
Sepsis	6.6	5.7
New OLT	6.6	3.8
Hospital admission	32.5	31.8
MELD worsening by > 2 points	**23.0**	**37.9***

**P* < .05 for treated vs untreated.

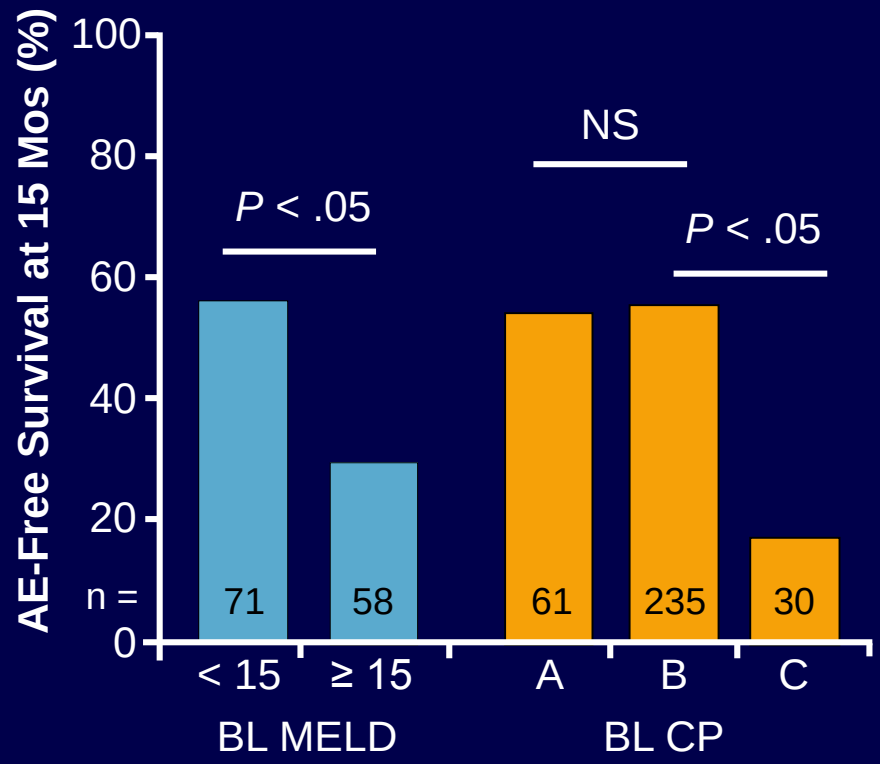
Cheung MCM, et al. EASL 2016. Abstract PS097. Reproduced with permission. Foster GR, et al. J Hepatol. 2016;[Epub ahead of print].

SOF + (DCV or LDV) ± RBV in Decomp. Cirrhosis: AEs and Survival With SVR

- In pts with SVR, AEs most frequent during therapy and decreased with time
- HCV treatment benefit limited to pts with SVR



- AE-free survival significantly greater for CP B vs CP C



Cheung MCM, et al. EASL 2016. Abstract PS097. Reproduced with permission.

HCC Risk Persists After DAA Therapy in Pts With HCV-Related Cirrhosis

- Retrospective analysis of 344 HCV-infected pts with CP A or B cirrhosis treated with DAAs (SVR: 89%)
  - Pts followed for 12-24 wks after treatment completion
  - No HCC at baseline, but previous HCC permitted
- Overall HCC incidence after DAA therapy: 7.6%
  - **In pts without previous HCC: 3.2%**
  - **In pts with previous HCC: 29.0%**

- More advanced liver disease and previous HCC significant risk factors for HCC after DAAs

Factor	No HCC (n = 318)	HCC (n = 26)	*P* Value
CP class B, %	10.1	26.9	.02
Mean liver stiffness, kPa	23.2	28.1	.01
Liver stiffness, n			.005
▪ kPa < 21.3	134	5	
▪ kPa > 21.3	101	16	
Mean platelets, x 1000/mm^3	124.4	102.3	.02
Previous HCC, n			.0001
▪ Yes	42	17	
▪ No	276	9	

Buonfiglioli F, et al. EASL 2016. Abstract LBP506.

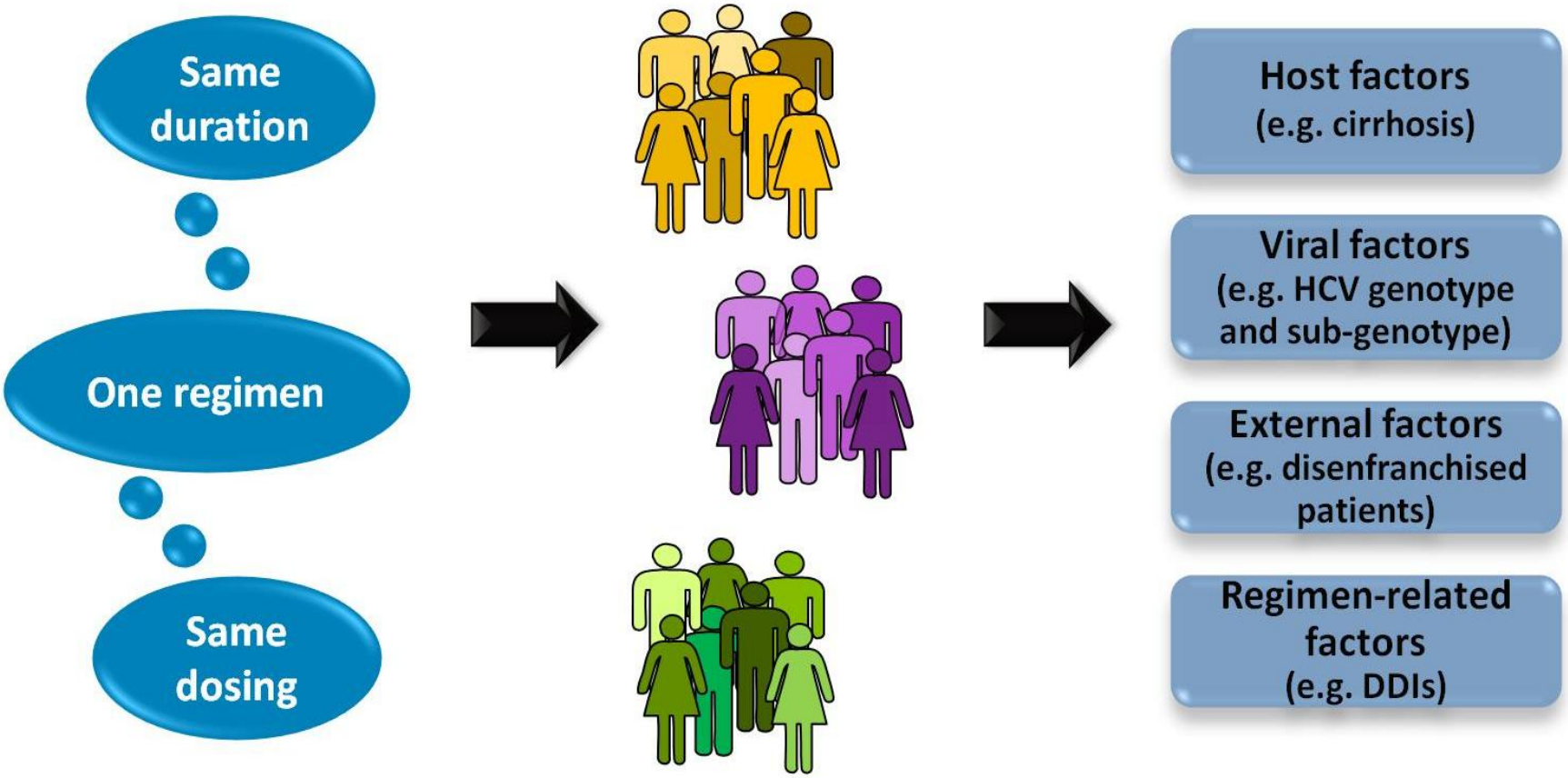
HCC Screening Guidelines

- EASL-EORTC Guidelines 2012[1]: "*Pts at high risk for developing HCC should be entered into surveillance programs. Surveillance should be performed by experienced personnel in all at-risk populations using abdominal ultrasound every 6 mos*"
  - High risk: cirrhosis CP A, B, or C (awaiting LT for CP C); noncirrhotic HBV carriers with active hepatitis or family HCC history; noncirrhotic pts with HCV and F3 fibrosis
- AASLD/IDSA HCV Guidance 2016[2]: "*Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for pts with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR*"

1. EASL-EORTC. J Hepatol. 2012;56:908-943.
2. AASLD/IDSA. HCV Guidance. 2016.

Le difficoltà della real-life:

NON TUTTI I PAZIENTI SONO UGUALI !



NON TUTTI I DAA$_S$ SONO UGUALI !

	Direct-Acting Antiviral					
	NS3[1]	NS3[2]	NS5A[1]	NS5A[2]	Non Nuc NS5B	Nuc NS5B
Efficacy	🟡	🟢	🟢	🟢	🟡	🟢
Resistance Profile	🟡	🟡🟢	🟡	🟡	🔴	🟢
Pangenotypic Activity	🔴	🟡	🟢	🟢	🔴	🟢
Adverse events	🔴	🟢	🟡	🟢	🟡	🟢
Drug-drug interactions	🔴	🟡	🟡	🟡	🟡	🟢

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

[1] 1st generation.
[2] 2nd generation.

Adapted from Schinazi et al, 2013

LE INTERAZIONI FARMACOLOGICHE

(Un problema reale !)

DDIs: Cardiovascular Drugs

		SIM	DCV	SOF	SOF/LDV	3D
Antiarrythmics	Amiodarone	■	●	●	●	●
	Digoxin	■	■	◆	■	■
	Flecainide	■	◆	◆	◆	■
	Vernakalant	◆	◆	◆	◆	■
Antiplatelet & anticoagulants	Clopidogrel	■	■	◆	◆	■
	Dabigatran	■	■	◆	■	■
	Warfarin	◆	◆	◆	◆	◆
Beta blockers	Atenolol	◆	◆	◆	◆	◆
	Bisoprolol	■	◆	◆	◆	■
	Propranolol	◆	◆	◆	◆	◆
Calcium channel blockers	Amlodipine	■	■	◆	■	■
	Diltiazem	■	■	◆	■	■
	Nifedipine	■	■	◆	◆	■
Hypertension & heart failure agents	Aliskiren	■	■	◆	■	●
	Candesartan	◆	◆	◆	◆	■
	Doxazosin	■	◆	◆	◆	■
	Enalapril	◆	◆	◆	◆	■

DAAS e ipolipemizzanti

Table 4C. Drug-drug interactions between HCV DAAs and lipid lowering drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

Sof/led e rosu: +++ rosu, controindicato

3D e atorv, lova, simva: controindicati: +++statine

3D e gemfibrozil: controindicato. +++ dasabuvir : QT lungo

DAAS e stupefacenti

Table 4B. Drug-drug interactions between HCV DAAs and illicit recreational drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

cannabis +
MDMA +
Cocaina + ?

DAAS E FARMACI SNC

Table 4D. Drug-drug interactions between HCV DAAs and central nervous system drugs.

		SIM	DCV	SOF	SOF/ LDV	3D
Anti-depressants	Amitriptyline	•	•	•	•	•
	Citalopram	•	•	•	•	•
	Duloxetine	•	•	•	•	•
	Escitalopram	•	•	•	•	•
	Fluoxetine	•	•	•	•	•
	Paroxetine	•	•	•	•	•
	Sertraline	•	•	•	•	•
	Trazodone	•	•	•	•	•
	Trimipramine	•	•	•	•	•
	Venlafaxine	•	•	•	•	•
Anti-psychotics	Amisulpiride	•	•	•	•	•
	Aripiprazole	•	•	•	•	•
	Chlorpromazine	•	•	•	•	•
	Clozapine	•	•	•	•	•
	Flupentixol	•	•	•	•	•
	Haloperidol	•	•	•	•	•
	Olanzapine	•	•	•	•	•
	Quetiapine	•	•	•	•	•
	Risperidone	•	•	•	•	•

HIV/HCV Drug–Drug Interactions

	SMV + SOF	LDV/SOF	DCV + SOF	OBV/PTV/RTV + DSV	EBR/GZR‡
Atazanavir + RTV	X	≈	≈	√	X
Darunavir + RTV	X	≈	√	≈†	X
Lopinavir/RTV	X	≈	√	X	X
Tipranavir + RTV	X	X	X	X	X
Efavirenz	X	≈	≈	X	X
Rilpivirine	√	√	√	X	√
Etravirine	≈	√	≈	≈	X
Raltegravir	√	√	√	√	√
Elvitegravir + COBI	X	≈	≈	≈	X
Dolutegravir	√	√	√	√	√
Abacavir/lamivudine	√	√	√*	√	√
Maraviroc	√	√	√	≈	≈§
Tenofovir DF/ emtricitabine	√	≈ nephrotoxicity	√	√	√

■ No clinically significant interaction expected ■ Potential interaction may require adjustment to dosage, timing of administration, or monitoring ■ Do not coadminister

*Liverpool Drug Interactions Group. †Ruane PJ, et al. EACS 2015. Abstract LBPS7/1. ‡EBR/GZR [package insert]. § No data.

Adapted from AASLD/IDSA. HCV guidelines. December 2015.

LE RESISTENZE VIRALI
(un reale problema?)

HCV-TARGET: Impact of Baseline RAVs on LDV/SOF and SMV + SOF Efficacy

- Multicenter, prospective, observational cohort study
- Current analysis includes data from pts with GT1 HCV who consented to BL serum collection and were treated with LDV/SOF or SMV + SOF, each ± RBV
  - Sequencing for RAVs with NGS using 10% threshold
  - N = 492 in RAV prevalence analysis; n = 472 in efficacy analysis
- Overall prevalence of BL RAVs: NS3: 45%; NS5A: 13%; NS5B: 8%; ≥ 2 classes: 10%
  - NS3 RAVs more frequent in GT1a vs GT1b; NS5A and NS5B RAVs more frequent in GT1b vs GT1a
  - Overall RAV prevalence similar regardless of cirrhosis status, treatment experience, or liver transplant status

Wang GP, et al. EASL 2016. Abstract PS102.

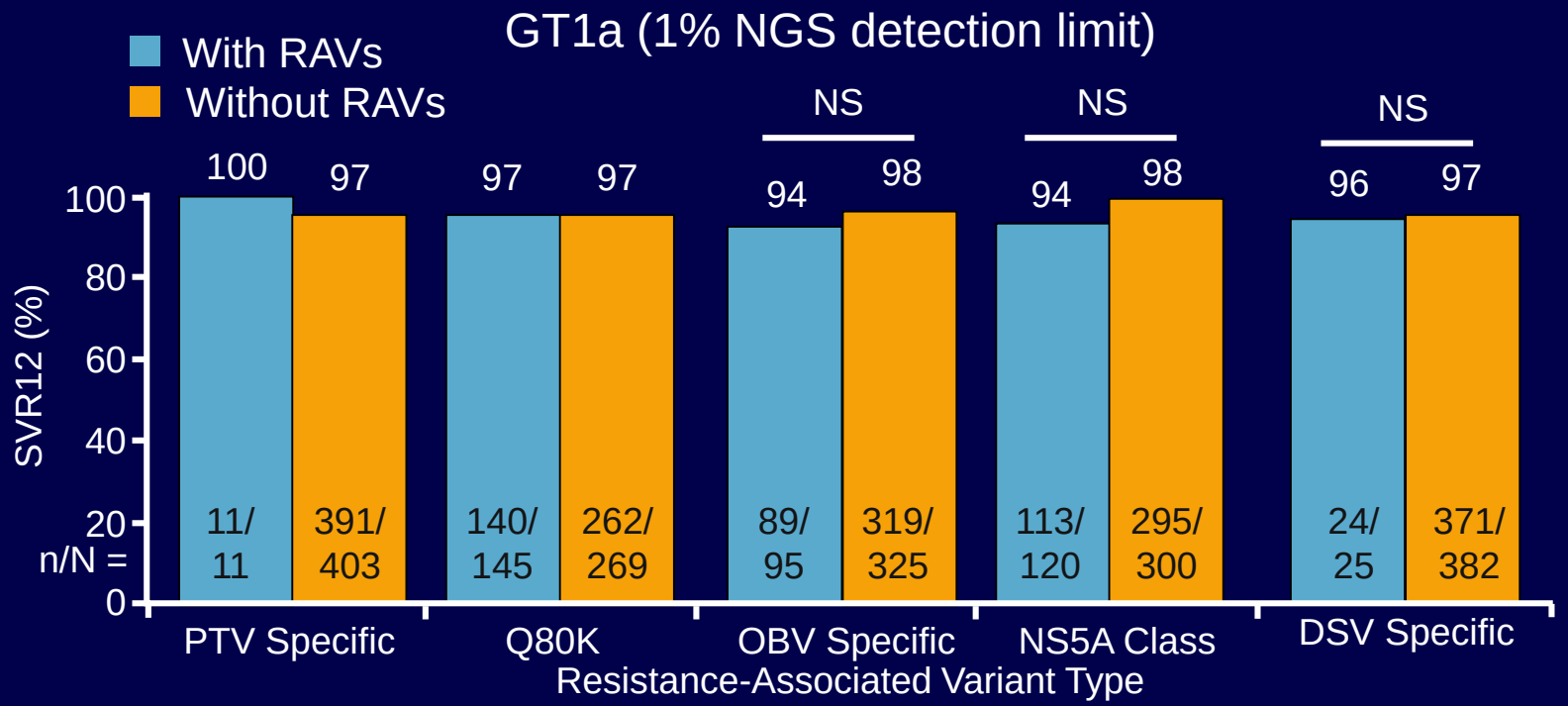
HCV-TARGET: LDV/SOF and SMV + SOF Efficacy Analysis by Baseline RAVs

- **LDV/SOF:** LDV RAVs (aa28, 30, 31, 58, 93) associated with nonsignificant 1% to 7% SVR12 rate differences across pt subgroups
  - Y93 LDV RAV infrequent (4%) but associated with significant decrease in SVR12 rate to LDV/SOF: 96% vs 75% (*P* = .046)
- **SMV + SOF:** SMV RAVs (aa80, 122, 155, 168, 170) associated with nonsignificant 0% to 9% SVR12 rate difference across pt subgroups

Wang GP, et al. EASL 2016. Abstract PS102.

Impact of Baseline RAVs on Efficacy of OBV/PTV/RTV + DSV ± RBV

- Analysis of data from 5 phase III trials using NGS; all pts treated with OBV/PTV/RTV + DSV ± RBV **on label** (based on subgenotype, previous treatment, and cirrhosis)
  - SVR12 rate 100% in pts with GT1b HCV, regardless of BL RAVs



Sarrazin C, et al. EASL 2016. Abstract LBP503.
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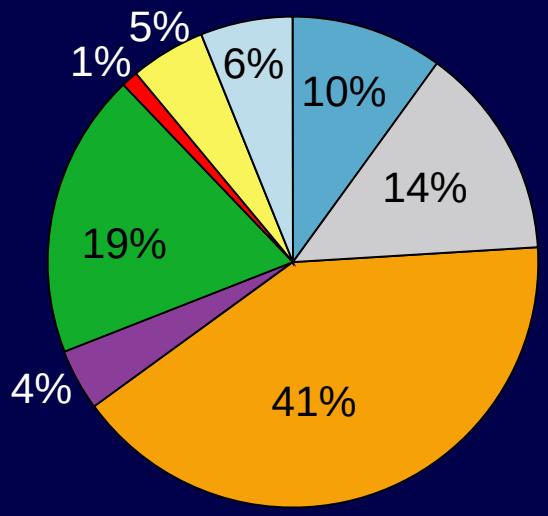
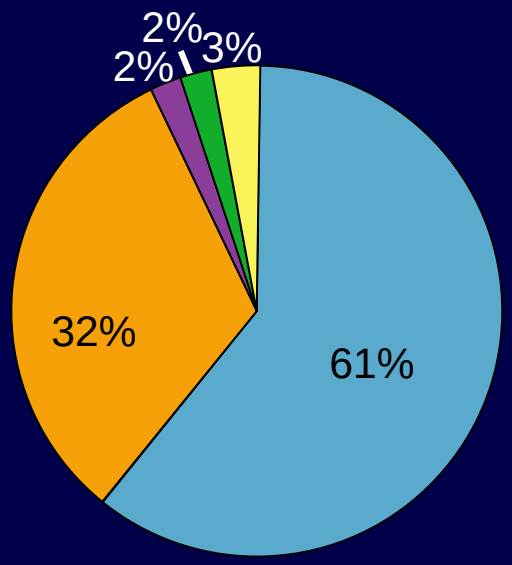
Real-World Data on Resistance and HCV Retreatment After DAA Regimen Failure

- Data from large German resistance database: N = 3549
  - 9% of pts with IFN-free DAA regimen failure (n = 310; excludes pts with GT1 HCV treated with SOF + RBV)
- Resistance analysis for drug class-specific RAVs with > 2-fold EC_{50} increase in 195 GT1 and 69 GT3 pts

GT1 (n = 195): 90% With RAVs



GT3 (n = 69)*: 39% With RAVs



*Previous GT3 tx: SOF + RBV (n = 33); DCV + SOF ± RBV (n = 20); LDV/SOF ± RBV (n = 15); SMV + SOF ± RBV (n = 1).

Vermehren J, et al. EASL 2016. Abstract PS103.

Real-World Data: Resistance-Based HCV Retreatment After DAA Regimen Failure

Previous DAA Regimen Failure	Retreatment Regimen	SVR12
GT1: SMV + SOF ± RBV	**NS5A inhibitor–containing regimen**	**91%**
	▪ LDV/SOF ± RBV 12 wks	8/8
	▪ LDV/SOF ± RBV 24 wks	9/10
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	3/3
	▪ OBV/PTV/RTV + DSV + RBV 24 wks	0/1
GT1: DCV or LDV + SOF ± RBV	**PI-containing regimen**	**86%**
	▪ SMV + SOF ± RBV 12 wks	2/2
	▪ SMV + SOF ± RBV 24 wks	1/1
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	3/4
GT3: SOF + RBV	**NS5A inhibitor–containing regimen**	**100%**
	▪ DCV + SOF + RBV 12 wks	2/2
	▪ DCV + SOF ± RBV 24 wks	4/4
	▪ LDV/SOF + RBV 24 wks	1/1

Vermehren J, et al. EASL 2016. Abstract PS103.

ULTIMA RACCOMANDAZIONE

nessuno di questi farmaci può essere usato in monoterapia

il numero/tipo di farmaci e la durata complessiva della terapia in grado di garantire la massima efficacia al ciclo terapeutico dipendono:

a) dal genotipo infettante (e nel genotipo 1, dal sottotipo);

b) dallo stadio della malattia epatica (presenza o meno di cirrosi);

c) nei pazienti già trattati, dalla risposta a precedenti trattamenti (in particolare nel caso dei pazienti con cirrosi)

A fronte dei tassi estremamente elevati di risposta, potrebbe essere inferiore nei pazienti con cirrosi, potendo in questo sottogruppo variare, a secondo del regime terapeutico, dal 60 al 90%. Sarà quindi opportuno:

a) informare il paziente del rischio di recidiva epatitica (che potrebbe causare un deterioramento anche rapido dell'epatopatia, in funzione dell'entità della recidiva stessa e dello stadio della cirrosi);

b) programmare un adeguato monitoraggio post-terapia in funzione dello stadio della cirrosi che sia in grado di cogliere tempestivamente la ripresa della replicazione virale;

c) pianificare un "trattamento di *rescue*".

nei pazienti con cirrosi Child B la malattia di fegato può progredire in corso di trattamento nonostante un'efficace azione antivirale: deve quindi essere mantenuto uno stretto monitoraggio della funzionalità epatica.

Where we go: The Future
Ten Commandments for the Magic Drug

1. HIGH **E**FFICACY
2. LOW **R**ESISTANCE (high genetic barrier)
3. FOR **A**LL-GENOTYPES
4. SHORT **D**URATION
5. TOLERAB**I**LITY
6. PHARMA**C**OKINETIC (Low pill burden)
7. ONLY OR**A**L REGIMEN (IFN free)
8. DRUGS IN**T**ERACTION
9. AVAILABLE : C**I**RRHOSIS, ELD, HIV-HCV…
10. C**O**ST REDUCTIO**N** (access program)

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SOD Malattie Infettive e Tropicali
-dati aggiornati al 11 settembre 2016-

252 pazienti affetti da epatite cronica HCV-correlata trattati con DAAs

CATEGORIA AIFA

- *CIRROSI EPATICA*: n. **149**
- *TRAPIANTO EPATICO*: n. **1**
- *MANIFESTAZIONI EXTRAEPATICHE*: n. **17**
- *FIBROSI EPATICA F3*: n. **85**

COINFEZIONE HIV

- *MONOINFETTI HCV*: n. **193**
- *COINFETTI HCV/HIV*: n. **59**

GENOTIPO

- *Gen 1a*: n. **58**
- *Gen 1b*: n. **96**
- *Gen 2*: n. **20**
- *Gen 3*: n. **54**
- *Gen 4* : n. **24**

DAA

- *SOF + RBV*: n. **14**
- *SOF + SIM*: n. **46**
- *SOF + DCV*: n. **65**
- *SOF + LDV*: n. **80**
- *2D*: n. **10**
- *3D*: n. **37**

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I COINFETTI

59 pazienti affetti da coinfezione HCV-HIV

- **n. 7 Fibrosi avanzata F3**
- **n. 50 Cirrosi epatica F4**
  - → **n. 47 (94%) Child Pugh A**
  - → **n. 3 (6%) Child Pugh B**
  - → **Punteggio MELD medio = 8,2**
- **n. 2 Manifestazioni extra-epatiche**

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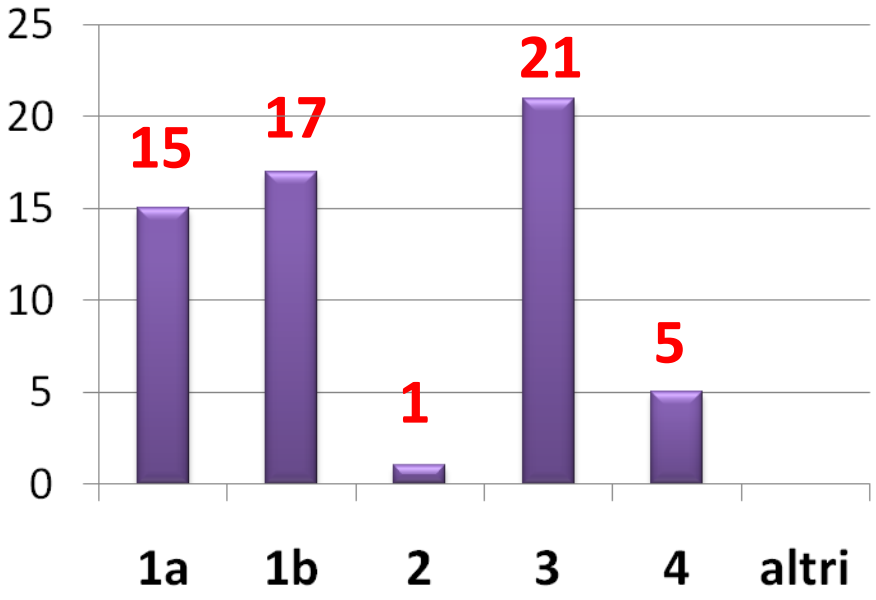
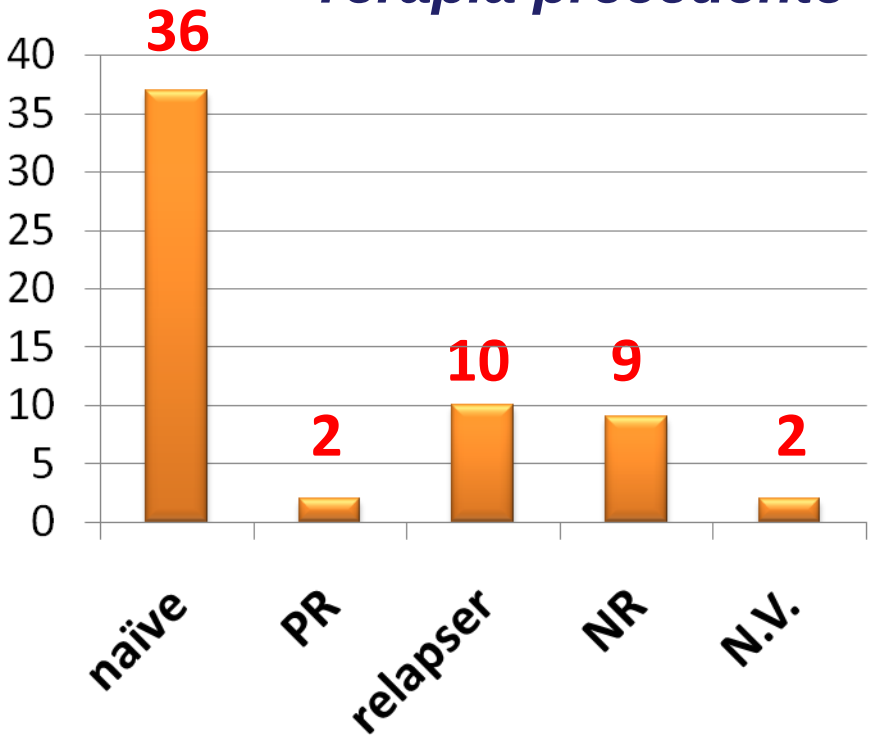
I COINFETTI

Genotipo



Terapia precedente



Dei 23 pazienti *experienced*:

→ **n.21 con *Standard of Care* (SoC)**
→ **n.1 con PEG-IFN + RBV + PI prima generazione**
→ **n.1 con DAAs (3D)**

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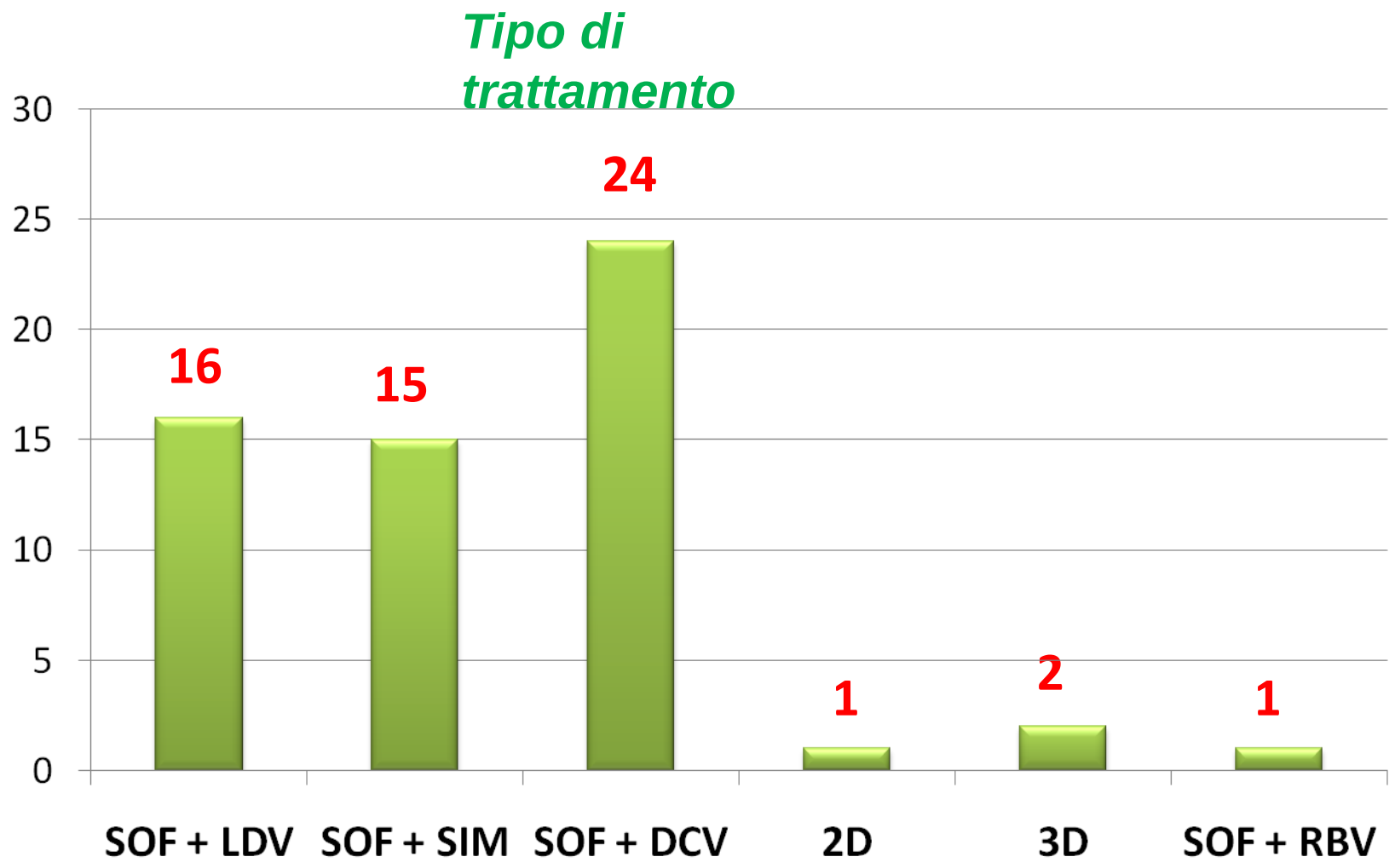
I COINFETTI



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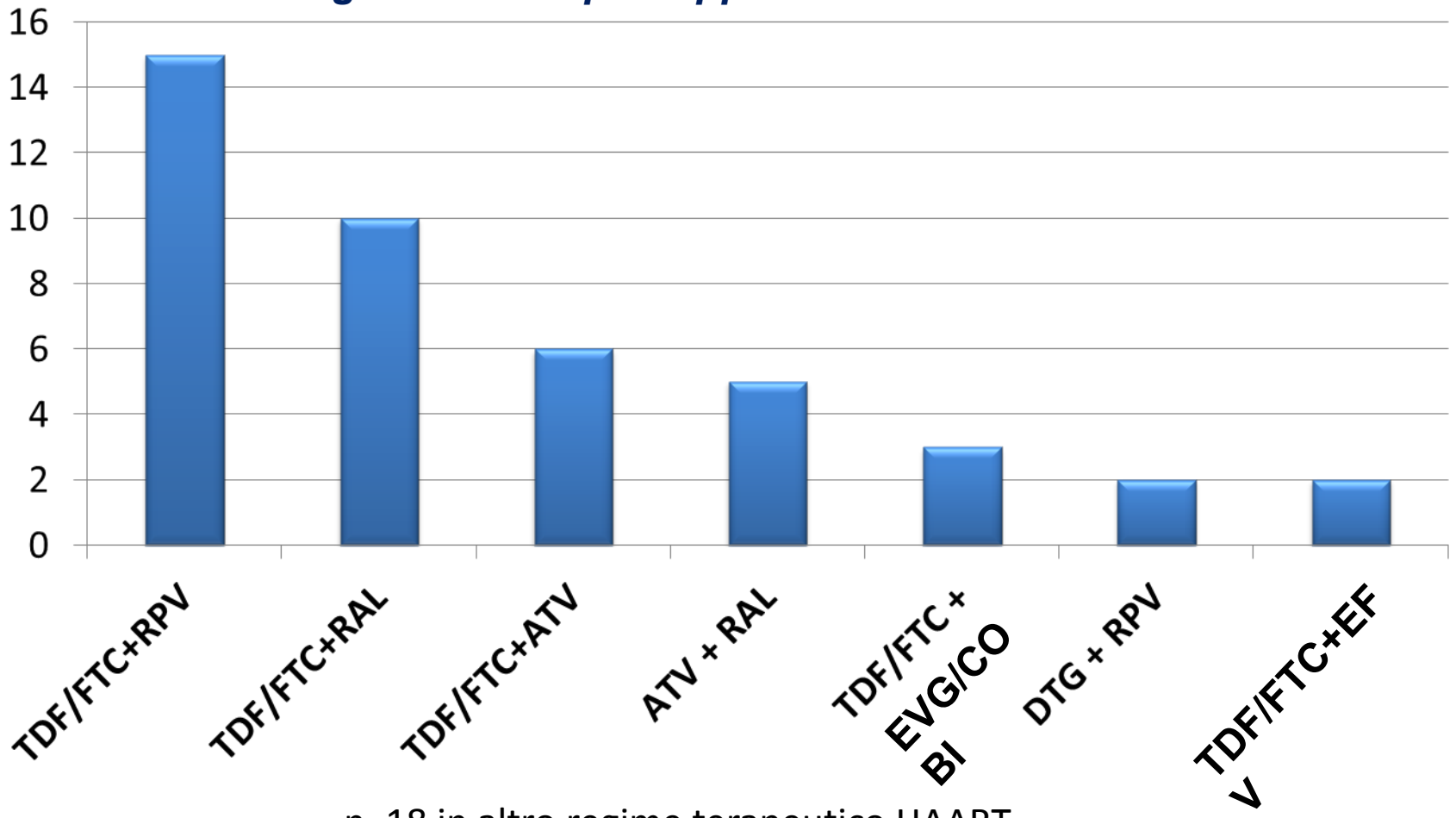
I COINFETTI

Regimi HAART più rappresentati all'inizio trattamento con DAAs



n. 18 in altro regime terapeutico HAART

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I COINFETTI

Modifiche HAART

In **17 pazienti** si è resa necessaria modifica della HAART per incompatibilità/interazione con il DAA per la terapia anti-HCV

CAUSA DELLA INCOMPATIBILITA'	MODIFICA HAART
• n. 12 **PI boosterato**	• n. 8 casi **PI -> INIBITORE INTEGRASI** • n. 2 caso **PI -> NNRTI** • n. 2 caso **PI -> altro agente**
• n. 3 **NNRTI**	• n. 2 casi **CAMBIO NNRTI** • n. 1 caso **NNRTI -> NRTI**
• n. 2 **NRTI**	• n. 1 casi **NNRTI** • n. 1 caso **INI**

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I COINFETTI

Risultati

- n. **38** **SVR12**
- n. **17** ***ongoing***
- n. **2** **decessi**

- ***n. 2 FALLIMENTI VIROLOGICI***

↓

BKT all'EOT
Gen. 3
F4
SOF + DCV per 24w
SENZA RBV (TALASSEMICO)

RELAPSE alla 12w FU
Gen. 1b
F4
3D per 24w

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I COINFETTI

Risultati

NESSUN CASO DI SOSPENSIONE DEL TRATTAMENTO
NESSUN CASO DI SCOMPENSO EPATICO

n.1 caso di SAE: **infarto acuto del miocardio**

n.6 casi di reazioni avverse minori: *insonnia, depressione, cefalea, mialgie…*

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LA POPOLAZIONE EMOFILICA

12 pazienti totali affetti da EMOFILIA trattati con DAAs

CATEGORIA AIFA

- *CIRROSI EPATICA*: n. **8**
- *FIBROSI EPATICA F3*: n. **4**

COINFEZIONE HIV

- *MONOINFETTI HCV*: n. **7**
- *COINFETTI HCV/HIV*: n. **5**

GENOTIPO

- *Gen 1a*: n. **7**
- *Gen 1b*: n. **5**

DAA

- *SOF + SIM*: n. **5**
- *SOF + LDV*: n. **5**
- *3D*: n. **2**

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LA POPOLAZIONE EMOFILICA

Risultati

- n. **8** **in SVR12**
- n. **4** ***ongoing***

NESSUN CASO DI SOSPENSIONE DEL TRATTAMENTO
NESSUN CASO DI SCOMPENSO EPATICO
NESSUNA REAZIONE AVVERSA SEGNALATA

EASL 2016, poster SAT-144

High SVR rates with SMV+SOF in HCV GT1 and GT4 patients with cirrhosis or advanced fibrosis: a real practice analysis from a large regional database in Tuscany, Italy.

Elena Salomoni[1], Elena Gianni[2], Laura Gragnani[3], Filippo Oliveri[4], Maurizia R. Brunetto[4], Sauro Luchi[5], Dario Bartolozzi[1], Paolo Forte[2], Spartaco Sani[6], Pierluigi Blanc[7], Rodolfo Sacco[8], Anna Linda Zignego[3], Andrea De Luca[9], Danilo Tacconi[10], Donatella Aquilini[11], Francesco Menichetti[12], Corrado Catalani[13], Cesira Nencioni[14], Paola Carrai[15], Silvia Chigiotti[14] and Piero Colombatto[4] *on behalf of* ***Epatologi Toscani*** *and* ***SIMIT Toscana***

[1]Malattie Infettive e Tropicali, [2]Gastroenterologia 2, [3]Centro MASVE - Medicina Sperimentale e Clinica, Azienda Ospedaliera Universitaria Careggi, Florence, [4]Epatologia, Azienda Ospedaliera Universitaria Pisana, Pisa, [5]Malattie Infettive e Epatologia, Ospedale San Luca, Lucca, [6]Malattie Infettive, Spedali Riuniti di Livorno, Livorno, [7]Malattie Infettive e Tropicali, Ospedale Santa Maria Annunziata, Florence, [8]Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliera Universitaria Pisana, Pisa, [9]Malattie Infettive Universitarie, Azienda Ospedaliera Universitaria Senese, Siena, [10]Malattie Infettive, Ospedale S. Donato, Arezzo, [11]Malattie Infettive, Ospedale di Prato, Prato, [12]Malattie Infettive, Azienda Ospedaliera Universitaria Pisana, Pisa, [13]Malattie Infettive, Ospedale del Ceppo, Pistoia, [14]Malattie Infettive, Ospedale Misericordia, Grosseto, [15]Chirurgia Epatica e del Trapianto di Fegato, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

ICAR 2016, poster

High rates of tolerability and efficacy of second generation Direct Acting Antivirals (DAA) regimens in a real life population of HCV/HIV co-infected patients with cirrhosis or advanced fibrosis from a large regional database in Tuscany.

Salomoni Elena[1], Valoriani Beatrice[2], Pozzi Marco[1], Sani Spartaco[3], Cinelli Roberta[3], Menichetti Francesco[4], Iapoce Riccardo[4], Rossetti Barbara[2], Nencioni Cesira[5], Tacconi Danilo[6], Nerli Alessandro[7], Blanc Pierluigi[8], Bartolozzi Dario[1] and De Luca Andrea[2,9] *on behalf of* ***SIMIT Toscana***

[1]Malattie Infettive e Tropicali, Azienda Ospedaliero-Universitaria Careggi, Firenze, [2] UOC Malattie Infettive Universitarie, AOU Senese, Siena, [3] Malattie Infettive, Spedali Riuniti di Livorno, Livorno, [4] Malattie Infettive, Azienda Ospedaliero-Universitaria pisana, Pisa [5] Malattie Infettive, Ospedale Misericordia, Grosseto, [6] Malattie Infettive, Ospedale S. Donato, Arezzo, [7] Malattie Infettive, Ospedale di Prato, Prato, [8] Malattie Infettive e Tropicali, Ospedale Santa Maria Annunziata, Firenze, [9]Dip Biotecnologie Mediche, Università di Siena, Siena

E quindi ….


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FORSE … MA CON LE NORMATIVE ATTUALI RIMANGO
IN NETTO CONFLITTO
DI INTERESSI CON LA REALTA’

GRAZIE DELL’ATTENZIONE