British HIV Association
BHIVA

Dr Janice Main

Imperial College Healthcare NHS Trust, London

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Janice Main	None
Date	**October 2014**

HEPATITIS C TREATMENT: FROM BENCH TO BEDSIDE

TREATMENT

Interferon, peginterferon, ribavirin +/- telaprevir/boceprevir

Side effects
Interactions
Disappointing results in HIV coinfection

TREATMENT

NOW
Oral only therapies
Directly acting antivirals (DAA)
Recognition of host and viral factors

Early access programme

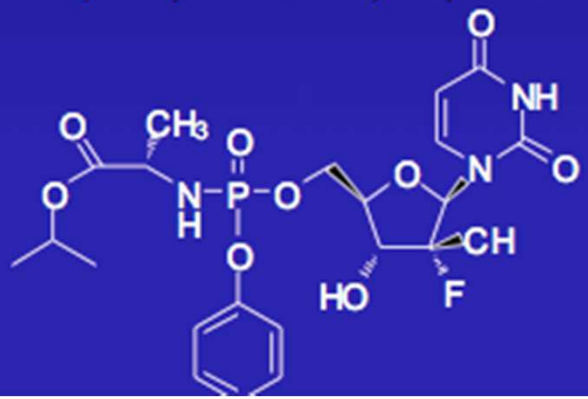
Global/WHO issues

EASL 2011
AASLD 2011

PSI-7977: ELECTRON
Interferon is not required for Sustained Virologic Response in Treatment-Naïve Patients with HCV GT2 or GT3

EJ Gane, CA Stedman, RH Hyland, RD Sorensen, WT Symonds, RG Hindes, MM Berrey

New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; Gastroenterology Department, Christchurch Hospital, Christchurch, New Zealand; Pharmasset, Inc., Princeton, NJ, United States.



PSI-7977 ELECTRON
100% concordance of SVR12 with SVR24

Time Wk	PSI-7977 RBV 12 weeks PEG		PSI-7977 RBV 8 weeks PEG		PSI-7977 RBV 4 weeks PEG		PSI-7977 RBV NO PEG	
	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
2	9/11	82	7/8	88	8/9	89	8/10	80
4	11/11	100	10/10	100	9/9	100	10/10	100
8	11/11	100	10/10	100	9/9	100	10/10	100
12	11/11	100	10/10	100	9/9	100	10/10	100
SVR4	11/11	100	10/10	100	9/9	100	10/10	100
SVR8	11/11	100	10/10	100	9/9	100	10/10	100
SVR12	11/11	100	10/10	100	9/9	100	10/10	100
SVR24	6/6	100	5/5	100	5/5	100	4/4	100

SOFOSBUVIR
genotype 2 and 3

TREATMENT	sofosbuvir 12 weeks n =10	Sofosbuvir ribavirin 8 weeks Plus PEG 8 weeks n =10
SVR n (%)	6 (60%)	9/9 (100%)

SOFOSBUVIR
genotype 1

TREATMENT	prev NR sofosbuvir ribavirin 12 weeks n = 10	treatment naïve Sofosbuvir ribavirin 12 weeks n = 25
SVR n (%)	1 (10%)	21 (84%)

PHARMA ISSUES

COSTS

Pharmasett (82 employees, net loss $91.2 million)

taken over by Gilead ($11 billion)

Sofosbuvir $1000/day

"SOVALDI –SO EXPENSIVE"

Products from different companies……

NEW TRIAL DESIGNS

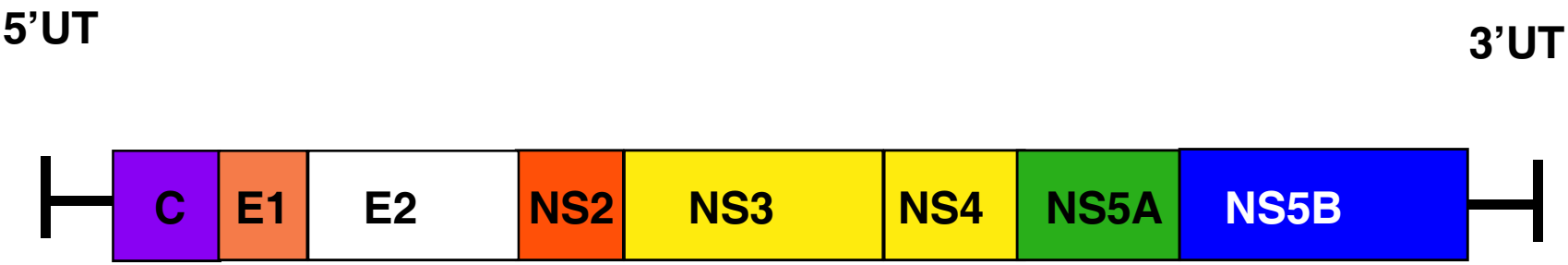
SVR12

Interferon free

Shorter treatment courses

Response guided therapy (RGT)

HEPATITIS C



NS3/4 serine protease, RNA helicase

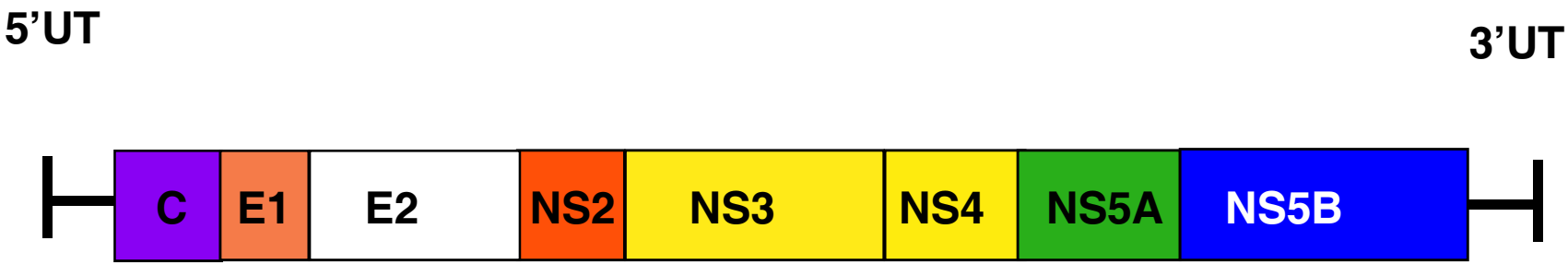
NS5A RNA dependent RNA polymerase

NS5B RNA dependent RNA polymerase

5'UTR antisense oligos

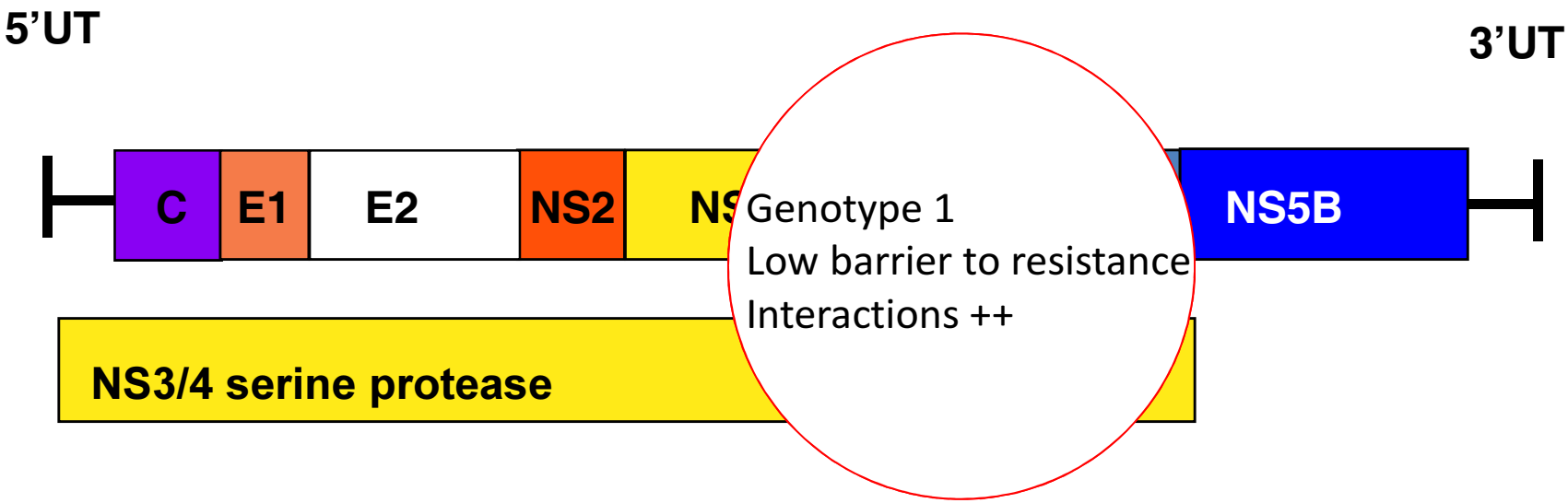
3'UTR ribozymes

HEPATITIS C – PI's

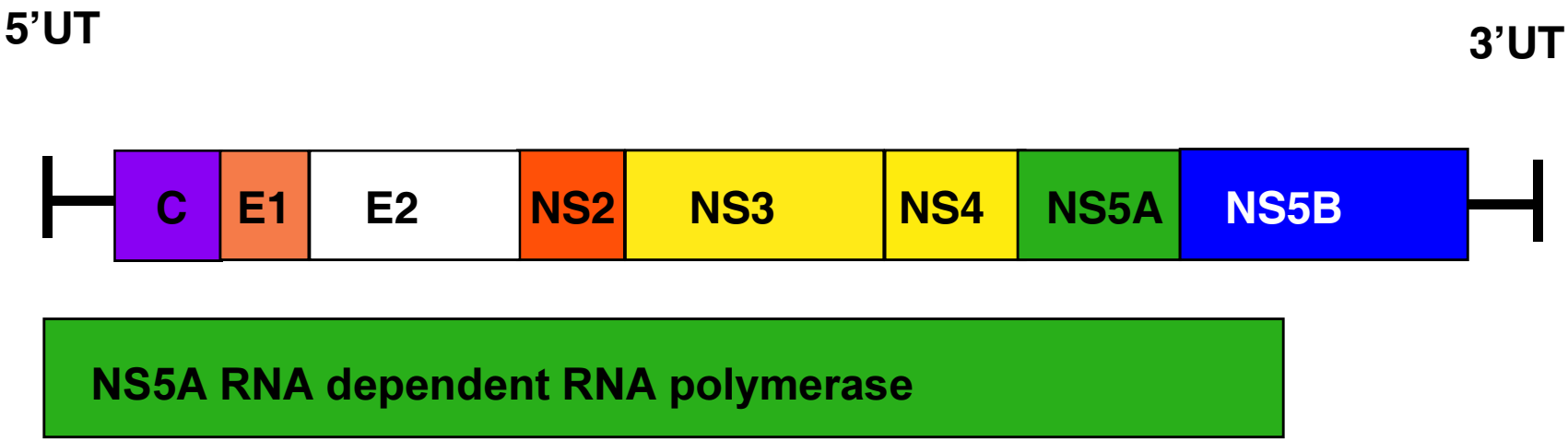


telaprevir
boceprevir
simeprevir
asunaprevir
ABT-450/r
MK5172
vaniprevir
faldaprevir
deleoprevir

HEPATITIS C –PI's

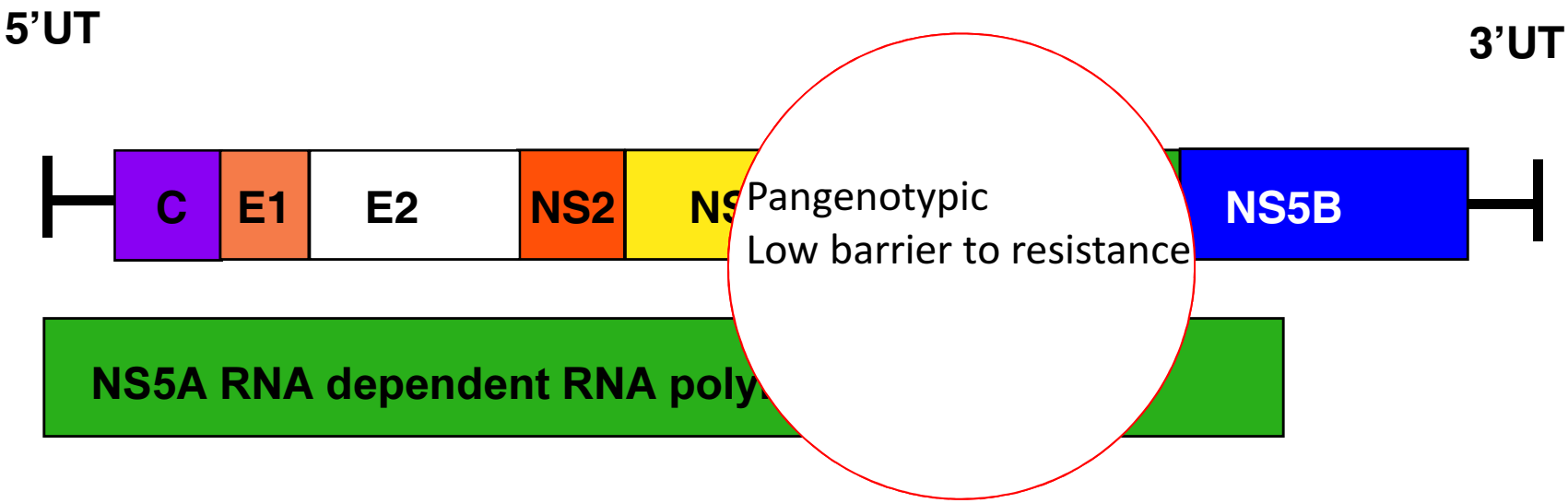


HEPATITIS C – NS5A inhibitors

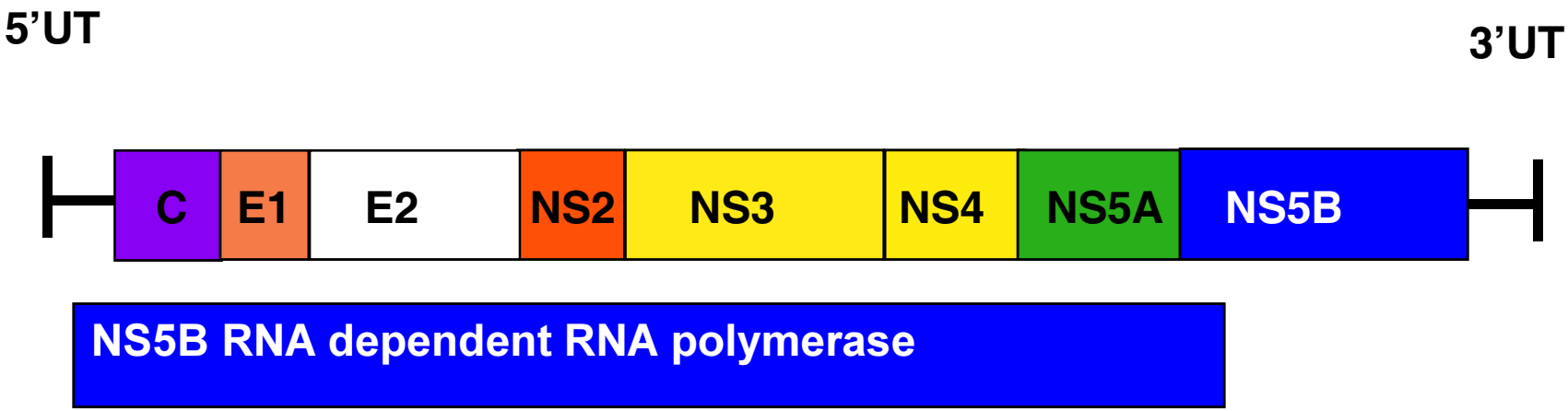


ledipasvir
daclatasvir
ombitasvir (ABT- 267)
MK8742

HEPATITIS C – NS5A inhibitors

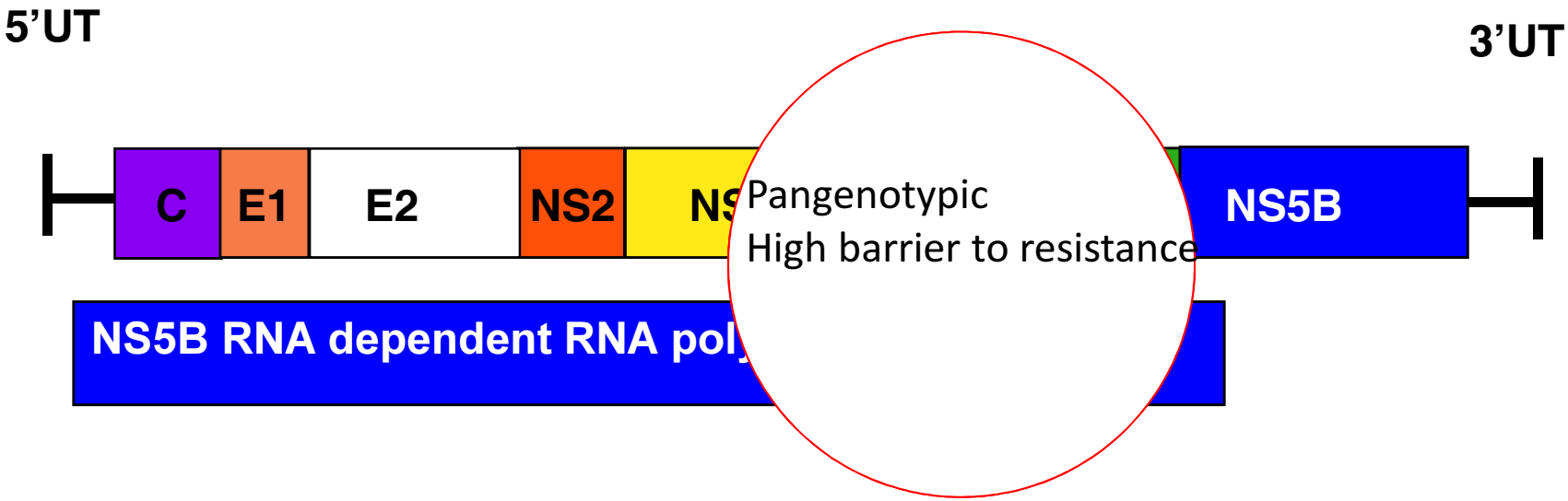


HEPATITIS C –NS5B inhibitors
NA's

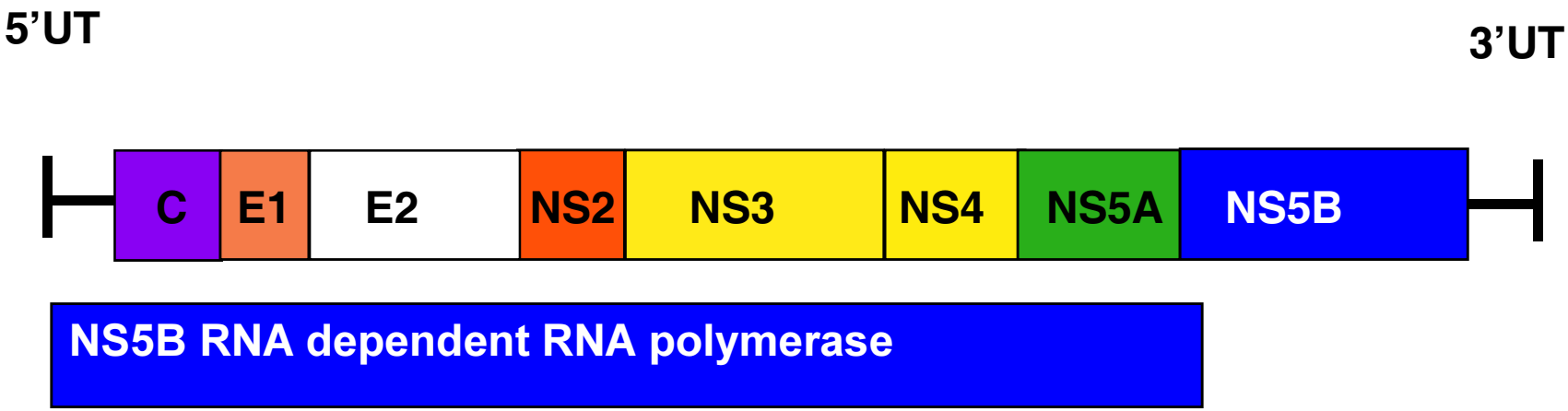


sofosbuvir

HEPATITIS C –NS5B inhibitors
NA's

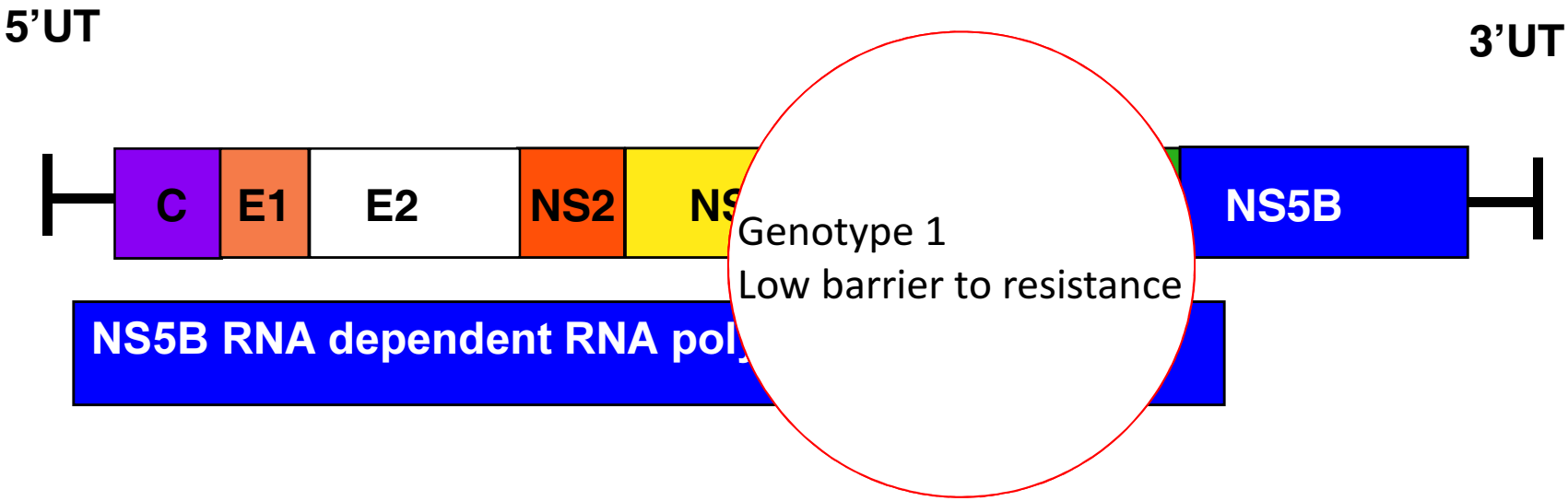


HEPATITIS C-NS5B inhibitors
NNA's



dasabuvir (ABT-333)
BMS- 791325
ABT-072
deleobuvir

HEPATITIS C-NS5B inhibitors
NNA's



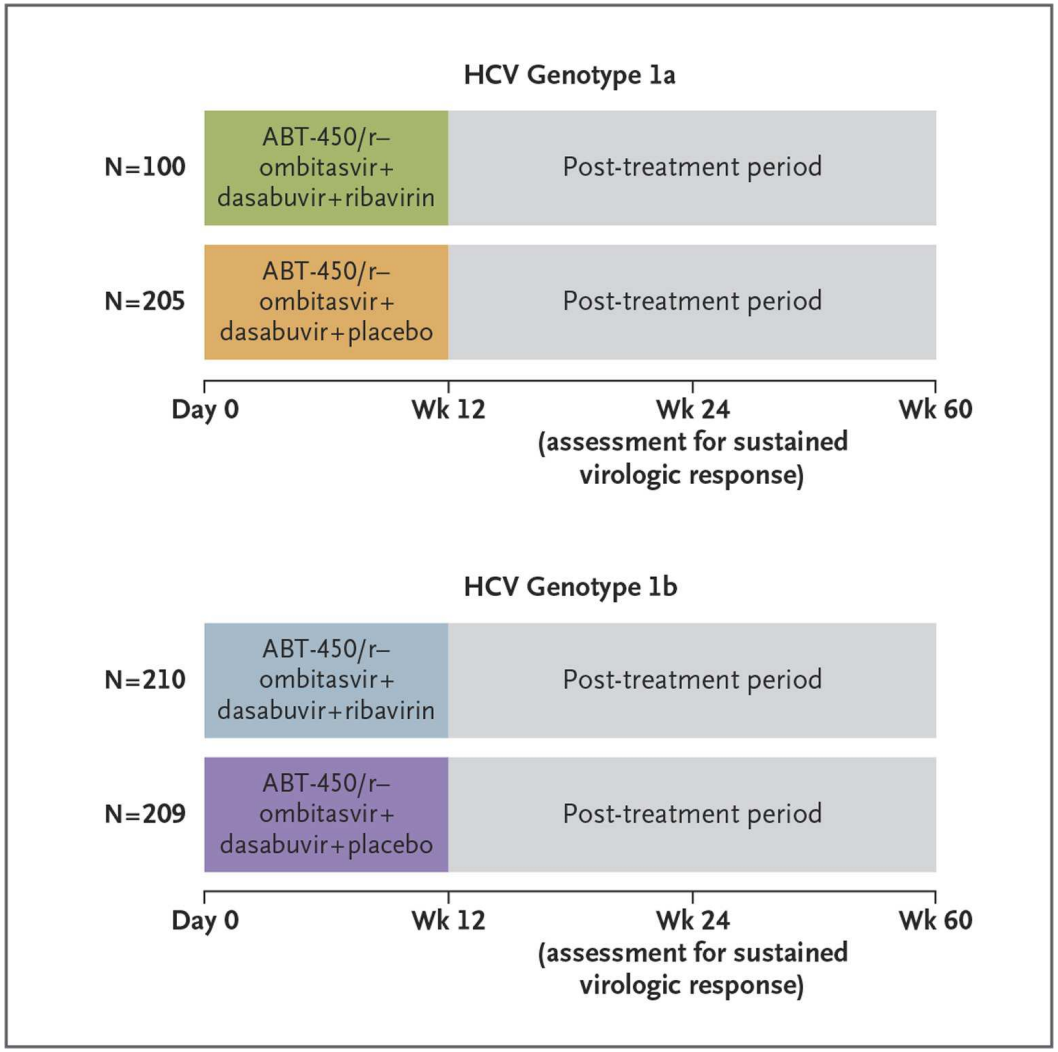
Original Article

ABT-450/r–Ombitasvir and Dasabuvir with or without Ribavirin for HCV

Ferenci P et al, NEnglJMed, 2014

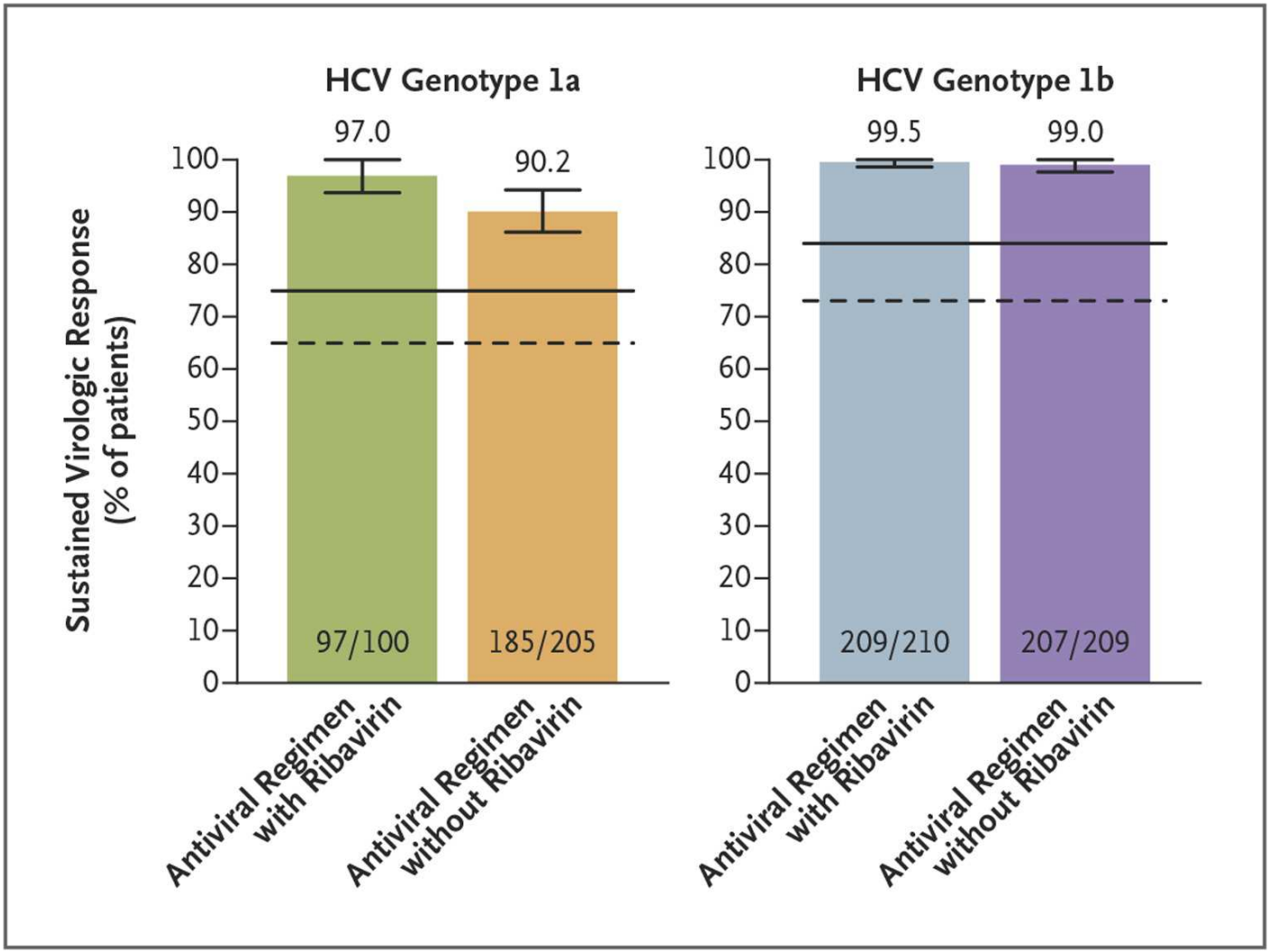
The NEW ENGLAND JOURNAL of MEDICINE

Study Designs.



The NEW ENGLAND JOURNAL of MEDICINE

Sustained Virologic Response at 12 Weeks after the End of Treatment.



Ferenci P et al. N Engl

HIV/HCV COINFECTION

Interferon based
Immunomodulatory > antiviral

PI's/IFN/RBV

DAA's +/- RBV +/- IFN

Drug interactions…..

ERADICATE: SOF/LDV in ARV-Treated and Untreated HCV/HIV-Coinfected Patients

- Single-arm phase II trial
- ARV use in 37 ARV-treated patients: efavirenz (41%), raltegravir (27%), rilpivirine (21%), rilpivirine and raltegravir (8%), efavirenz and raltegravir (3%)
- Median baseline CD4+ count: ARV treated 576 cells/mm^3 (range: 113-1612), ARV untreated 687 cells/mm^3 (range: 319-1287)
- SVR12 in ARV-treated patients: 100%; not yet available in ARV-untreated patients
- No clinically significant changes in HIV-1 RNA or CD4+ cell count
- SOF/LDV well tolerated, no discontinuations or grade 4 AEs

Sofosbuvir/ledipasvir 400/90 mg FDC tablet once daily.

Osinusi A, et al. EASL 2014. Abstract O14. Reproduced with permission.

C-WORTHY (genotype 1)

- MK-5172 (PI)
- MK-8742 (NS5A)
- +/- RBV

12 weeks

HIV pos n= 59

Sulkowski et al, EASL 2014

C-WORTHY (genotype 1)

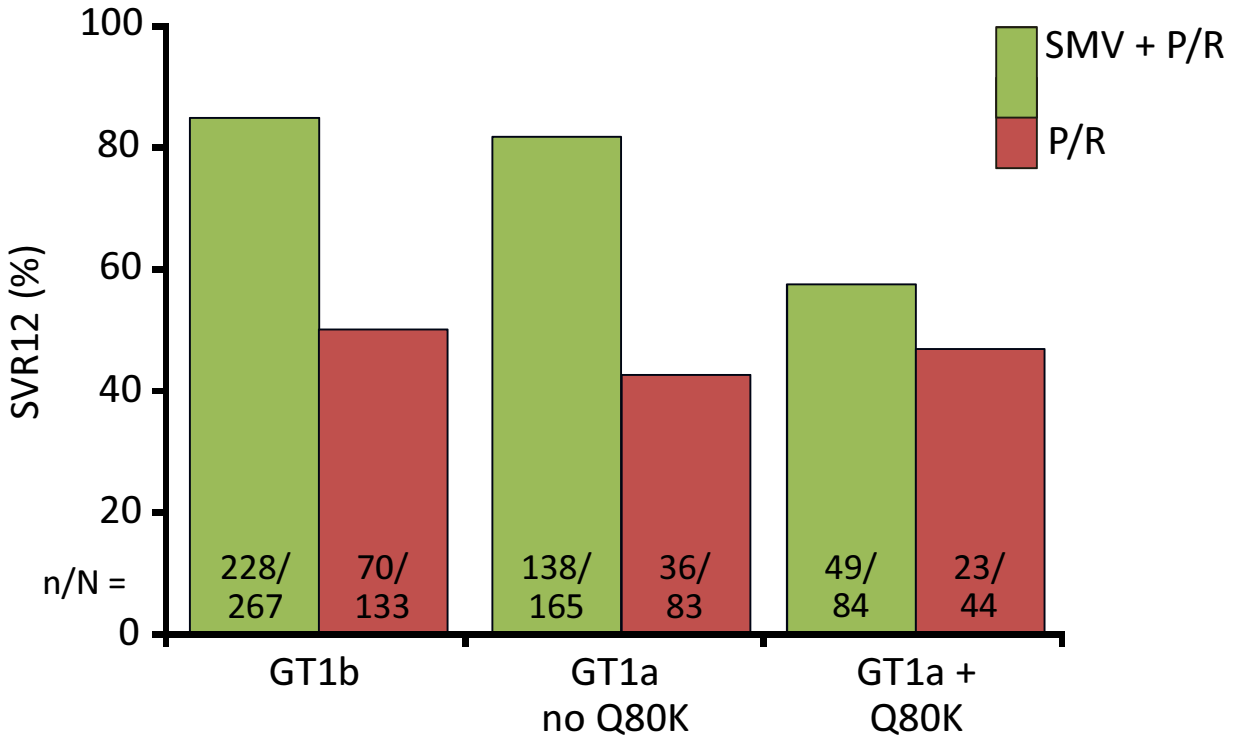
- SVR4
- 90% no RBV
- 97% with RBV

Simeprevir (TMC435) with Peginterferon/Ribavirin in Patients Coinfected with HCV Genotype-1 and HIV-1: A Phase III Study

Dieterich D et al, Clin Infect Dis 2014
n = 106, RGT
Triple therapy 12 weeks
Treatment naïve (non-cirrhotic), prior relapsers –RGT PR 24 or 48 weeks
Prior nullresponders, prior partial responders, cirrhosis – PR 48 weeks

SVR12
79.2% in treatment naïve
57.1% in prior null responders
86.7% in prior relapsers
70.0% in prior partial responders

QUEST: No Benefit of Simeprevir if Q80K Positive



Q80K present in 34% of GT1a patients. No benefit of simeprevir if Q80K positive

Jacobson I, et al. AASLD 2013. Abstract 1122.

Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV (PHOTON-1)

Sulkowski et al, JAMA 2014

Open-label, non-randomised, uncontrolled phase 3

Treatment naïve
Genotype 2 or 3 (n = 68)
SOF/RBV 12 weeks
Genotype 1 (n = 114)
SOF/RBV 24 weeks

Treatment experienced
Genotype 2 or 3 (n=41)
SOF/RBV 24 weeks

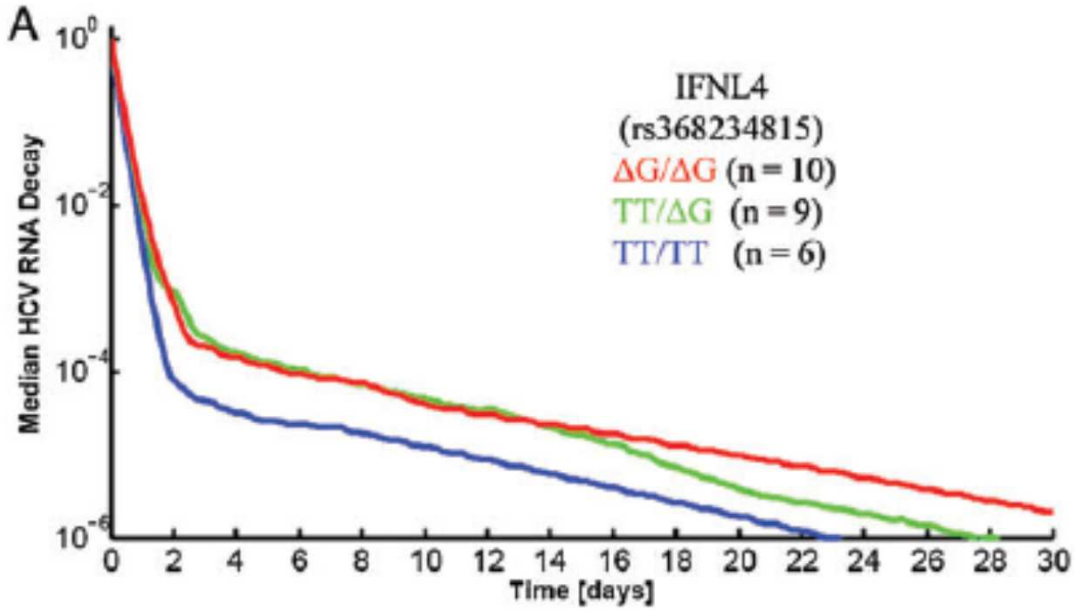
Sofosbuvir and Ribavirin for Hepatitis C in Patients With HIV (PHOTON-1)

Sulkowski et al, JAMA 2014

Open-label, non-randomised, uncontrolled phase 3

Treatment naïve	**SVR12**
Genotype 1	76%
Genotype 2	88%
Genotype 3	67%
Treatment experienced	
Genotype 2	92%
Genotype 3	94%

IFλN3 (IL28) and IFλN4 and sofosbuvir



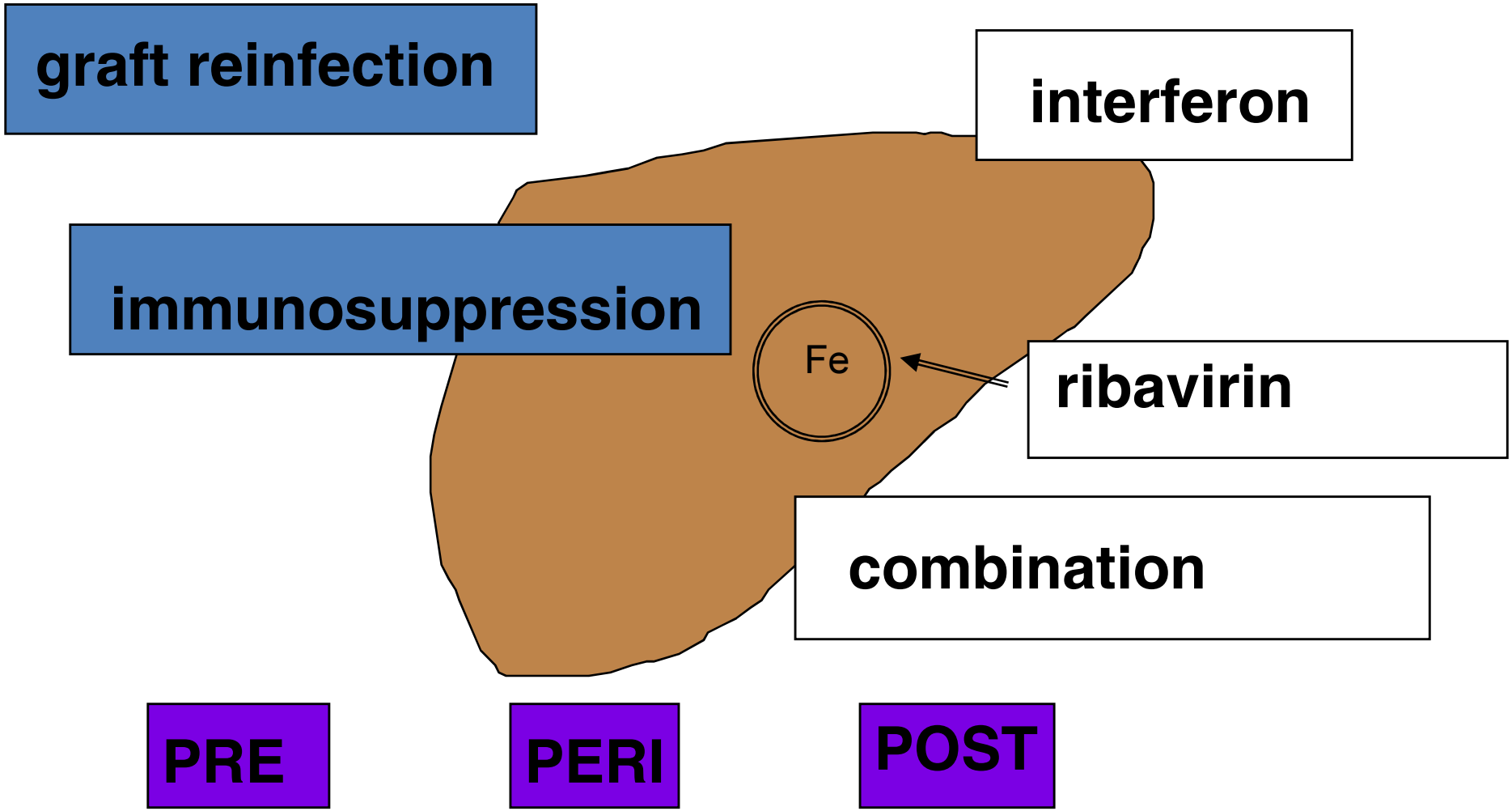
Impact on 2nd phase of viral decay
N=60 with 24/52 SOF/RBV, no significant effect on SVR

Meissner JID (2014)

EARLY ACCESS PROGRAMME

Background
Some odd “results”

LIVER TRANSPLANTATION AND HCV



AASLD guidelines

GENOTYPE 1

TREATMENT NAÏVE

Eligible to receive IFN

PEG/RBV/SOF 12 weeks

Not eligible to receive IFN

SOF/SIM +/- RBV 12 weeks

AASLD guidelines

GENOTYPE 2
TREATMENT NAÏVE
RBV/SOF 12 weeks

GENOTYPE 3
TREATMENT NAÏVE
RBV/SOF 24 weeks

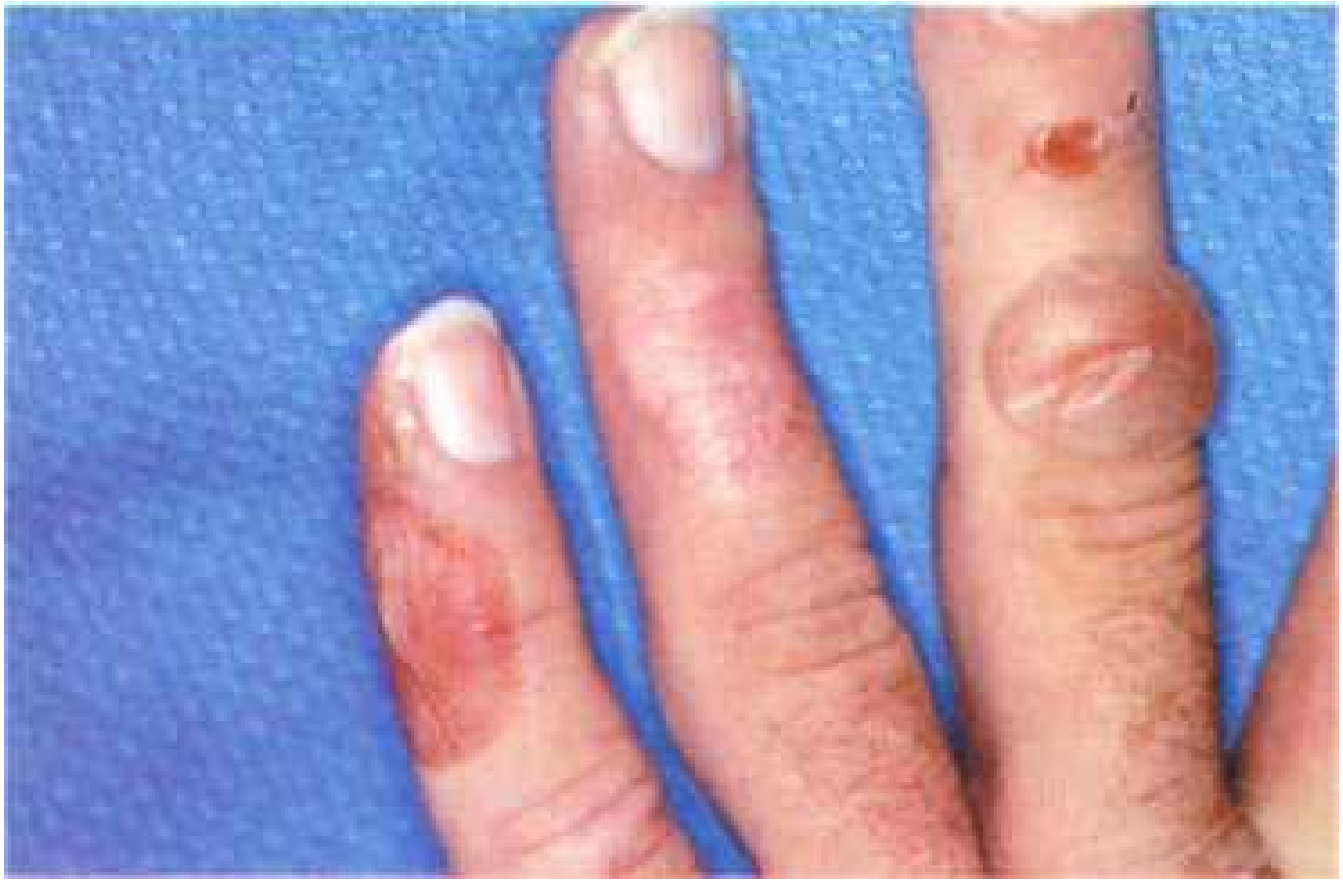
AASLD guidelines

GENOTYPE 4, 5, 6

TREATMENT NAÏVE

PEG/RBV/SOF 12 weeks

BEDSIDE



SUMMARY

Exciting new drugs/combinations
Shorter treatment courses
More effective (HIV pos = HIV neg)
Less toxic
Rapidly changing guidelines
Host and viral factors
Early access programme
Expensive
Can we eradicate HCV?