Efficacy and tolerability of **grazoprevir/elbasvir** in peginterferon alfa plus ribavirin experienced patients with chronic genotype 1 HCV and HIV co-infection: a non-randomised, open-label clinical trial

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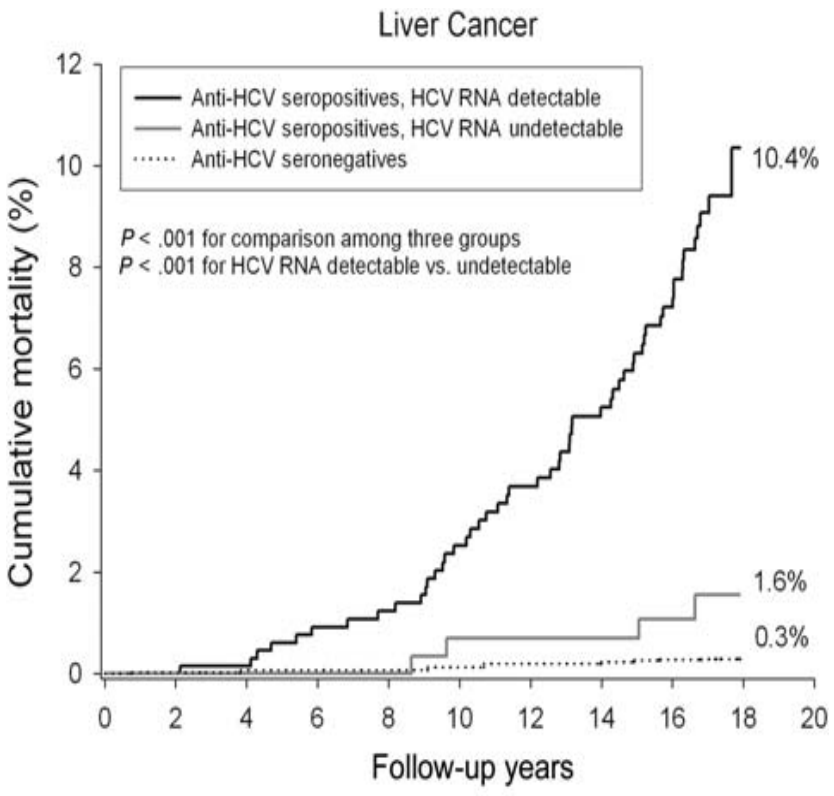
Background

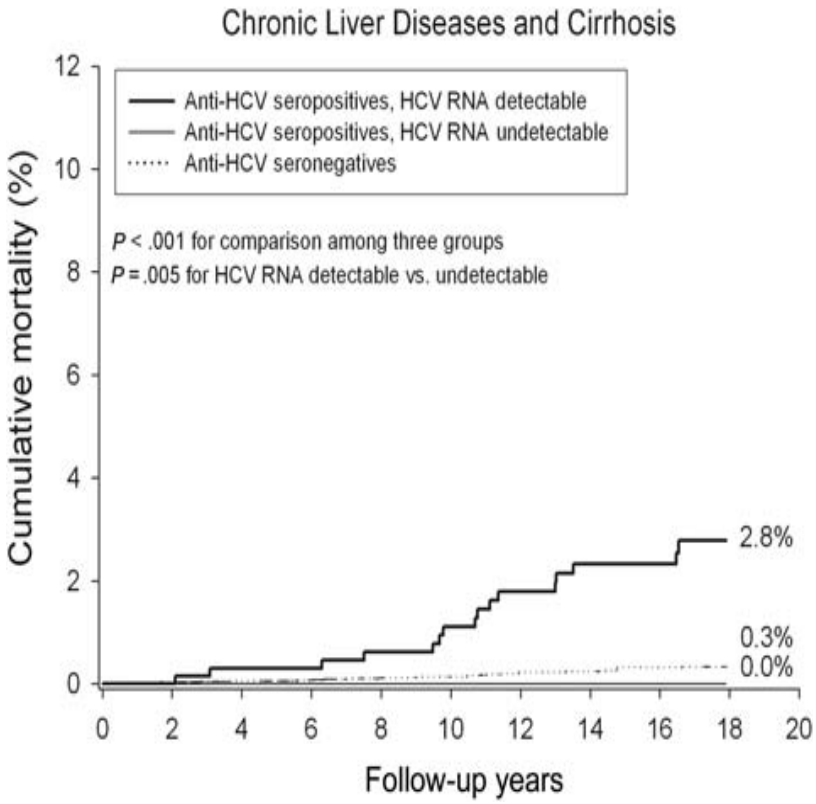
Chronic Hepatitis C and Liver-related **Mortality** in Taiwan

23820 patients: aged 30–65 years old; follow-up: 1991 to 2008

Liver Cancer



Chronic Liver Disease and Cirrhosis

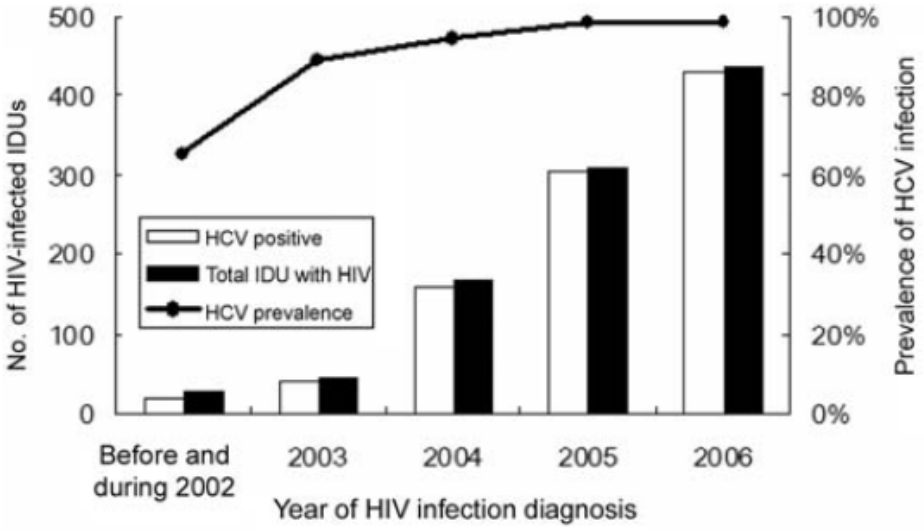


Lee MH; *J Infect Dis* 2012; 206:469–77

HCV prevalence rate in HIV+ co-infected patients

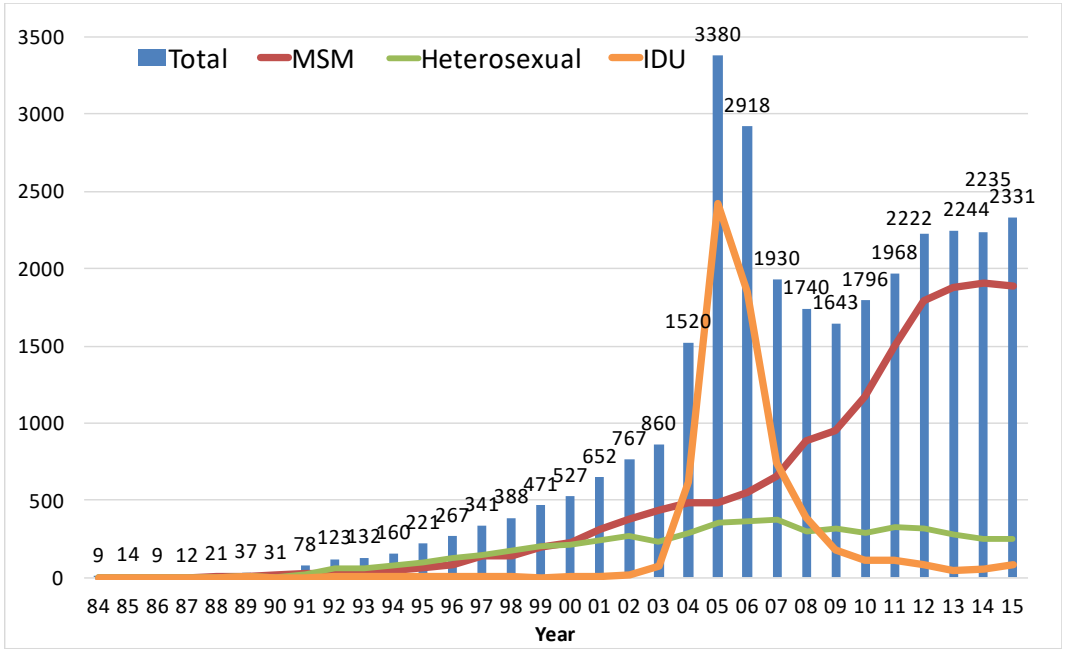
- 1993-2006, NTUH, CKNH, KHVGH, ETH
- 990 injection drug users (IDU) patients, HCV, HIV co-infection (96%)

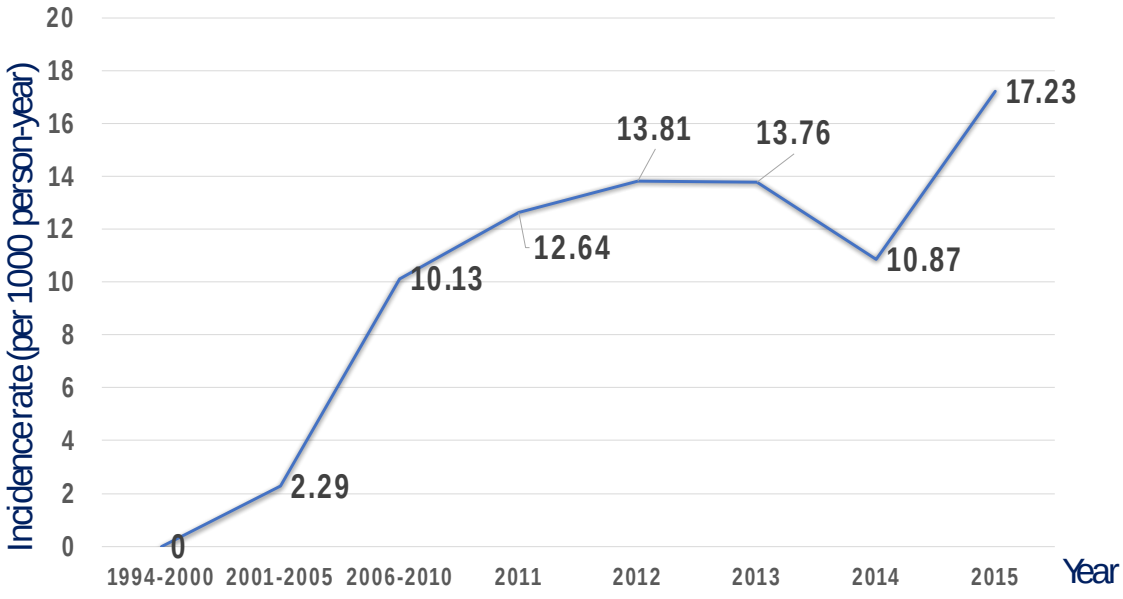
Demographic characteristic	Patients (n = 990)
Age, years	
≤20	12 (1.2)
21–30	327 (33.0)
31–40	409 (41.3)
41–50	203 (20.5)
>51	40 (4.0)
Mean ± SD (range)	35.1 ± 8.2 (17–70)
Sex	
Male	916 (92.5)
Female	74 (7.5)
CD4 cell count, mean cells/mm^3 ± SD (range)	510.0 ± 232.3 (0–1524)
HIV load, mean $\log_{10}$ copies/mL ± SD	3.89 ± 0.73
AST level	
Median IU/L (IQR)[a]	36 (27–59)
>40 U/L × ULN	98 (42.1)
ALT level	
Median IU/L (IQR)[b]	39 (29–70)
>37 U/L × ULN	122 (53.7)
ART use	137 (13.8)



Liu JY, et al. *Clin Infect Dis.* 2008; 46:1761–8

Incident HCV infection among HIV-positive patients





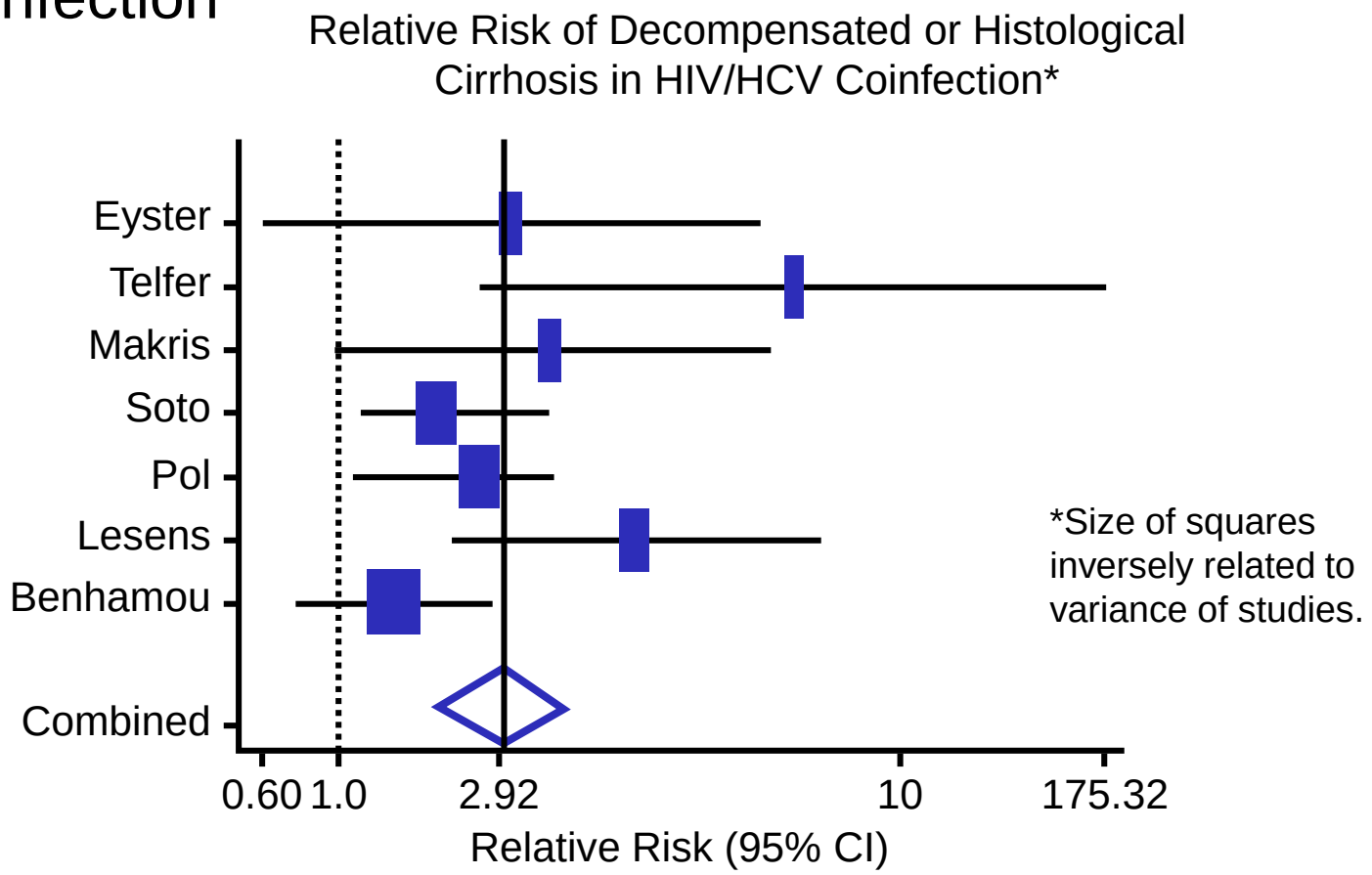
HIV/HCV outbreak among IDU, 2004-2006

Increasing trend of HCV infection among HIV-positive MSM

Taiwan CDC.
Huang MH, et al. IDST 2018.

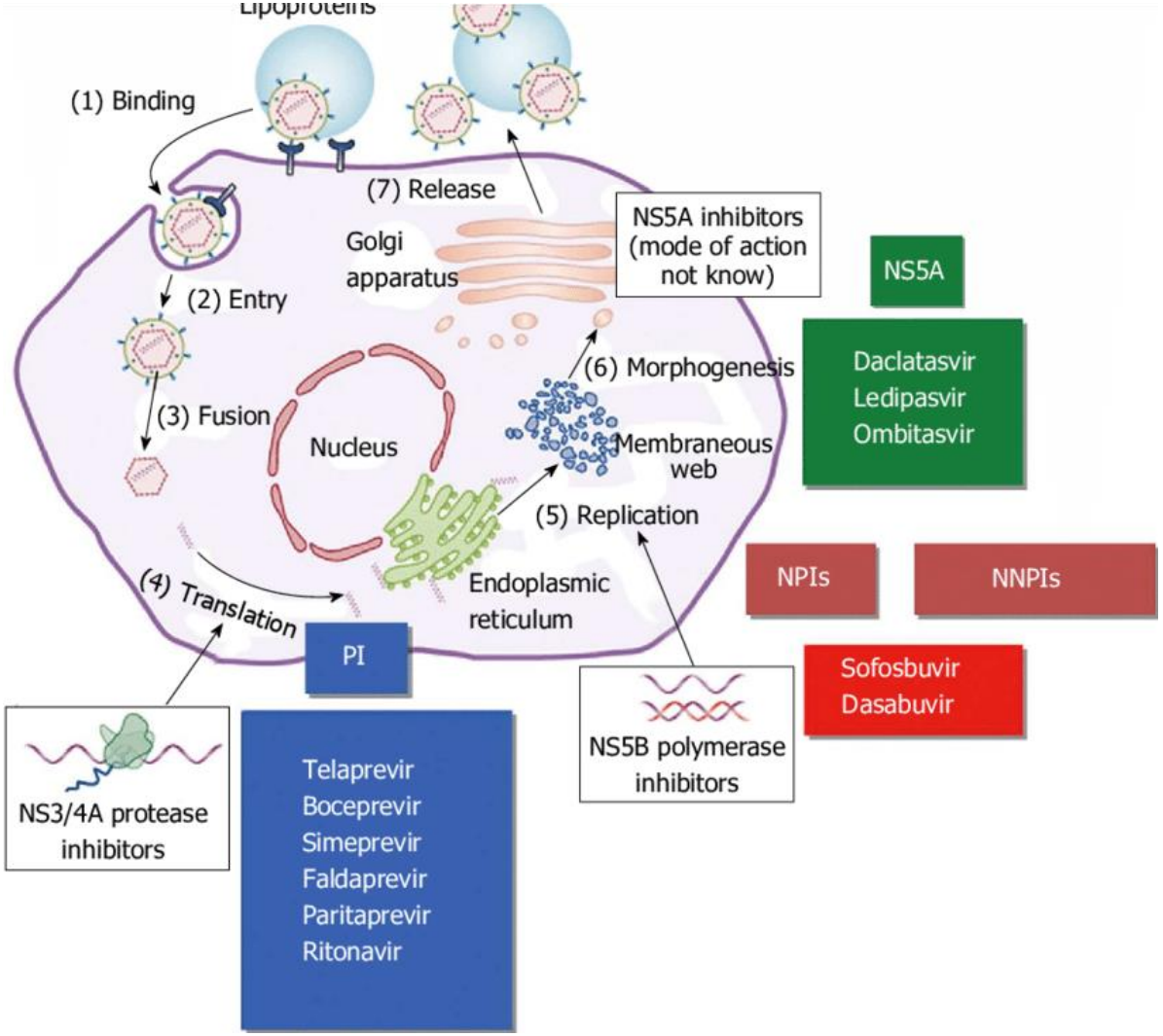
Increased risk of liver disease progression with HIV/HCV co-infection

- Meta-analysis of 8 studies of HIV/HCV coinfection vs HCV monoinfection



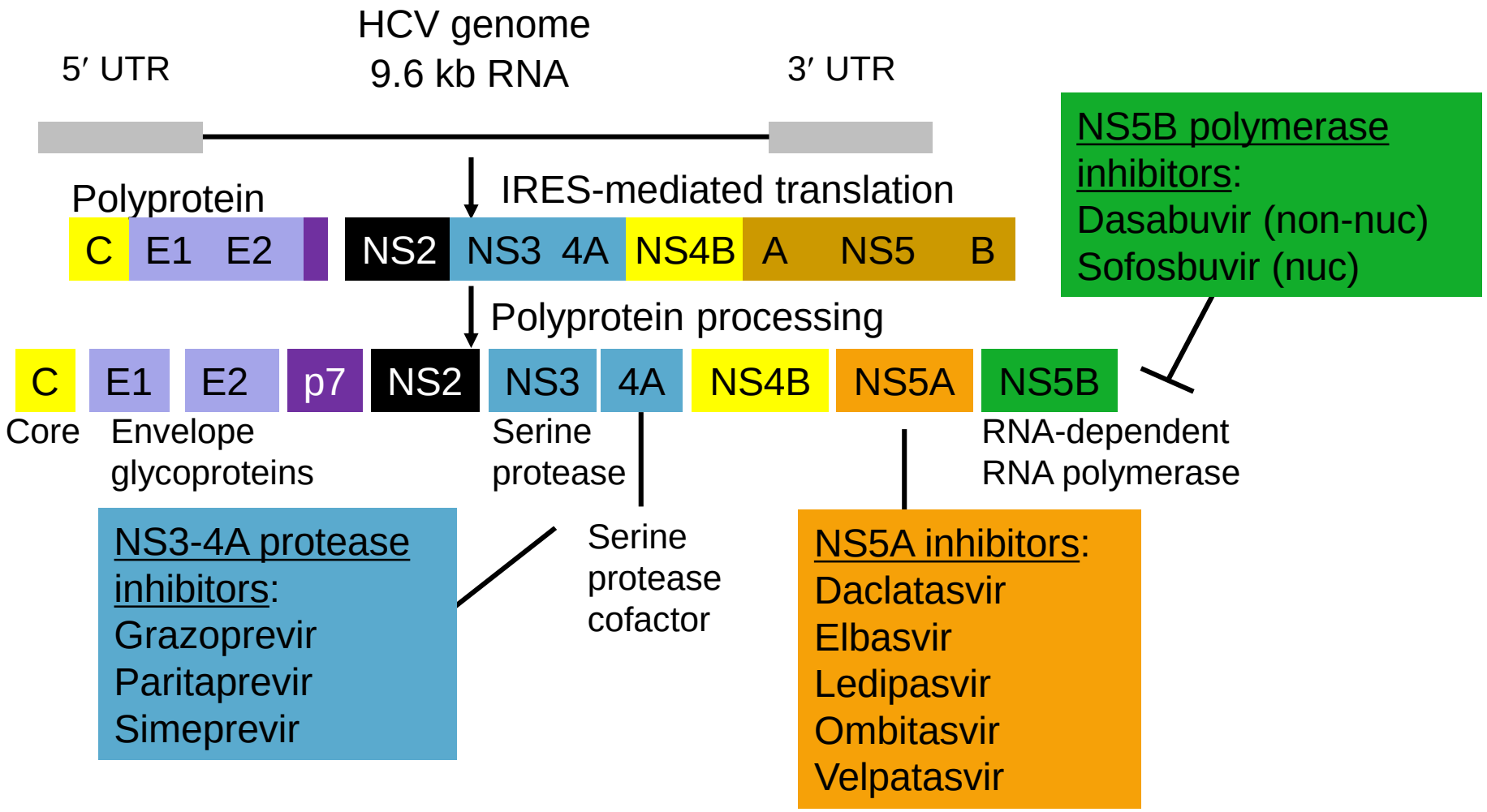
Graham C, et al. *Clin Infect Dis.* 2001;33:562-569.

Hepatitis C virus life cycle



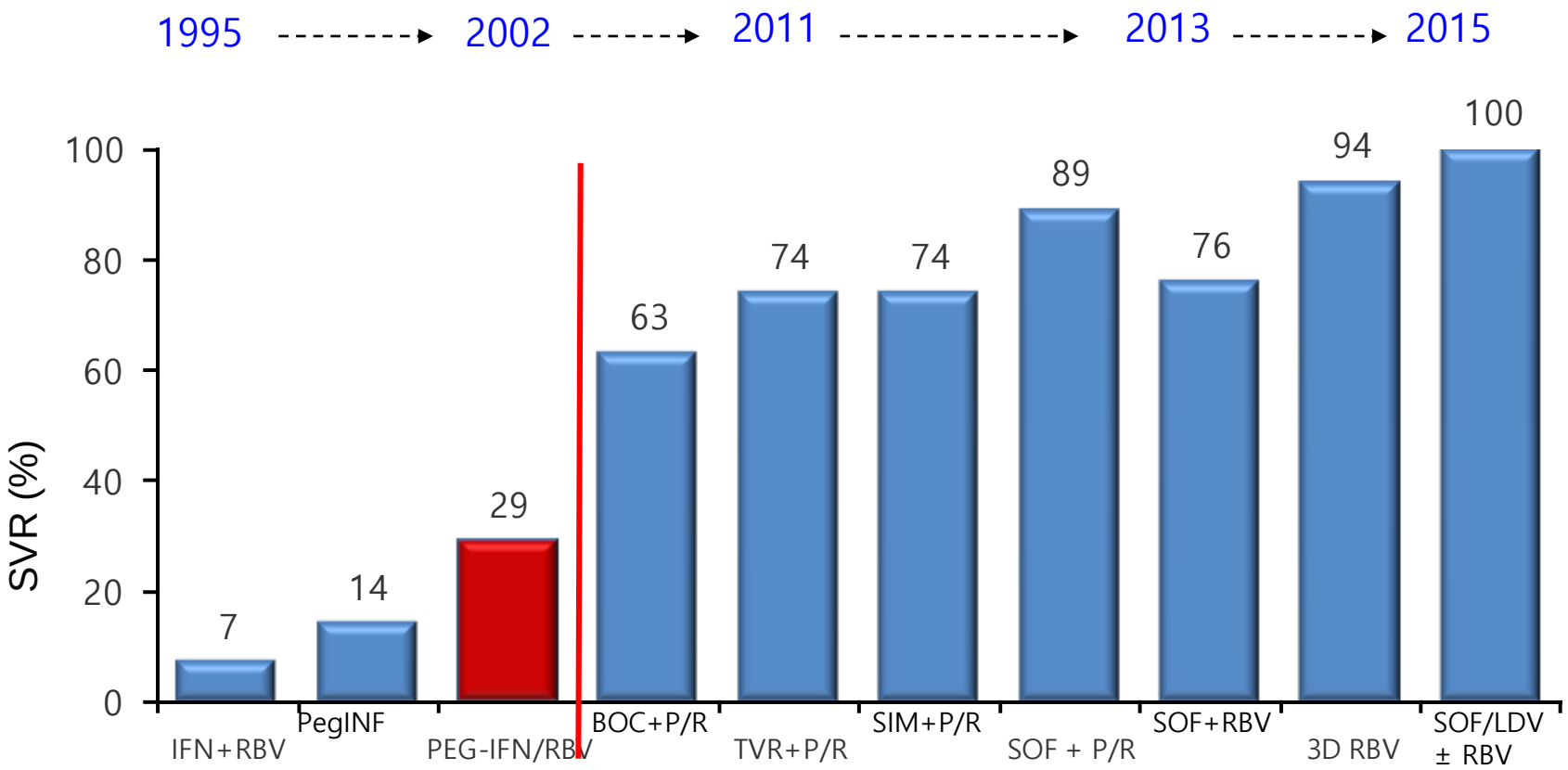
Gaetano, et al. World J Hepatol. 2016; 8(2): 92–106.

HCV Proteins Targeted by direct antiviral agents (DAAs)



Naggie S, et al. *J Antimicrob Chemother*. 2010;65:2063-2069.

SVR12/24 in HIV & HCV co-infected patient with chronic GT1



IN THE DAA ERA HIV+ PATIENTS WILL ACHIEVE SIMILAR SVR RATES

Dieterich D et al. CROI 2014; P#24; Rodriguez-Torres M et al. IDWeek 2013; P#714; Sulkowski M et al. Lancet Infect Dis 2013; 13:597–605; Sulkowski M et al. Ann Intern Med 2013;159:86–96; Sulkowski M et al Lancet 2014;314:653–61; Sulkowski M et al. AIDS 2014; P#104 LB; Torriani FJ, et al. N Engl J Med 2004; 351:438–450;

台灣健保給付 DAAs

	Ledipasvir/ Sofosbuvir (Harvoni)	Elbasvir/ Grazoprevir (Zepatier)	Daclatasvir+ Asunaprevir (Sunvepra+ Daklinza)	Paritaprevir/ritonavir/ Ombitasvir/Dasabuvir (Viekira Pak, 3D)
DAA Class	NS5A NS5B	NS3 NS5A	NS3 NS5A	NS3 NS5A NS5B
Genotype coverage	1, 4, 5, 6	1, 4	1b	1, 4
Reimbursed genotype				
Daily Pills	1	1	3	3
Treatment duration (week)	12-24	12-16	24	12-24
Ribavirin	+/-	+/-	-	+/-

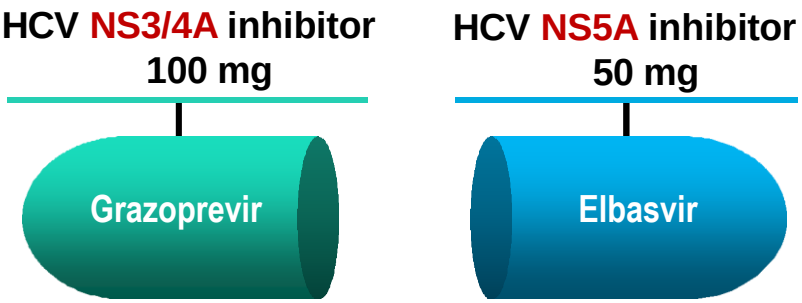
*Sofosbuvir + Ribavirin for HCV-2 for 12 weeks

C型肝炎全口服新藥健保給付執行計畫, 2018.

Efficacy of 12 weeks of DAAs across separate studies of GT1-4 HCV infection

Sustained HCV Virologic Response, % (n/N)	HCV Monoinfection	HIV/HCV Coinfection
SMV + SOF	97 (112/115)[1]	92 (11/12)[2]
LDV/SOF	99 (211/214)[3]	95 (143/150)[4]
DCV + SOF	100 (41/41)[5]	97 (98/101)[6]
OBV/PTV/RTV + DSV + RBV	96 (455/473)[7]	94 (29/31)[8]
EBR/GZR	95 (299/316)[9]	95 (207/218)[10]

- **All-oral, once-daily, single-tablet**
- **Renal Impairment** - **no dosage adjustment** in hemodialysis patients
- Hepatic Impairment - no dosage adjustment in **Child-Pugh A**



1. Kwo P, et al. EASL 2015 Abstract LP14. 2. Del Bello DP, et al. AASLD 2014. Abstract 994. 3. Afdhal N, et al. N Engl J Med. 2014;370:1889-1898. 4. Naggie S, et al. N Engl J Med. 2015;373:705-713. 5. Sulkowski M, et al. N Engl J Med. 2014;370:211-221. 6. Wyles D, et al. N Engl J Med. 2015;373:714-725. 7. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603. 8. Sulkowski M, et al. JAMA. 2015;313:1223-1231. 9. Zeuzem S, et al. Ann Intern Med. 2015;163:1-13. 10. Rockstroh JK, et al. AASLD 2015. Abstract 210.

Cost-effectiveness of pegIFN/rib and DAA in TYGH

genotype	Agents of treatment	Population	Number	SVR (%)	cost per treatment	cost per SVR
G1	PegIFN/RBV	Tsai et al.[18]	829	68.6	RMB 36,940	RMB 53,853
G1	PegIFN/RBV	our study	80	56.3	36,940	65,670
G1	PegIFN/RBV	HIV-negative prisoners	17	82.4	36,940	44,857
G1	PegIFN/RBV	HIV-positive prisoners	25	72.0	36,940	51,305
G1	PegIFN/RBV	HIV-positive patients in community	38	36.8	36,940	100,380
G1	Elbasvir/grazoprevir	Zeuzem S et al.[17]	1,070	97.2	52,416	53,924
G2	PegIFN/RBV	our study	17	82.4	26,611	32,292
G3	PegIFN/RBV	our study	26	88.5	26,611	30,069
G6	PegIFN/RBV	our study	47	61.7	36,940	59,872
G6	PegIFN/RBV	Prisoners	23	87.0	36,940	42,458
G6	PegIFN/RBV	Non-prisoners	24	37.5	36,940	98,508

1. PC Tsai, et al. Medicine (Baltimore). 2017 Jun;96(22):e6984.
2. MS. Sulkowski, et al. *JAMA*. 2015;313(12):1223-1231.
3. Cheng CY, et al. EACS 2017, Milano, poster PE 16/19

Aims

- Aim: Efficacy of **grazoprevir/elbasvir** in peginterferon alfa plus ribavirin experienced patients with chronic genotype 1 HCV and HIV co-infection
- Primary objective: To assess the by determining the proportion of sustained virological response 12 weeks after the end of therapy (SVR12; HCV RNA concentration less than 10 IU/ mL at follow-up week 12)
- Secondary objective:
  - To assess tolerability by measuring frequency of SAEs and AEs leading to discontinuation.
  - Interval change of liver fibrosis by Fibrosis-4 score [Age (years) x AST (U/L)]/ [Platelet count (10^9/L) x $\sqrt{\text{ALT}}$ (U/L)]

Method

- A non-randomised, open-label, single arm, single center clinical trial
- IRB approval: TYGH 105034 (NCT03098121)
- Treatment course:
  - For GT 1a: grazoprevir(100mg)/elbasvir(50mg) STR QD+ ribavirin 800mg for 16 weeks
  - For GT 1b: grazoprevir(100mg)/elbasvir(50mg) STR QD for 12 weeks

Inclusion criteria

- Men and non-pregnant women ≥ 20 years of age
- HCV RNA > 10,000 IU/mL
- HIV-1 RNA < 200 copies/mL
- CD4 T-cell count > 100 cells/μL
- peginterferon alfa plus ribavirin failure:
  - null response <1 $\log_{10}$ IU/mL reduction in HCV at week 4
  - detectable HCV RNA since week 12 to the end of treatment
  - detectable HCV RNA for 12 to 24 weeks after the end of treatment
  - discontinuation of peginterferon alfa plus ribavirin due to grade 3 or grade 4 adverse effects at any moment.

Exclusion criteria

- Decompensated liver disease
- Liver cirrhosis with Child-Pugh class B or C, or with a Child-Turcotte-Pugh score of more than 6 points and albumin below 3 g/dL or platelet count below 75,000/ µL
- History of malignant disease, or evidence of hepatocellular carcinoma
- HBsAg positive patients

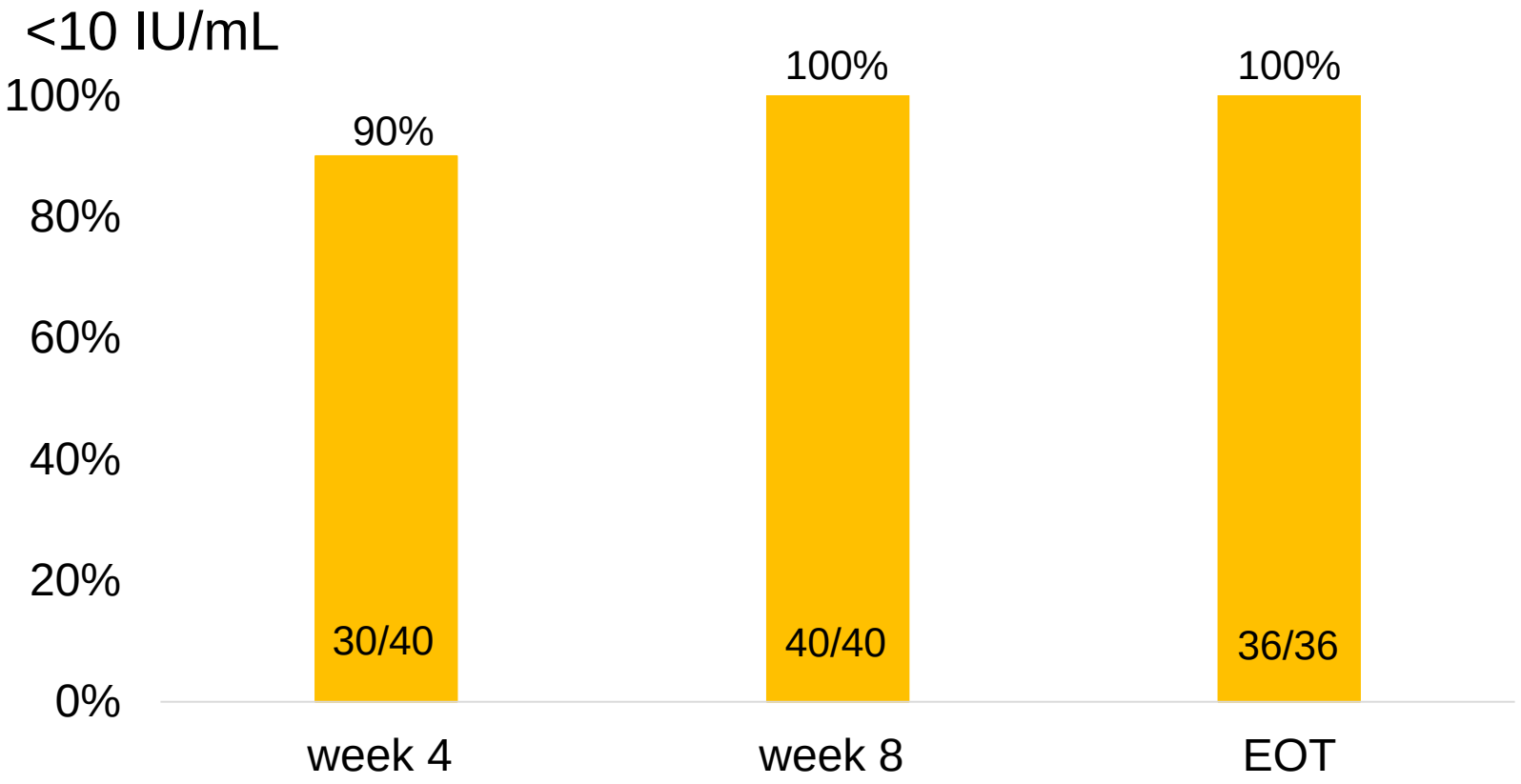
Baseline characteristics

	Subject number (n=40)
age, y/o (SD)	45 ± 7
male, n (%)	37 (92.5%)
mode of HIV transmission	
IDU, n (%)	37 (92.5%)
MSM, n (%)	2 (5%)
Heterosexual, n (%)	1 (2.5%)
HIV status	
CD4, cells/uL (SD)	546 ± 272
HIV RNA <50 copies/mL, n (%)	36 (90%)
HIV RNA 50-199 copies/mL, n (%)	4 (10%)
HAART regimens	
ABC/3TC/DTG (triumeq), n (%)	16 (40%)
TDF/FTC/RPV (complera), n (%)	20 (50%)
Truvada + DTG or RAL, n (%)	2 (5%)
Kivexa + RAL, n (%)	1 (2.5%)

Baseline characteristics

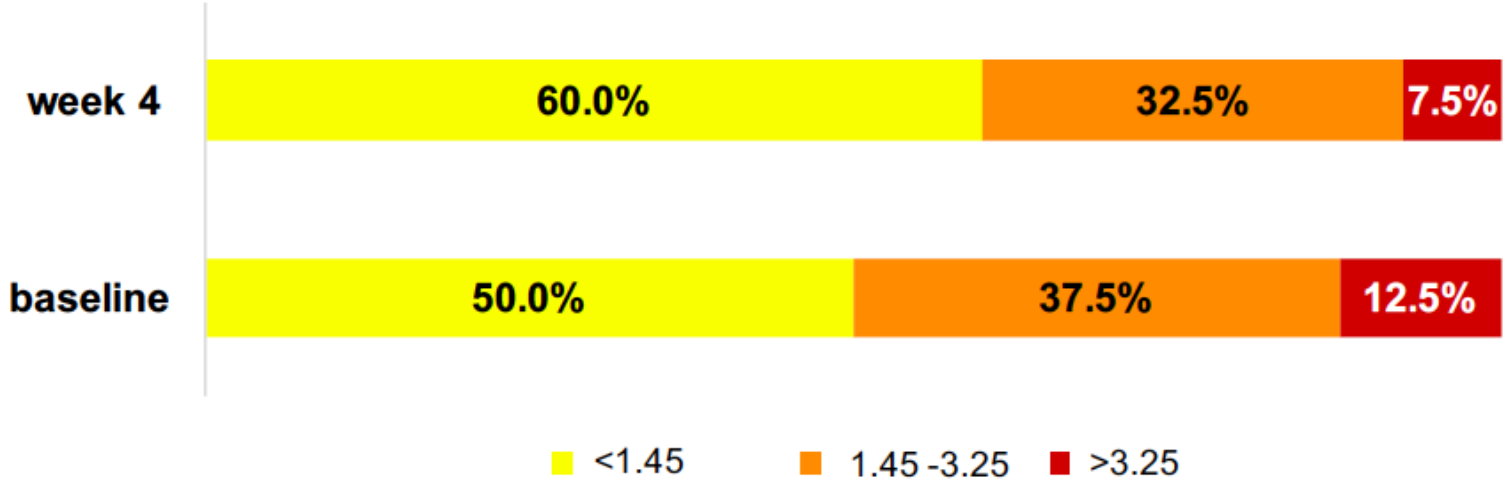
	Subject number (n=40)
HCV genotype	
1a, n (%)	16 (40%)
1b, n (%)	24 (60%)
relapse or re-infection, n(%)	28 (70%)
treatment failure, n (%)	12 (30%)
HCV RNA, $\log_{10}$, IU/mL, median (IQR)	6.3 (4.01-7.12)
> 6.0 $\log_{10}$ IU/mL, n (%)	29 (72.5%)
> 7.0 $\log_{10}$ IU/mL, n (%)	4 (10%)
Fibrosis-4 score, n (%)	
<1.45	20 (50%)
1.45-3.25	15 (37.5%)
>3.25	5 (12.5%)
Resistance associated variants (RAV) in GT 1a, n	M28 (n=2); L31 (n=1)

Outcome


<10 IU/mL
100%
80%
60%
40%
20%
0%
90%
100%
100%
30/40
40/40
36/36
week 4
week 8
EOT

Fibrosis-4 score

subjects > 1.45 (n=20)	baseline	Week 4	*p*
Fibrosis-4 [median (IQR)]	2.8 (1.1)	1.6 (0.7)	0.037



Proportion of adverse effects

adverse event, n (%)	GT 1a (n=16)	GT 1b (n=24)	Total (n=40)
fatigue	6 (37.5%)	5 (20.8%)	11 (27.5%)
irritable	3 (18.8%)	0	3 (7.5%)
depression	2 (12.5)	4 (16.7%)	6 (15%)
headache	3 (18.8%)	0	3 (7.5%)
nausea	3 (18.8%)	3 (12.5%)	6 (15%)
pruritus	3 (18.8%)	0	3 (7.5%)
insomnia	2 (12.5%)	1 (4.2%)	3 (7.5%)
Discontinuation due to AE	0	0	0

Laboratory abnormalities

adverse event, n (%)	GT 1a (n=16)	GT 1b (n=24)
ALT, Grade $\geq$ 3 (> 5 x ULN)	0	0
AST, Grade $\geq$ 3 (> 5 x ULN)	0	0
Total bilirubin, Grade $\geq$ 3 (> 3 x ULN)	0	0
Decrease in Hemoglobin, Grade $\geq$ 3	1 (6.3%)	0
RBV doses reductions due to toxicity	2 (12.6%)	0

Discussion

- Preliminary data showed that grazoprevir/elbasvir is highly effective at week 4, week 8 and some subjects at end of treatment (EOT) in peginterferon alfa plus ribavirin experienced patients with chronic genotype 1 HCV and HIV co-infection
- The improvement of liver fibrosis was seen in short term

- Limitation: small population and short observation

Acknowledge

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