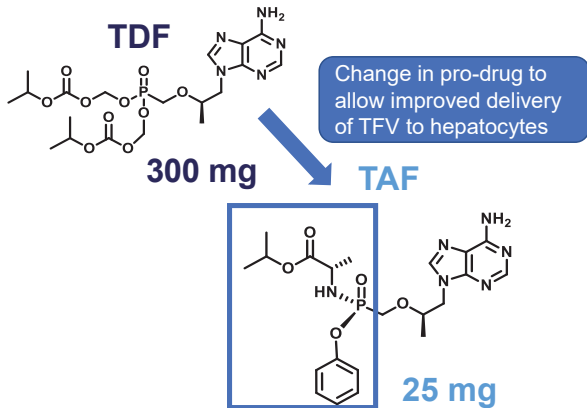
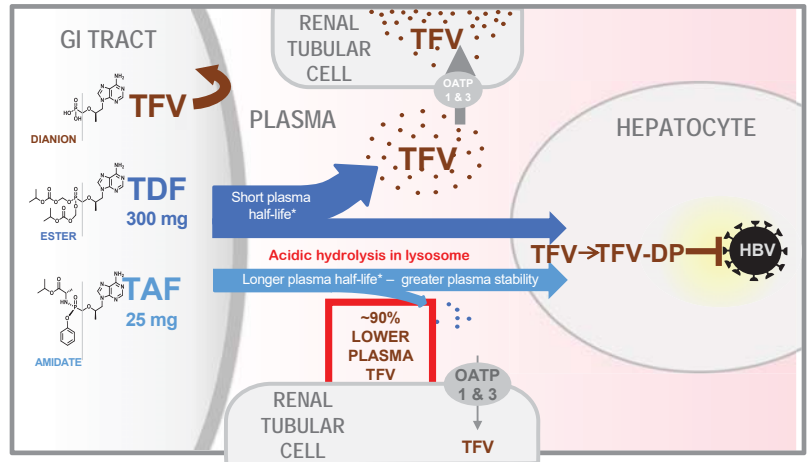


The challenges in patients with renal impairment were addressed by optimisation of TDF delivery in TAF

Challenge to be overcome:
maintain favourable efficacy and resistance
profile of TDF but reduce the renal effects



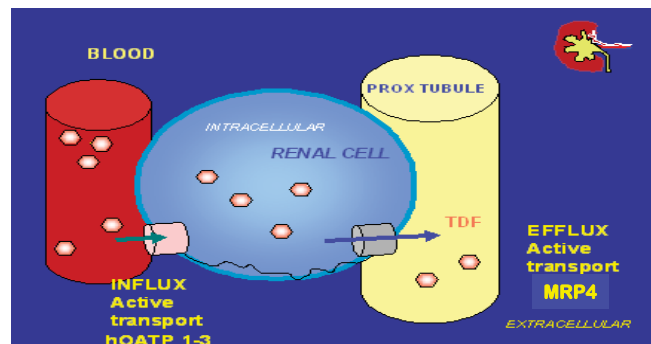
Optimised delivery of tenofovir with TAF



Gilead Sciences Press Release November 10, 2016. Available at: <https://www.marketwatch.com/press-release/us-food-and-drug-administration-approves-gileads-velivdy-tenofovir-alafenamide-for-the-treatment-of-chronic-hepatitis-b-virus-infection-2016-11-10> (accessed February 2019); Ray AS, et al. Antiviral Res 2016;125:63–70; Gilead Sciences Europe Ltd. VEMLDY (tenofovir alafenamide) SmPC, June 2018; Gilead Sciences Europe Ltd. VIREAD (tenofovir disoproxil fumarate) SmPC, January 2019

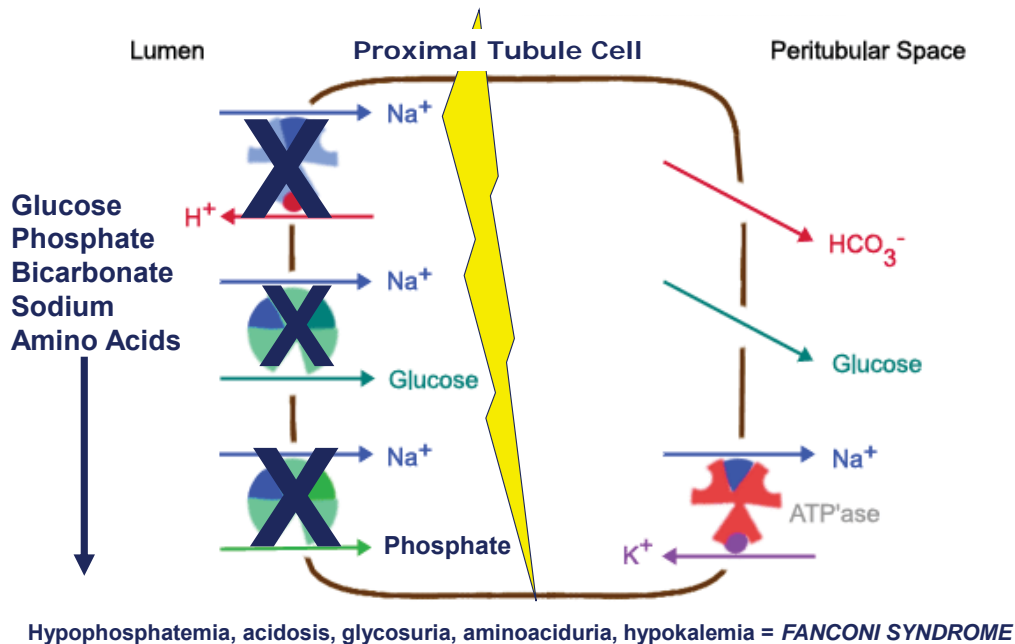
*Half-life based on *in vitro* plasma data: TDF=0.4 minutes, TAF=30–90 minutes
GI: gastrointestinal; OATP: organic anion-transporting polypeptide;
TFV-DP: tenofovir disphosphate

Mechanism of nucleotide toxicity on kidney proximal tubule: MRP4 inhibition



- TDF is actively transported by MRP4 from the epithelial cell of the proximal tubule into its lumen
- When MRP4 is saturated, TDF accumulates in the intracellular environment leading to tubular damage
- Tubular damage results in phosphorus loss with consequent mobilization from the bone and decreased bone density

Fanconi Syndrome



Choosing Among Nucleos(t)ide Analogues

If no comorbidities (for most pts)

Monotherapy with ETV, TDF, or **TAF**^[1,2]

If risk of or preexisting bone or renal disease, prioritize **ETV** or **TAF**^[2]

- Age > 60 yrs
- Bone disease
 - Chronic steroids or other meds that affect bone
 - History of fragility fracture
 - Osteoporosis
- Renal abnormalities
 - eGFR < 60 mL/min/1.73 m²
 - Albuminuria > 30 mg or moderate proteinuria
 - Low phosphate (< 2.5 mg/dL)
 - Hemodialysis

When to prioritize **TAF** over **ETV**

- Previous nucleoside exposure^[2]
 - Lamivudine with or without adefovir resistance
- HIV/HBV coinfection
- No dose adjustment for CrCl ≥ 15 mL/min

When to prioritize **ETV** over **TAF**

- If less expensive (generic available)
- Dosing guidelines for CrCl < 15 mL/min

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR < 50 mL/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥ 12 years and ≥ 35 kg body weight) with estimated CrCl ≥ 15 mL/min or in patients with CrCl < 15 mL/min who are receiving hemodialysis

1. Terrault NA, et al. Hepatology. 2016;63:261-283. 2. EASL. J Hepatol. 2017;67:370-398.

	Hazard ratio (95% CI)	β coefficient	p value	Risk score
Sex				
Female	1.00	1.00	..	0
Male	2.2 (1.4-3.4)	0.78798	0.0004	<u>2</u>
Age (years)				
Per 5 years	1.64 (1.48-1.81)	0.49295	<0.0001	1
30-34	0
35-39	1
40-44	2
45-49	3
50-54	4
55-59	<u>5</u>
60-65	6
ALT (U/L)				
<15	1.00	1.00	..	0
15-44	1.5 (1.0-2.2)	0.38823	0.0559	1
≥ 45	2.6 (1.5-4.4)	0.96311	0.0003	<u>2</u>
HBeAg				
Negative	1.00	1.00	..	0
Positive	2.3 (1.3-3.8)	0.81308	0.0026	<u>2</u>
HBV DNA level (copies per mL)				
<300 (undetectable)	1.00	1.00	..	0
300-9999	1.1 (0.4-2.9)	0.11648	0.8063	0
10 000-99 999	3.7 (1.6-8.5)	1.31467	0.0017	3
100 000-999 999	9.7 (4.4-21.3)	2.27028	<0.0001	5
$\geq 10^6$	8.1 (3.5-19.0)	2.09258	<0.0001	<u>4*</u>

ALT=alanine aminotransferase. HBV=hepatitis B virus. *The risk score attributed to HBV DNA $\geq 10^6$ copies per mL was less than that for HBV DNA of 100 000-999 999 copies per mL because most patients with HBV DNA $\geq 10^6$ copies per mL were also HBeAg positive, thus sharing the associated higher score for this category.

Reach B model of HCC risk

	3 years	5 years	10 years
0	0.0%	0.0%	0.0%
1	0.0%	0.0%	0.1%
2	0.0%	0.0%	0.1%
3	0.0%	0.1%	0.2%
4	0.0%	0.1%	0.3%
5	0.1%	0.2%	0.5%
6	0.1%	0.3%	0.7%
7	0.2%	0.5%	1.2%
8	0.3%	0.8%	2.0%
9	0.5%	1.2%	3.2%
10	0.9%	2.0%	5.2%
11	1.4%	3.3%	8.4%
12	2.3%	5.3%	13.4%
13	3.7%	8.5%	21.0%
14	6.0%	13.6%	32.0%
15	9.6%	21.3%	46.8%
16	15.2%	32.4%	64.4%
17	23.6%	47.4%	81.6%

Yang HI et al. JCO 2010;28:2437-2444

NA discontinuation

	THASL, APASL 2015	EASL 2017	AASLD 2018
	HBsAg loss	HBsAg loss	HBsAg loss
HBeAg positive, Noncirrhotic	HBeAg seroconversion > 12 months, 3 years preferred	HBeAg seroconversion > 12 months	HBeAg seroconversion with a period of consolidation
	HBsAg loss	HBsAg loss	HBsAg loss
HBeAg negative	> 2 years of HBV DNA suppression, compensated cirrhosis included	Possible after 3 years of HBV DNA suppression, noncirrhotic	Until HBsAg loss

Treatment in specific situations

	APASL 2015	EASL 2017	AASLD 2018
HBeAg positive with high HBV DNA and normal ALT	Biopsy should consider if non invasive test suggests significant fibrosis Age > 35 or with family history HCC >> biopsy and treat if significant fibrosis	May be treated if age > 30 regardless of histology	Treat selected group if age > 40 and HBV DNA >1,000,000 IU and liver biopsy significant fibrosis
Compensated cirrhosis	HBV DNA detectable (elevated ALT); > 2,000 (normal ALT) , PegIFN not contraindicated	HBV Detectable, regardless of ALT level	HBV Detectable, regardless of ALT level, PegIFN not contraindicated
Decompensated cirrhosis (NA only)	Irrespective of HBA DNA level	Irrespective of HBV DNA and assess for OLT	Irrespective of HBV DNA and assess for OLT

HBV in healthcare workers

APASL 2015	EASL 2017
Screen and HBV should not preclude anyone from clinical practice	Screen but HBV is not the reason to disqualify
Treatment as usual guideline Can conduct exposure-prone procedure if HBV DNA < 1,000 IU/mL	Treat if HBV DNA > 200 IU/mL to reduce transmission risk

HBV in pregnancy

	APASL 2015	EASL 2017	AASLD 2018
Mild CHB	Postpone treatment	Postpone treatment	
Advanced CHB	Treat with category B NA	TDF, if already treated with other NA, switch to TDF	Treated as non-pregnant, TDF preferred
Prevention of perinatal transmission	HBV DNA > 6-7 log IU At wks 28-32 Category B drug Stop at birth Breastfeeding discourage with NA	HBV DNA > 200,000 and/or HBsAg > 4 log₁₀ IU At wks 24-28 Continue to up to wks 12 postpartum Breastfeeding not contraindicated for TDF	HBV DNA > 200,000 At wks 28-32 Continue to up to wks 12 postpartum Breastfeeding not contraindicated

Thailand: Pregnant women with HBeAg positive: TDF in 3rd trimester

HBV-HCV coinfection

Recommendations	Grade of evidence	Grade of recommendation
Treat with the same anti-HCV regimens, following the same rules as HCV monoinfected patients	B	1
Patients fulfilling the standard criteria for HBV treatment should receive NA treatment according to EASL 2017 CPG on the management of HBV infection	A	1
Patients who are HBsAg+ should receive NA prophylaxis at least until Week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped	B	1
In patients who are HBsAg-, anti-HBc Ab+ on anti-HCV therapy <ul style="list-style-type: none"> • Monitor serum ALT levels monthly • Test HBsAg and HBV DNA if ALT levels do not normalise or rise • Initiate NA therapy if HBsAg and/or HBV DNA are present 	B	1

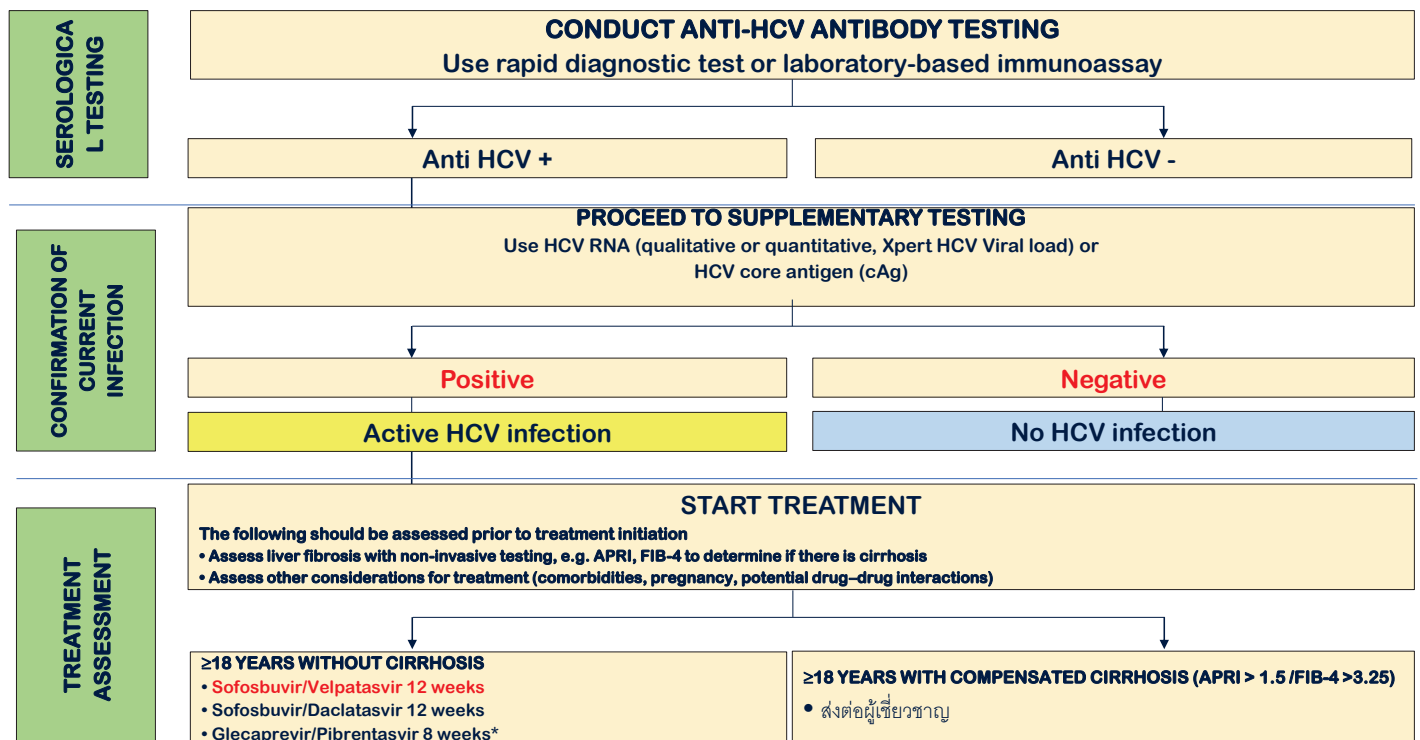
WHO TO TEST FOR CHRONIC HCV INFECTION

Testing approach and population	Recommendations*
Focused testing in most affected populations	<p>1. In all settings (and regardless of whether delivered through facility- or community- based testing), it is recommended that serological testing for HCV antibody (anti-HCV) be offered with linkage to prevention, care and treatment services to the following individuals:</p> <ul style="list-style-type: none"> Adults and adolescents from populations most affected by HCV infection (ie. who are either part of a population with high HCV seroprevalence or who have a history of exposures and/or high-risk behaviors for HCV infection); Adults and children with a clinical suspicion of chronic viral hepatitis3 (ie. symptoms, signs, laboratory markers). <p>Strong recommendation, low quality of evidence</p> <p>Note: Periodic re-testing using HCV NAT should be considered for those with ongoing risk of acquisition or reinfection.</p>
General population testing	<p>2. In settings with a $\geq 2\%$ or $\geq 5\%$ HCV antibody seroprevalence in the general population it is recommended that all adults have access to and be offered HCV serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or facility-based testing opportunities or programmes such as HIV or TB clinics, drug treatment services and antenatal clinics5.</p> <p>Conditional recommendation, low quality of evidence</p>
Birth cohort testing	<p>3. This approach may be applied to specific identified birth cohorts of older persons at higher risk of infection6 and morbidity within populations that have an overall lower general prevalence.</p> <p>Conditional recommendation, low quality of evidence</p>

WHO guidelines on HBV and HCV testing 2016

ประชากรกลุ่มเสี่ยง

- ผู้ติดเชื้อเอชไอวี/เอดส์ ชายรักชาย และพนักงานบริการทางเพศ
- ผู้ที่มีประวัติใช้เข็มฉีดยาร่วมกับผู้อื่น
- ผู้ต้องขังหรือผู้เคยมีประวัติต้องขัง
- ผู้ที่เคยได้รับเลือดและ/หรือรับบริจาคอวัยวะก่อนปี 2535
- ผู้ที่เคยสักผิวหนัง เจาะผิวหนังหรืออวัยวะต่างๆ ในสถานประกอบการที่ไม่ใช่โรงพยาบาล
- ผู้ที่มีภาวะไตวายเรื้อรังที่จำเป็นต้องได้รับการฟอกไตเป็นประจำ
- ผู้ที่เป็นกลุ่มสมรส หรือ ผู้ที่มีเพศสัมพันธ์กับผู้ป่วยโรคไวรัสตับอักเสบ ซี เรื้อรัง
- ผู้ที่มีมารดาเป็นผู้ป่วยโรคไวรัสตับอักเสบ ซี เรื้อรัง
- ผู้ที่เคยรับการรักษาจากผู้ที่ไม่ใช่บุคลากรทางการแพทย์และสาธารณสุข เช่น ฉีดยา ทำฟัน หรือ หัตถการอื่นๆ
- ผู้ที่มีค่าเอนไซม์ของตับผิดปกติ
- ผู้ที่สัมผัสหรือมีประวัติสัมผัสเลือดหรือสารคัดหลั่งของผู้ป่วยที่ติดเชื้อไวรัสตับอักเสบ ซี



ฉบับร่าง: แนวทางการรักษาไวรัสตับอักเสบ ซี กระทรวงสาธารณสุขและสมาคมโรคตับ 2019

Specifications of available HCV rapid diagnostic tests

Test	Manufacturer	Nature of device	Matrices	Volume needed	Time to result	CE-marked	FDA-approved	WHO-prequalified
OraQuick® HCV rapid antibody test	OraSure Technologies, Bethlehem, PA	Lateral flow	Oral fluid, whole blood, serum, plasma	5 µl or 40 µl (oral fluid)	20-40 min	Yes	Yes	Yes
TOYO® anti-HCV test	Turklab, Izmir, Turkey	Lateral flow	Whole blood, serum, plasma	60 µl (whole blood) or 30 µl (serum, plasma)	5-15 min	Yes	No	No
Signal HCV Ver 2.0	Span Divergent, Udhna, India	Flow-through	Serum, plasma	100 µl	10 min	Yes	No	No
Labmen HCV test*	Turklab, Izmir, Turkey	Lateral flow	Whole blood, serum, plasma	10 µl	15 min	No	No	No
MultiSure HCV	MP Biomedicals, Singapore	Lateral flow	Whole blood, serum, plasma	25 µl	15 min	Yes	No	No
Assure HCV Rapid Test	MP Biomedicals, Singapore	Lateral flow	Whole blood, serum, plasma	50 µl (whole blood) or 5 µl (serum, plasma)	15 min	No	No	No
First Response HCV Card Test	Premier Medical Corporation, Daman, India	Lateral flow	Whole blood, serum, plasma	35 µl	20-30 min	Pending	No	No
SD Bioline HCV	Standard Diagnostics, Yongin, Korea	Lateral flow	Whole blood, serum, plasma	10 µl	5-20 min	No	No	Yes
Advanced Quality Rapid Anti-HCV Test	Intec Products Inc., China	Lateral flow	Whole blood, serum, plasma	10 µl	15-20 min	Yes	No	No

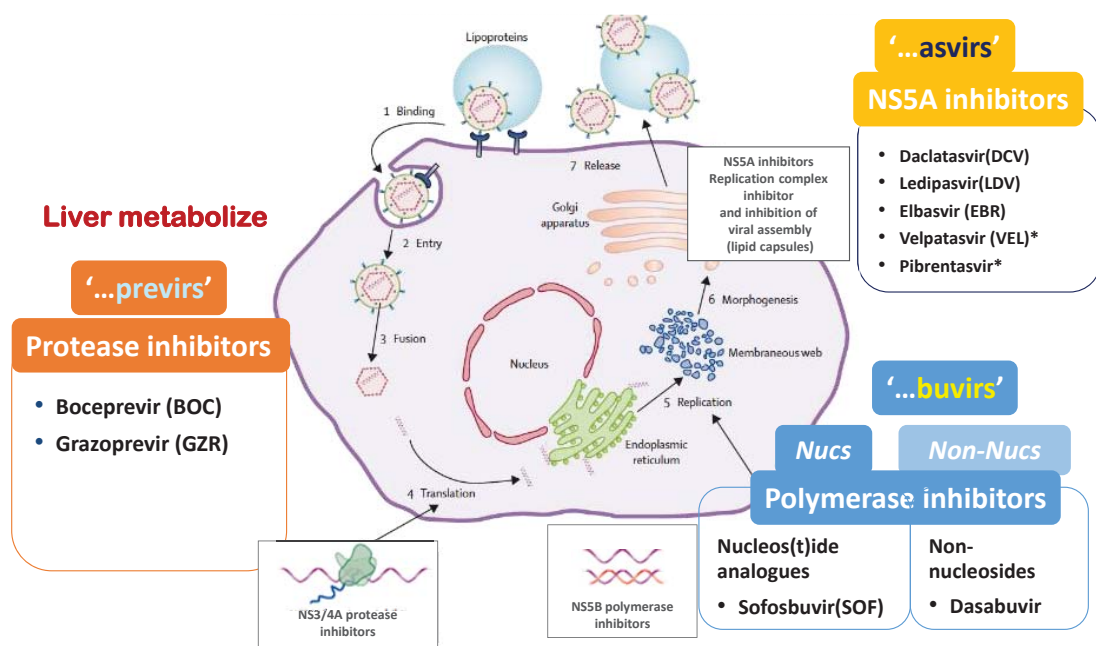
* Compatible with automated reader ICA-R Turklab. CE, European Conformity; HCV, hepatitis C virus.

Chevaliez S. and Pawlotsky JM. J Hepatology 2018: 916-926.

ผู้ป่วยที่ควรส่งต่อเพื่อให้แพทย์ผู้เชี่ยวชาญโรคทางเดินอาหารเป็นผู้พิจารณาให้การรักษา

- ผู้ป่วยที่เคยได้รับการรักษาด้วยยาต้านไวรัสกลุ่ม (DAA) ในการรักษาไวรัสตับอักเสบ ซี มาก่อน หรือ
- ผู้ป่วยที่เคยติดเชื้อไวรัสตับอักเสบ ซี และรักษาหายมาก่อน หรือ
- ผู้ป่วยที่เป็น cirrhosis หรือ
- ผู้ป่วยที่มีลักษณะทางคลินิกอื่น ๆ นอกตับที่รุนแรง หรือ
- ผู้ป่วยที่มีภาวะไตวายเรื้อรังที่มีค่า GFR < 30 มิลลิลิตร/นาที หรือ
- ผู้ป่วยที่มีประวัติปลูกถ่ายตับ

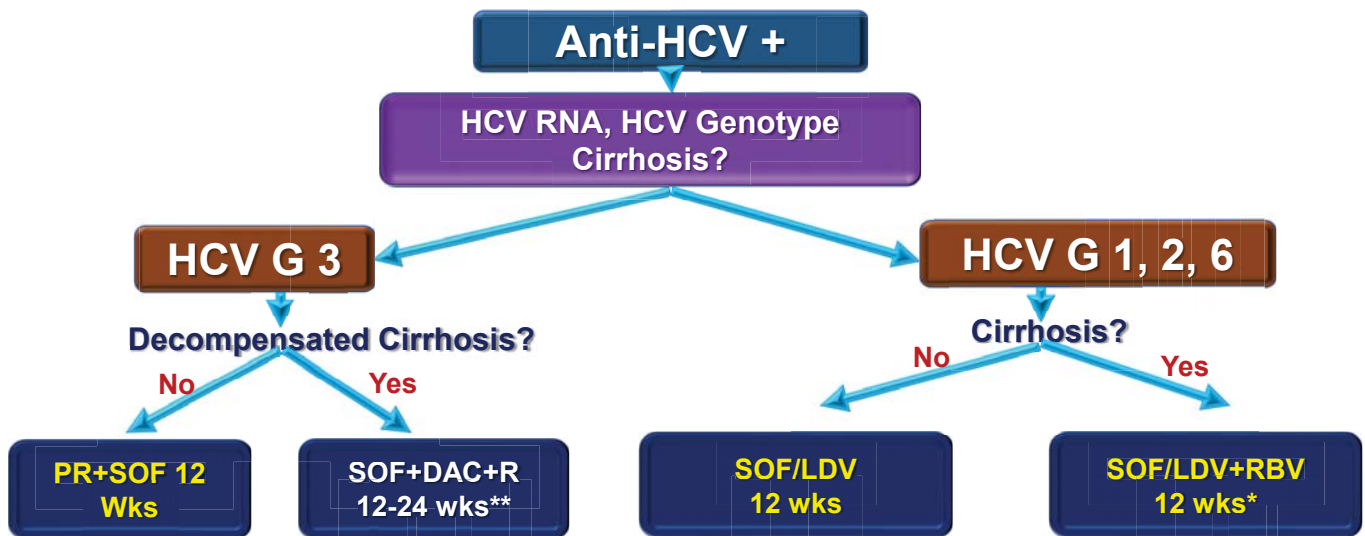
Currently approved DAAs against HCV



*Not available as for Feb 2018

HCV Treatment 2018 for Thailand (P/R/SOF/LDV) ๓2

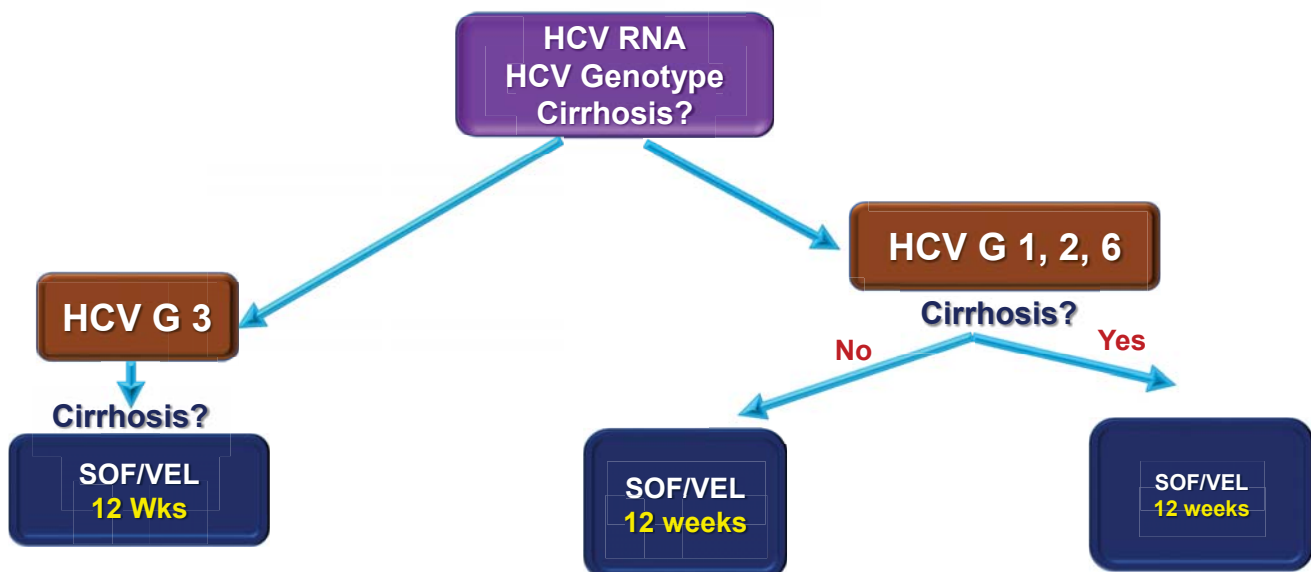
Treatment naïve, PR experienced



* Including decompensated cirrhosis

** Not cover by universal re-imburement

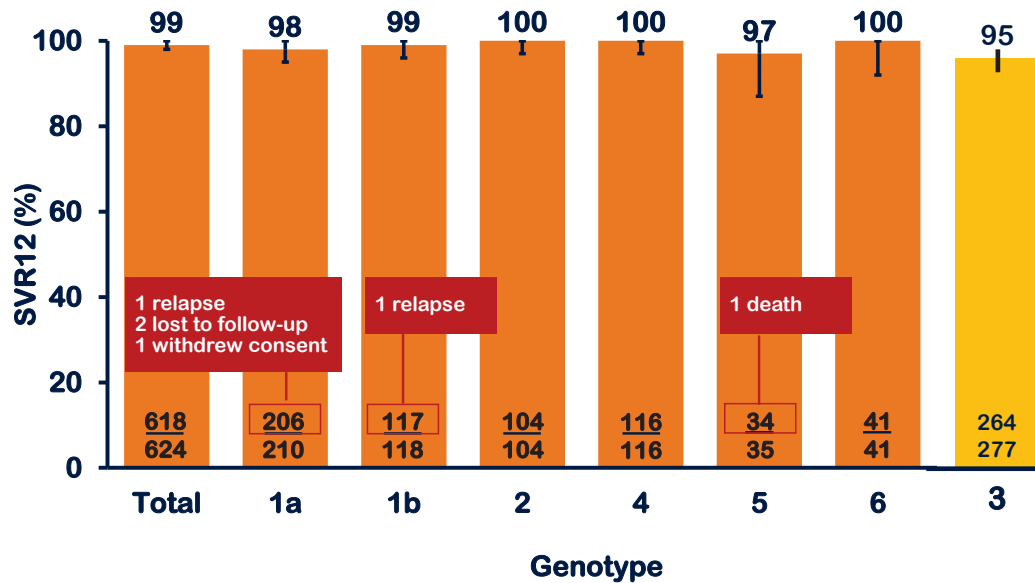
HCV Treatment 2017 for Thailand



G3 cirrhosis RBV added?

SOF/VEL/RBV in decompensated cirrhosis of all genotypes

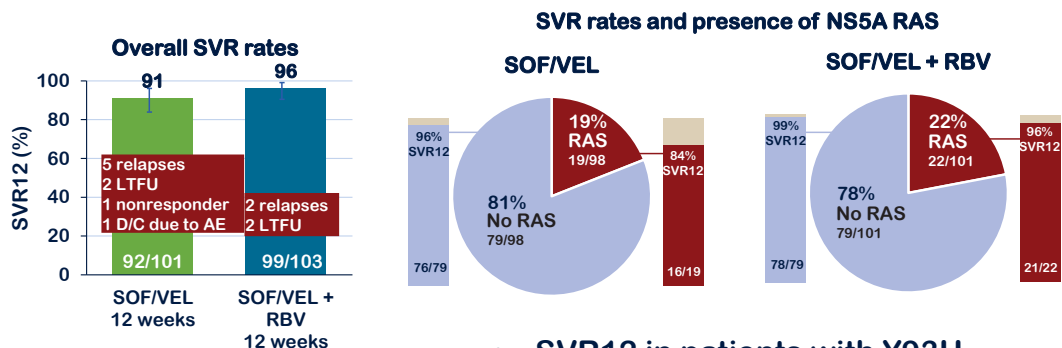
SOF/VEL: SVR12 by HCV Genotype



Feld J, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. LB-2.
Mangia A, et al. 66th AASLD; San Francisco, CA; November 13-17, 2015; Abst. 249.

Sofosbuvir/velpatasvir with and without ribavirin in GT 3 HCV-infected patients with cirrhosis

- 204 patients were randomised to receive SOF/VEL or SOF/VEL + RBV for 12 weeks in an open-label study in GT 3 patients with compensated cirrhosis (TN and TE)

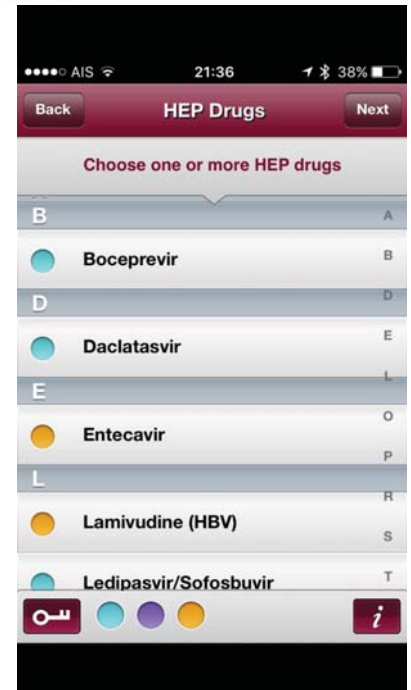
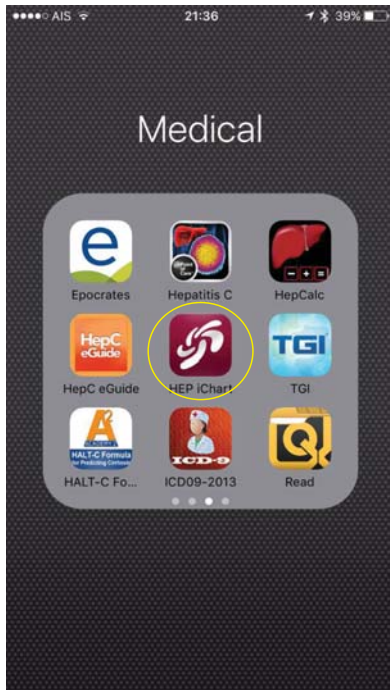


- SVR12 in patients with Y93H
 - SOF/VEL: 50% (2/4)
 - SOF/VEL + RBV: 89% (8/9)

HCV G3b

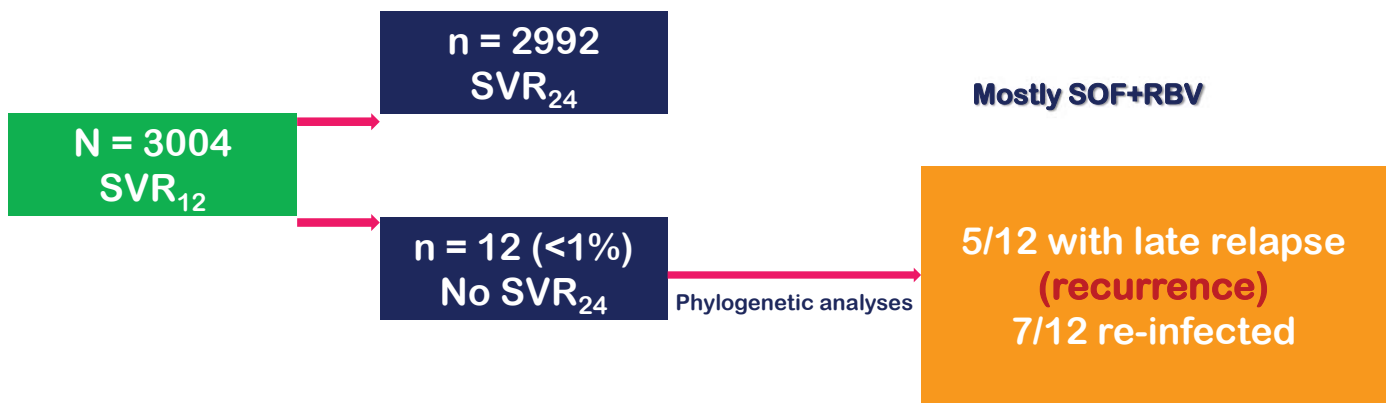
This study was not powered to assess noninferiority of the two treatment arms, and the numeric difference in relapse rate between the two treatment arms does not suggest a clinically meaningful difference in outcome

Drug-Drug interaction U Liverpool HEP iChart



Relapse beyond SVR-12 with DAA therapy

Analysis of recurrent viremia after SVR in 11 SOF± LDV phase III trials



- Risk of late relapse very low, but can happen

Recommendations for varices and HCC surveillance after SVR

Organization	Recommendations	
	Noncirrhotics	Cirrhotics
AASLD/IDSA and EASL	No specific recommendations	Endoscopy to screen for varices Pts with varices should be managed as indicated
Organization	Recommendations	
	F0-F2	F3-F4
AASLD/IDSA	Follow-up same as for those never infected with HCV	Ultrasound surveillance every 6 m
EASL	None	Ultrasound surveillance every 6 m

AASLD/IDSA Guidelines. May 2018. EASL Guidelines 2018

Viral Hepatitis B and C The Changing Concept for Thailand

- Chronic Hepatitis B and C previously considered specialist diseases
- Now, we should consider as public health issue
- Treatment should be simplified and tailored according to resource available
- Address adherence before and during treatment for both HBV, HCV
- HCC surveillance in high risk HBV and HCV with advanced fibrosis, even after SVR