LA CURA DELLE COMORBILITÀ DEL FEGATO: EPATITI E STEATOSI EPATICA

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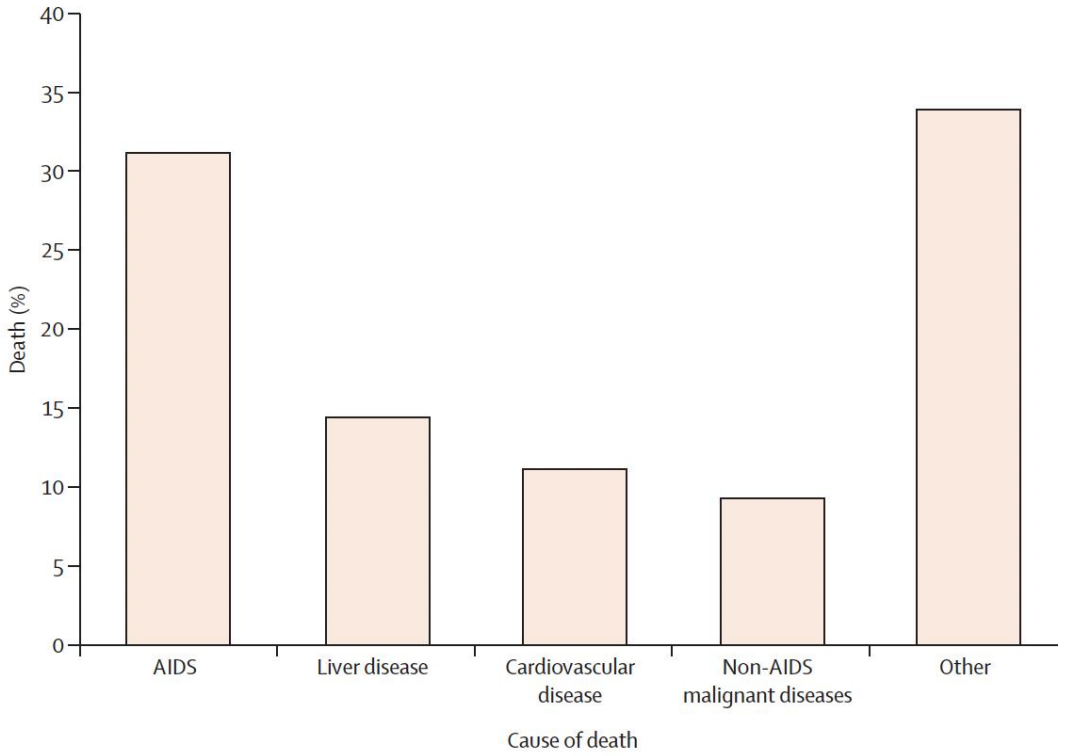
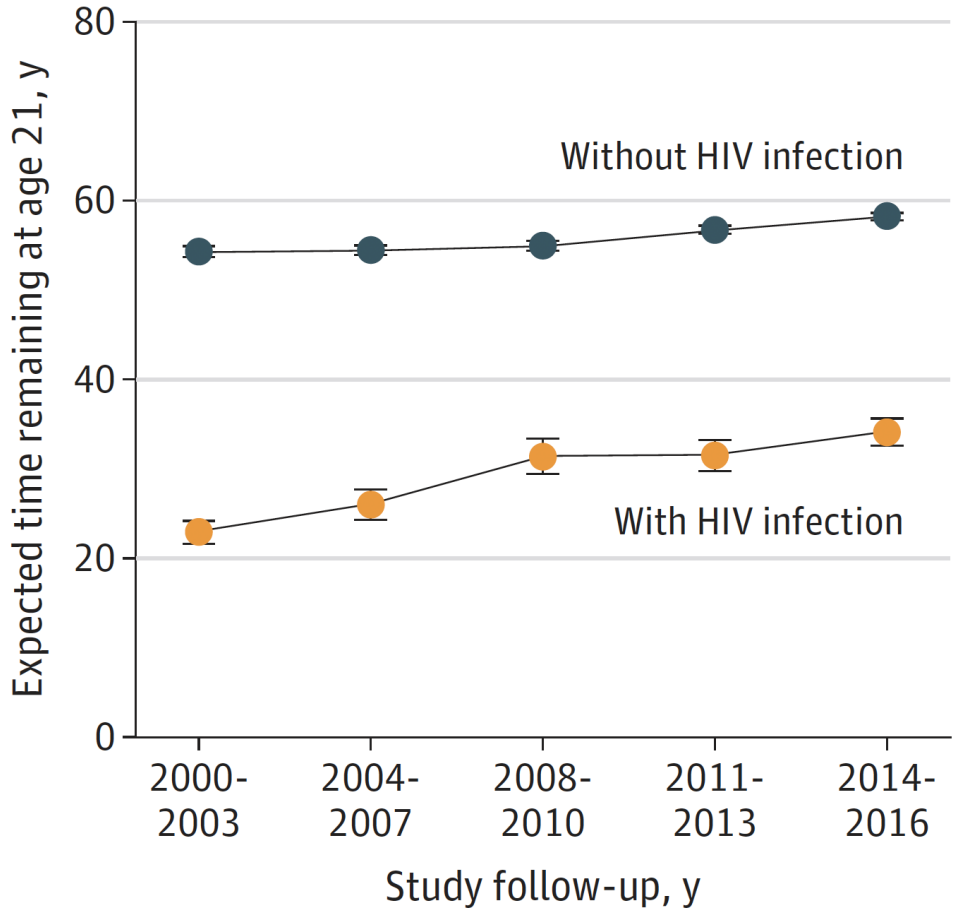
Disclosures

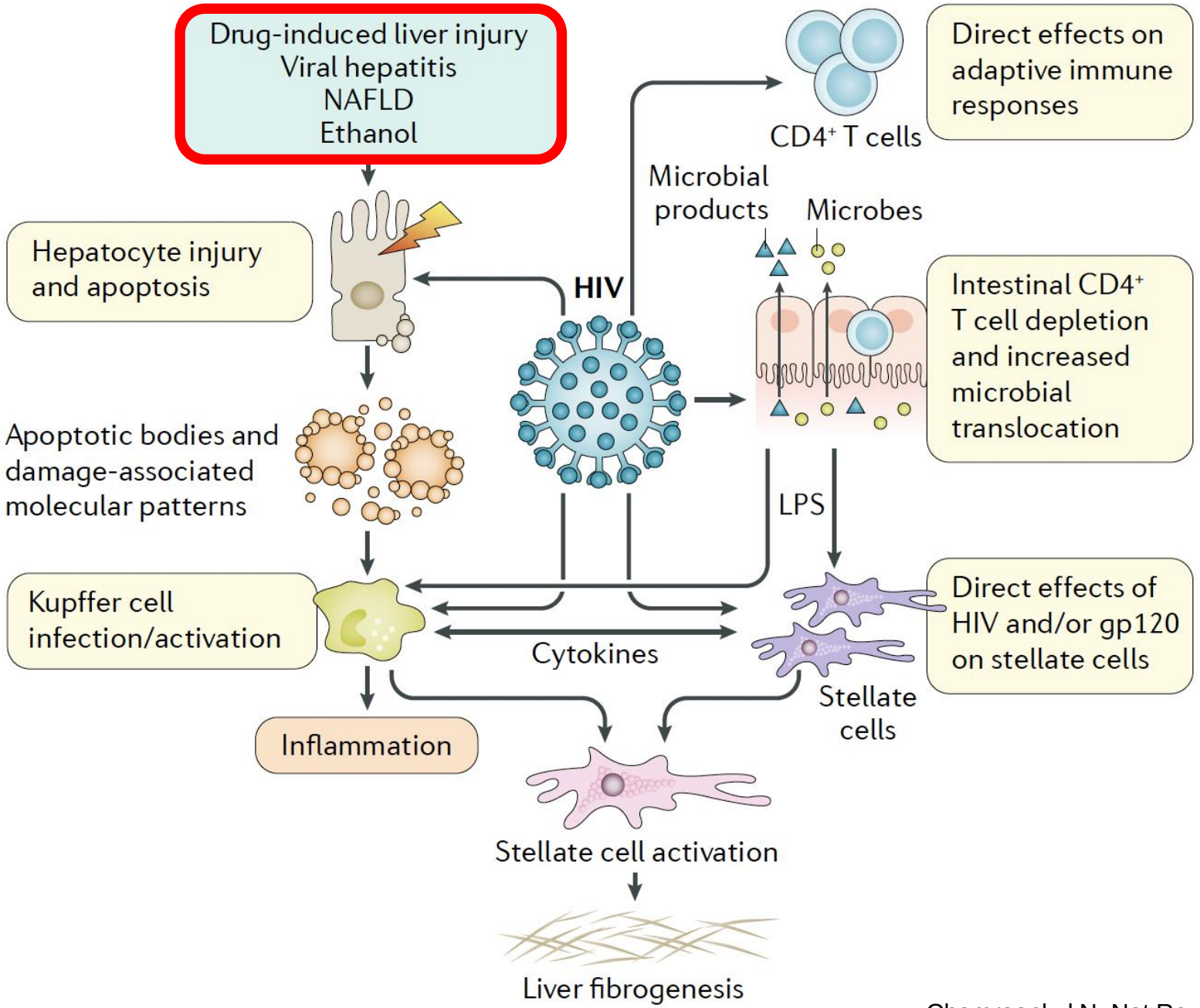
Speaker: Gilead, Abbvie, MSD, Intercept Pharma, AlfaSigma, GSK, Incyte

Consultant: Intercept Pharma, AlfaSigma, Takeda, AstraZeneca, Albireo





Weber R. 2006
Marcus JL 2020

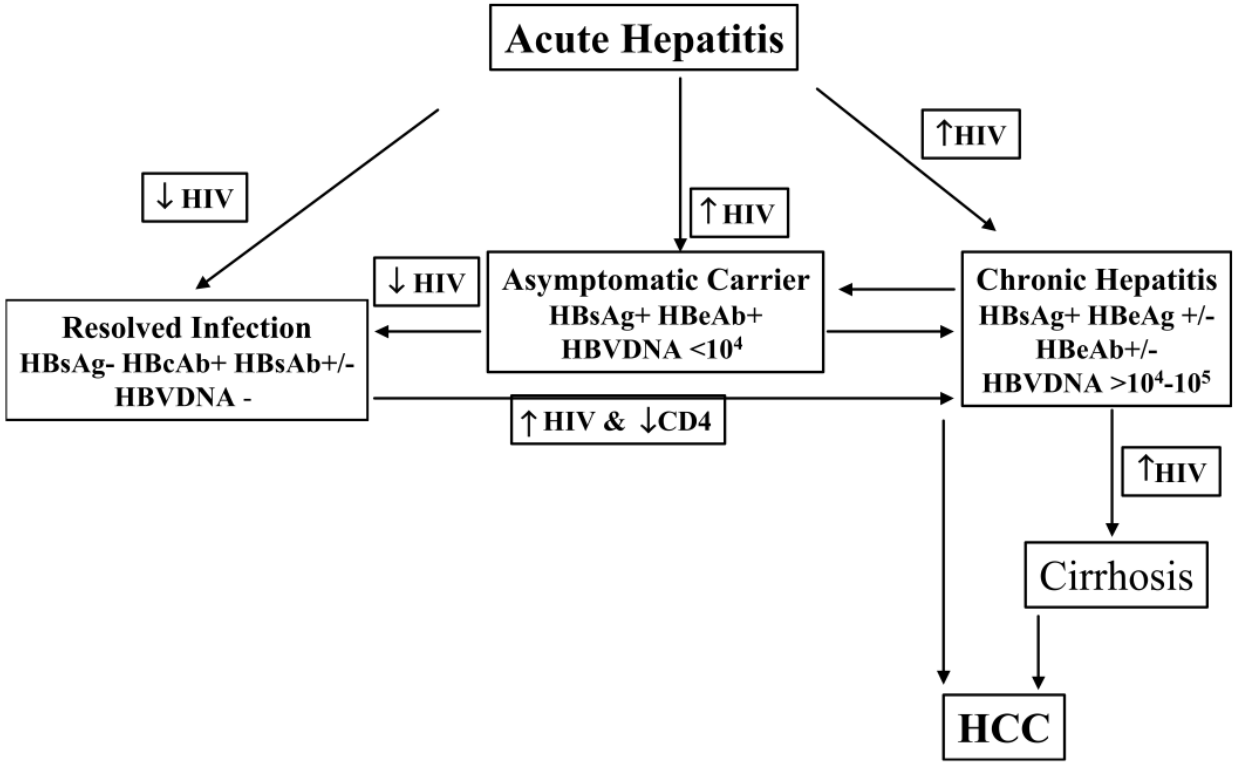


Chamroonkul N, Nat Rev Gastroenterol Hepatol, 2019

Co-infection with HIV significantly modifies the natural history of HBV infection

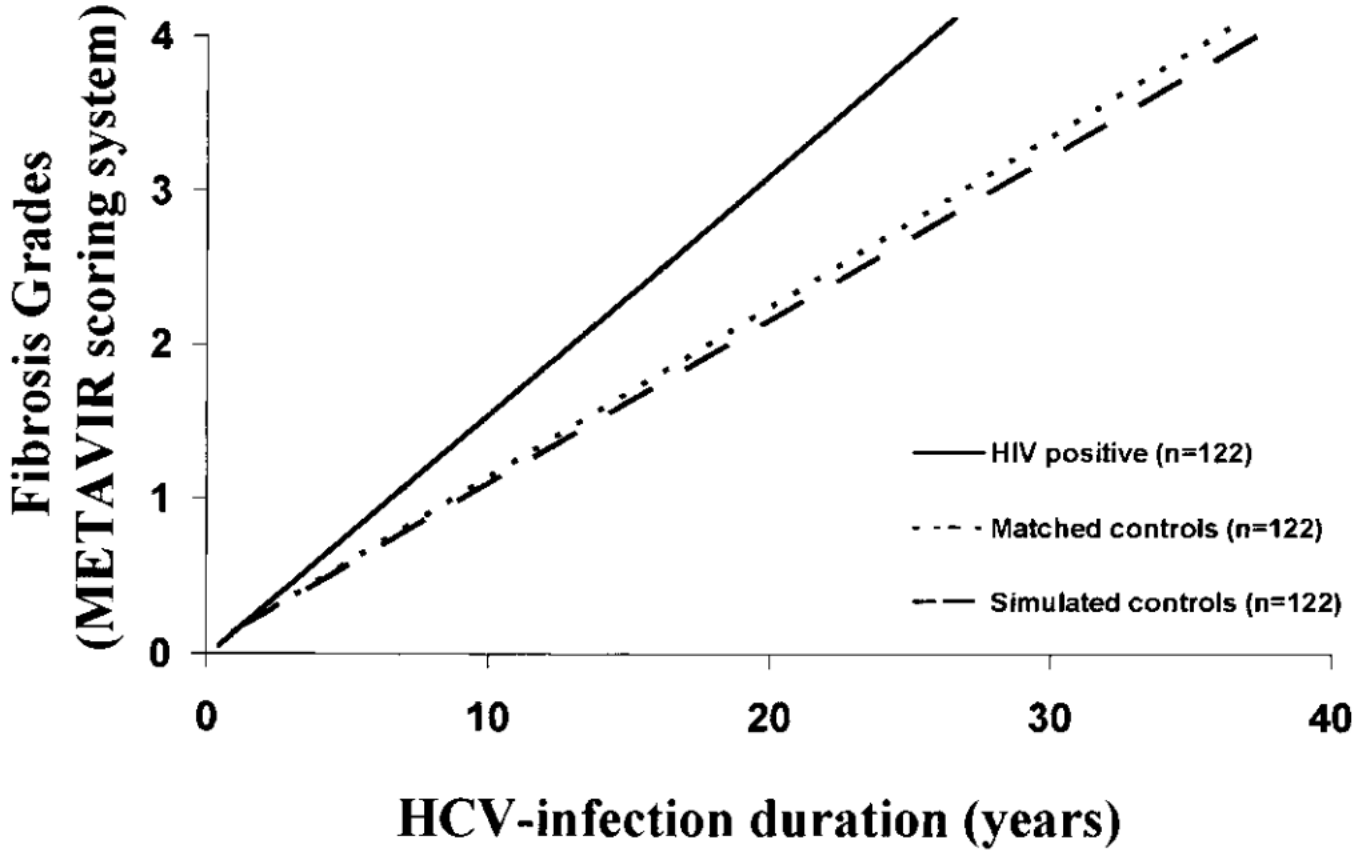
In patients with HBV infection, HIV co-infection is associated with:

- ✓ Higher chronicity rate of acute hepatitis B
- ✓ Higher levels of HBV replication, even in the presence of HDV super-infection related to HIV-induced CD4 depletion
- ✓ lower rate of spontaneous loss of HBeAg and/or HBsAg and seroconversion to anti-HBe and anti-HBs

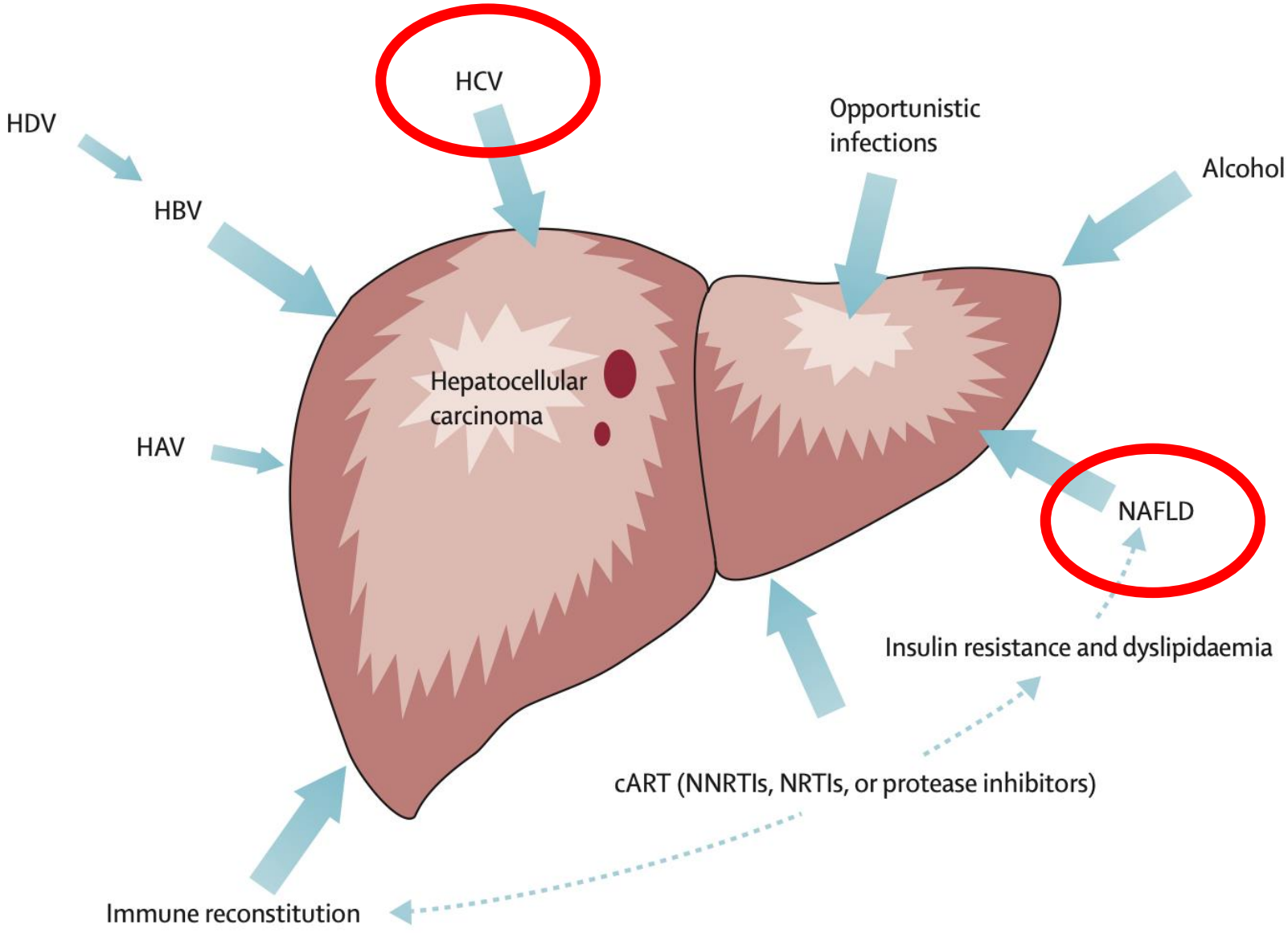


Puoti, M. et al. J. Hepatol. 2006

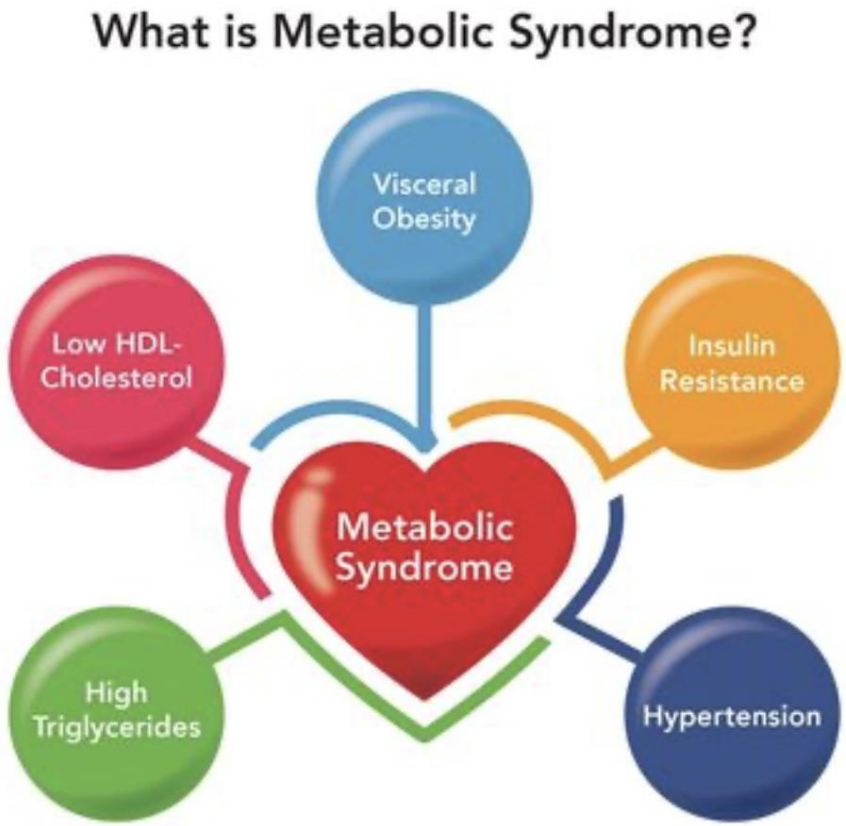
Co-infection with HIV significantly modifies the natural history of HCV infection



Benhamou, Y. et al. Hepatology 1999
Mohsen, Gut 2003

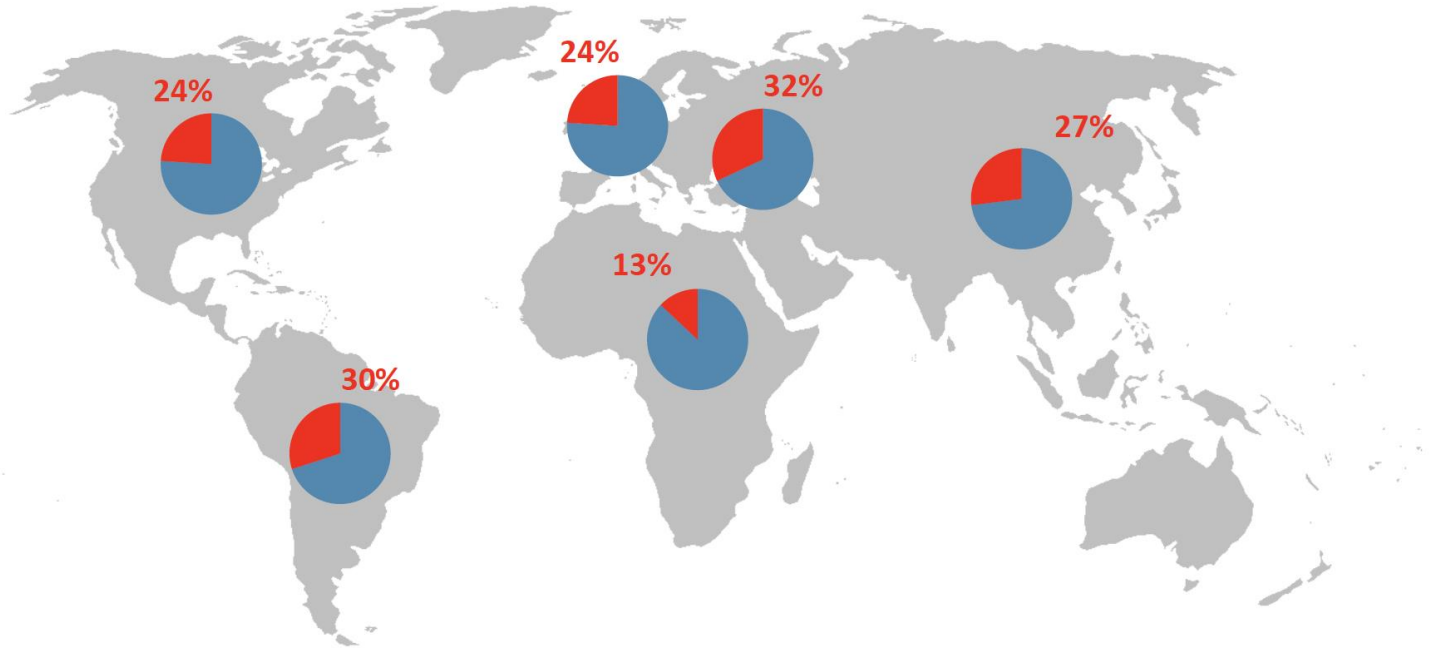

HCV
HDV
HBV
HAV
Opportunistic infections
Alcohol
Hepatocellular carcinoma
NAFLD
Insulin resistance and dyslipidaemia
cART (NNRTIs, NRTIs, or protease inhibitors)
Immune reconstitution

STEATOEPATITE NON ALCOLICA



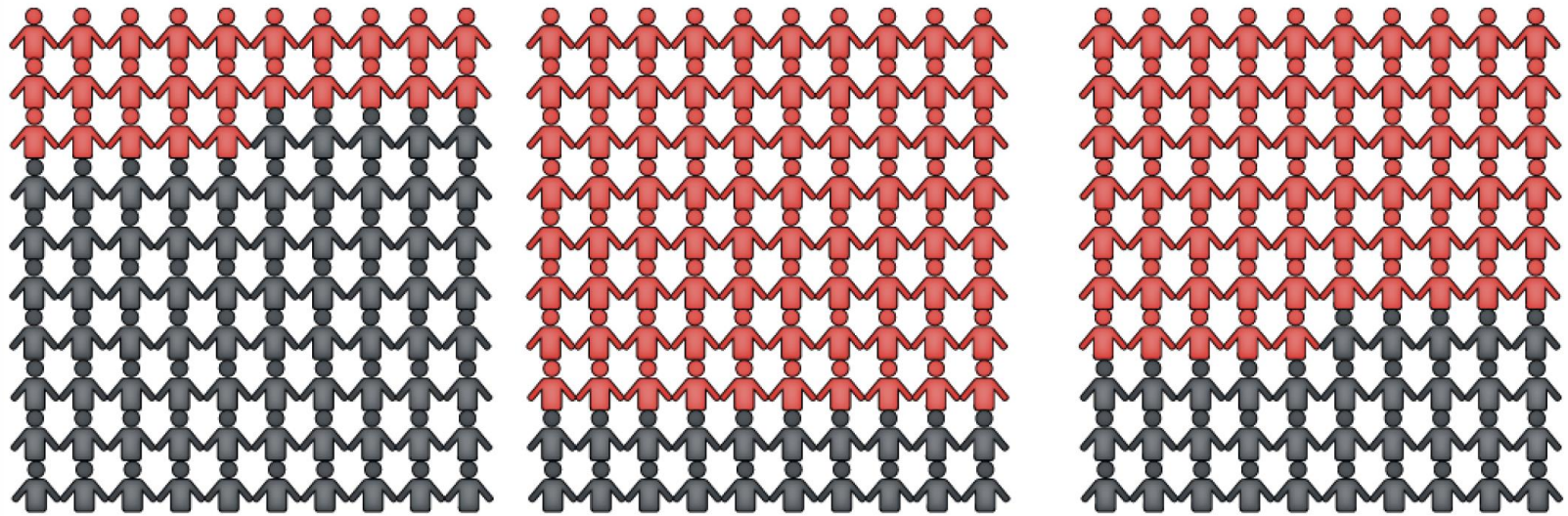
Component	Clinical Cutoff Values
Waist Circumference	≥102 cm in men ≥88 cm in women
Triglycerides	≥150 mg/dL
HDL Cholesterol	<40 mg/dL in men <50 mg/dL in women
Blood Pressure (BP)	≥130 mmHg Systolic BP or ≥85 mmHg Diastolic BP
Fasting Glucose	≥100 mg/dL
Diagnosis	Any 3 of the 5 features above

25% of the world population has fatty liver



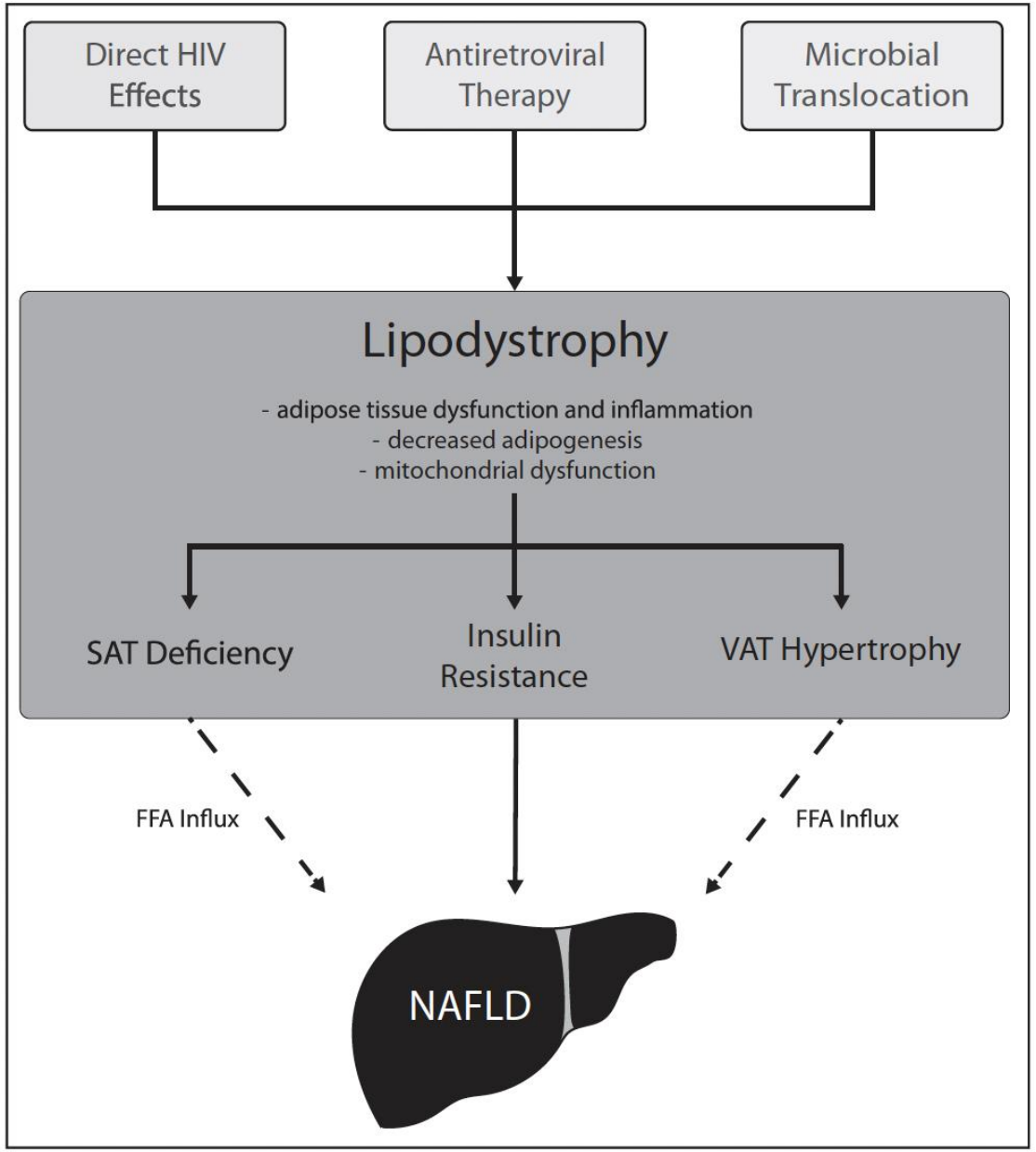
Modifié de Younossi et al. Hepatology 2016;64:73

Fatty Liver in different populations



Community (25% NAFLD) Obesity (80% NAFLD) Type 2 diabetes (65% NAFLD)

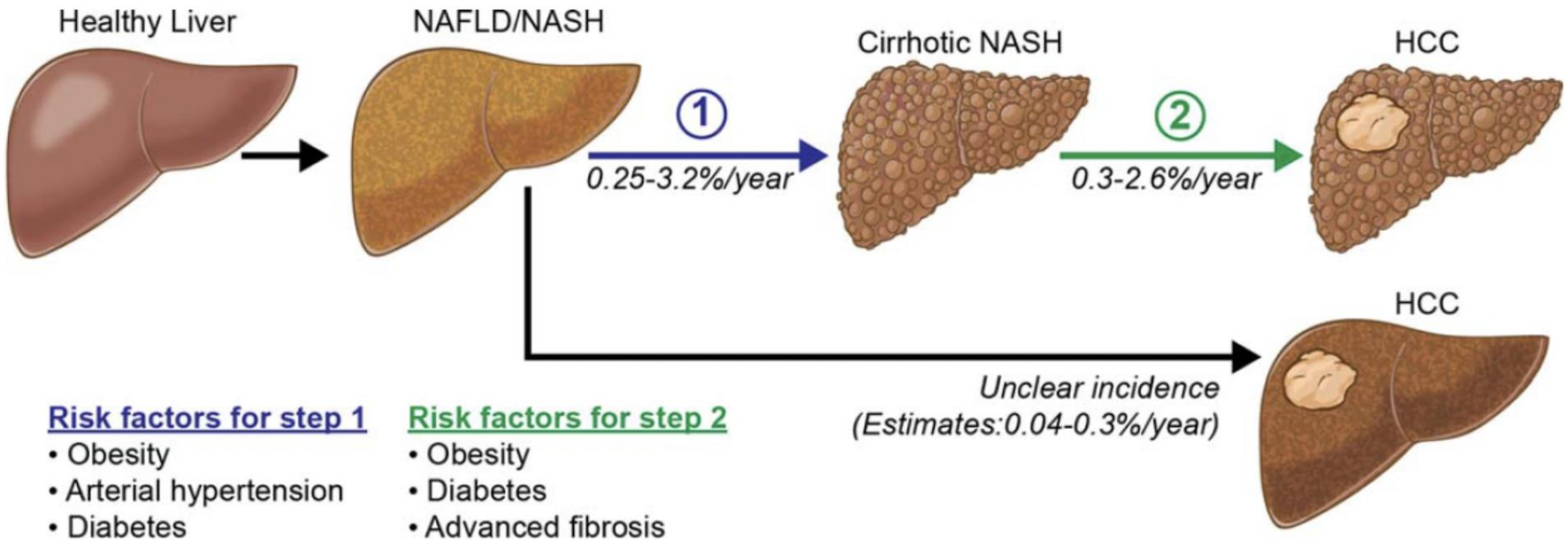
Francque et al. J HEP Report 2021



- The prevalence of NAFLD in patients who are HIV mono-infected ranges from 30% to 60%
- NAFLD in HIV-infected patients occurs at a significantly lower BMI than those without HIV
- HIV-associated NAFLD is not only associated with a high prevalence of fibrosis but also rapid fibrosis progression

Yen DW, Curr Opin HIV AIDS 2022
Lemoine, Curr. Opin. Infect. Dis. 2012

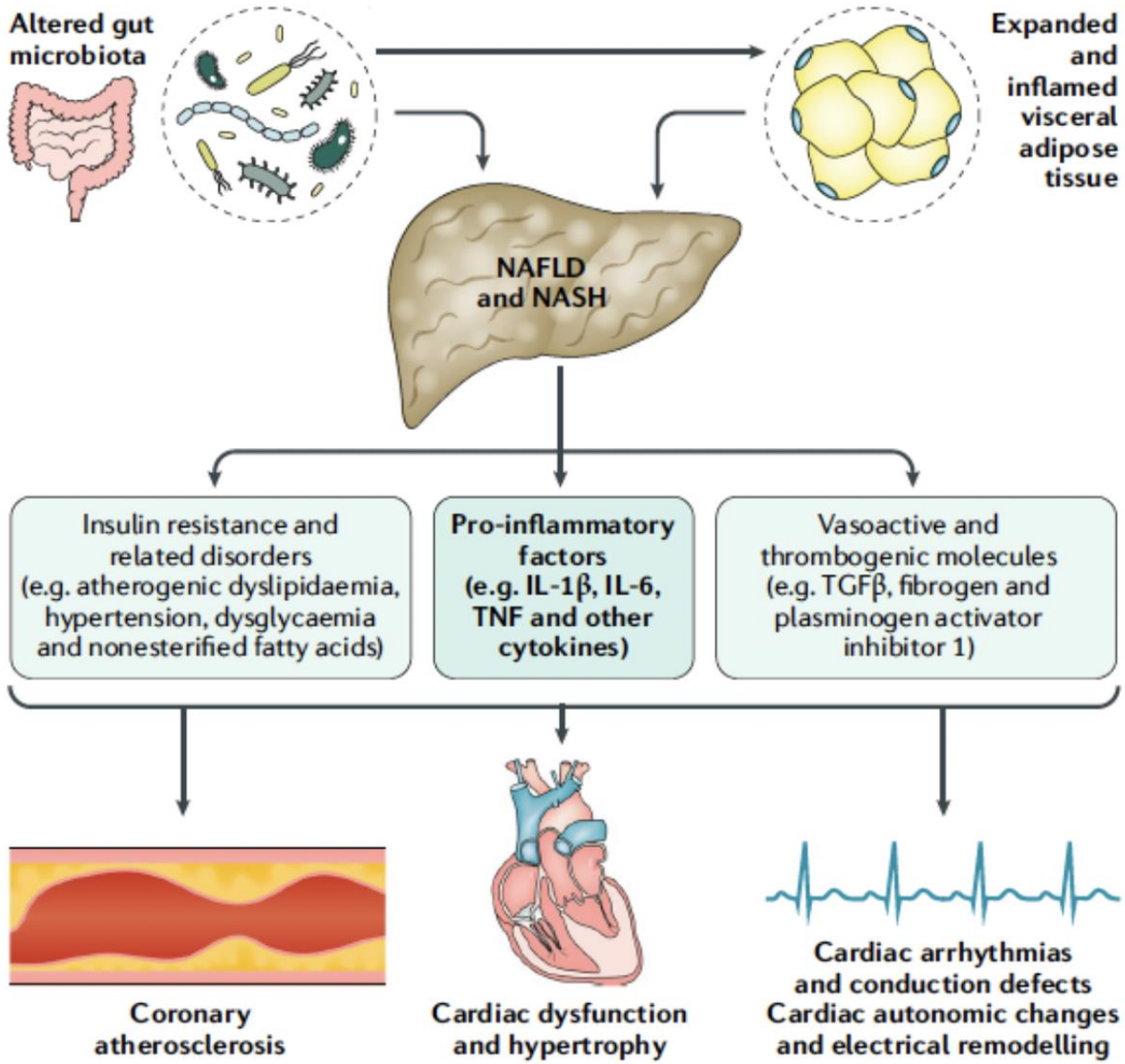
Natural history of NAFLD



Risk factors for step 1
- Obesity
- Arterial hypertension
- Diabetes
- Dyslipidemia
- PNPLA3/TM6SF2 Polymorphisms
- Gut microbiota
- Dietary habits

Risk factors for step 2
- Obesity
- Diabetes
- Advanced fibrosis
- PNPLA3/TM6SF2 Polymorphisms
- Age

D'Avola et al., Clin Liver Dis 2016



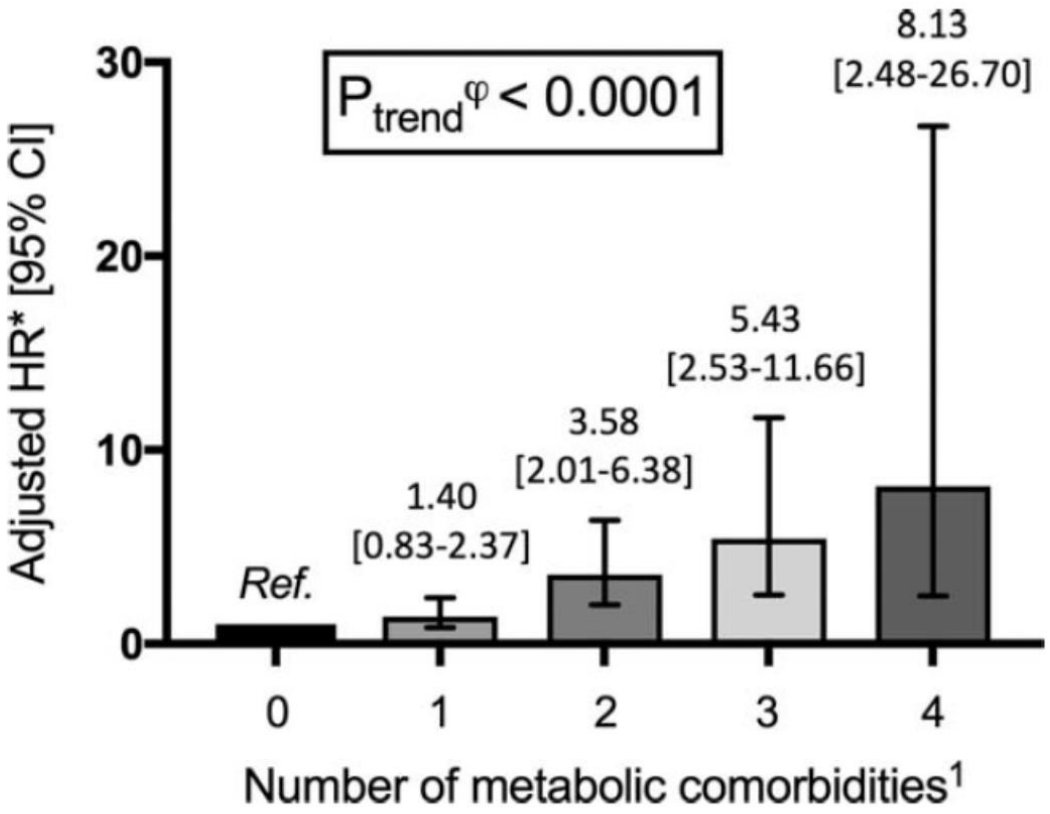
Anstee et al.,
Nat Rev Gastro Hep 2018

Causes of death of NAFLD patients

Outcome	Number
Death or OLT	*n* = 193
Cardiovascular disease	74 (38.3%)
Non-liver cancer	36 (18.7%)
Cirrhosis complications	15 (7.8%)
HCC	2 (1%)
Liver transplantation	1 (0.5%)
Infections	15 (7.8%)
Others	35 (18.1%)

Angulo *et al*. Gastro 2015

Metabolic comorbidities and the risk of HCC

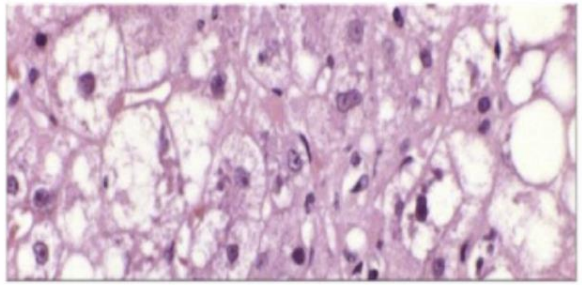


[1]Obesity, dyslipidemia, hypertension and type 2 diabetes

Simon et al., Hepatology 2018

Diagnostic modalities for NAFLD, NASH and fibrosis

- Invasive Modalities:
  - Histology (liver biopsy is the imperfect gold standard to diagnose NASH and stage fibrosis)
- Non-invasive Modalities:
  - Non-invasive modalities for NASH are not very fruitful.
  - Better opportunities to find non-invasive tests for fibrosis
  - International efforts to find NITs: LITMUS and NIMBLE



Clinical/lab tests

- NAFLD fibrosis score
- FIB-4 index
- AST:ALT ratio
- AST:platelet ratio index
- Hepascore®
- FibroTest®
- FibroMeter®
- Fatty liver index
- Index of NASH

Imaging

- Ultrasound
- Computer tomography
- Magnetic resonance imaging
- Magnetic resonance spectroscopy
- Transient elastography
- Acoustic radiation force impulse
- Magnetic resonance elastography

Biomarkers

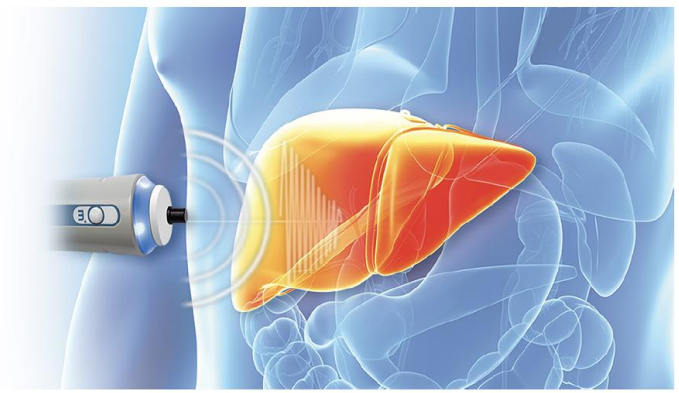
- Hyaluronic acid
- Fucosylated haptoglobin (Fuc-Hpt)
- Macroglobulin-2 binding protein (Mac-2bp)
- Fuc-Hpt + Mac-2bp
- ELF score
- FIBROSpect®
- PRO C3

Younossy & Henry, Gastroenterology 2020

Commonly used noninvasive tests for advanced fibrosis in NAFLD

FIB-4 → AST, ALT, Age, Platelet count

NFS → AST/ALT, IFG/T2DM, age, BMI, platelet count, albumin



Vibration-controlled transient elastography (**Fibroscan®**)

Fibrosis-4 (FIB-4) Calculator

Share

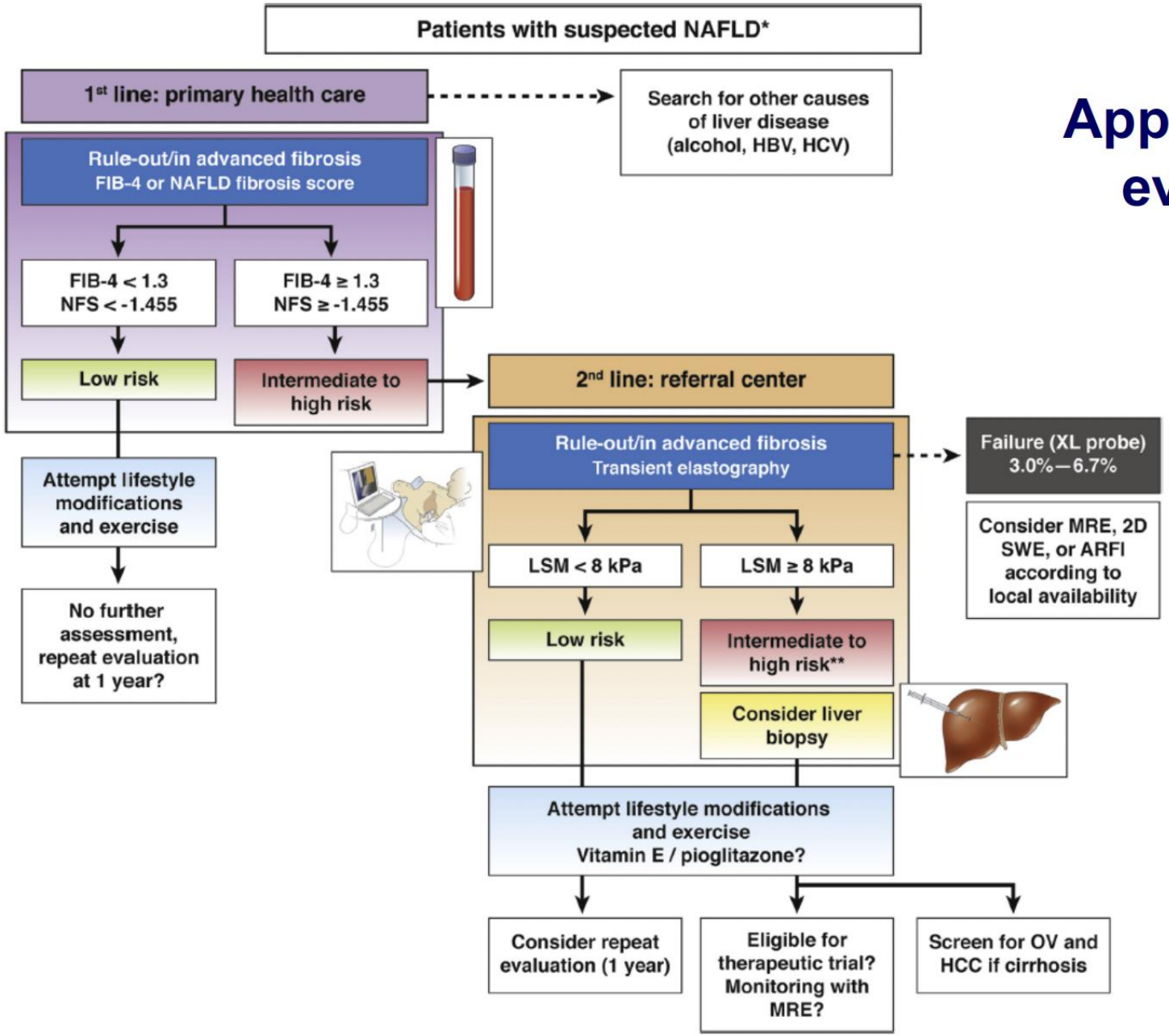
The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age } (\textit{years}) \times \text{AST Level } (\textit{U/L})}{\text{Platelet Count } (\textit{10}^9\textit{/L}) \times \sqrt{\text{ALT } (\textit{U/L})}} =$$

Interpretation:

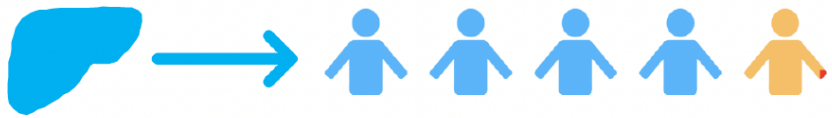
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Approach to noninvasive evaluation of NAFLD



Castera et al., Gastroenterology 2019

Change in FIB-4 Risk Group from baseline and at 3 year from NAFLD diagnosis



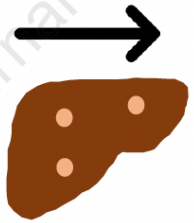
Low-risk FIB-4
FIB-4 < 1.3
N=151194

20% progressed to **indeterminate**/**high** risk

Indeterminate-risk FIB-4
FIB-4 1.3 - 2.67
N=43341

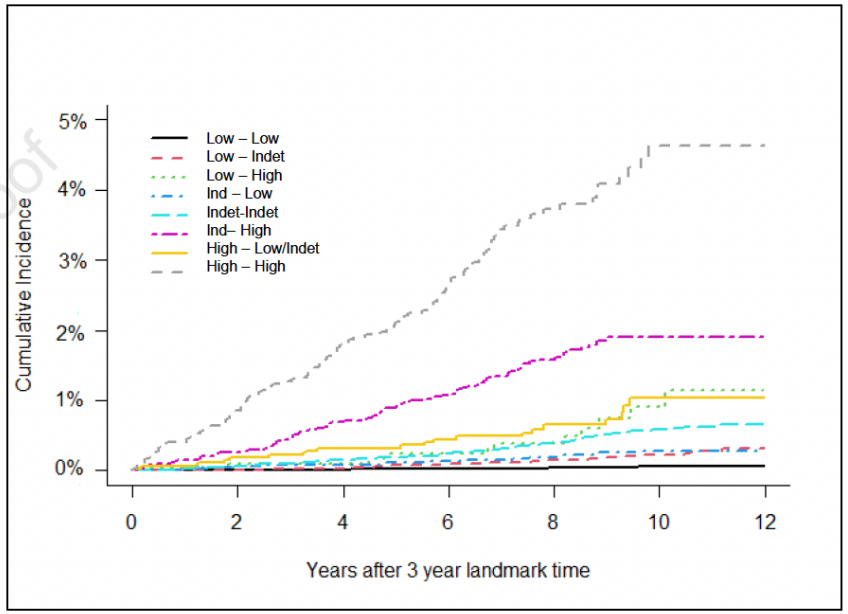
16% progressed to **high** risk

High-risk FIB-4
FIB-4 > 2.67
N=7784



HCC Risk

HCC risk after change in FIB-4 at 3 years



Annual IR for HCC per 1,000 PY
Low-Low 0.05 per 1,000 PY (reference)
Low-Indeterminate 0.21 per 1,000 PY, adjusted HR 3.45
Indet-Indet 0.53 per 1,000 PY, adjusted HR 7.96
Indet-High 1.90 per 1,000 PY, adjusted HR 26.52
High-High 4.56 per 1,000 PY, adjusted HR 57.69

Risk of developing cirrhosis or HCC corresponded to a subsequent increase or decline in FIB-4 over 3 years

Cholankeril G, J Hepatol 2022

Lifestyles and Fatty Liver

Weight

Sport

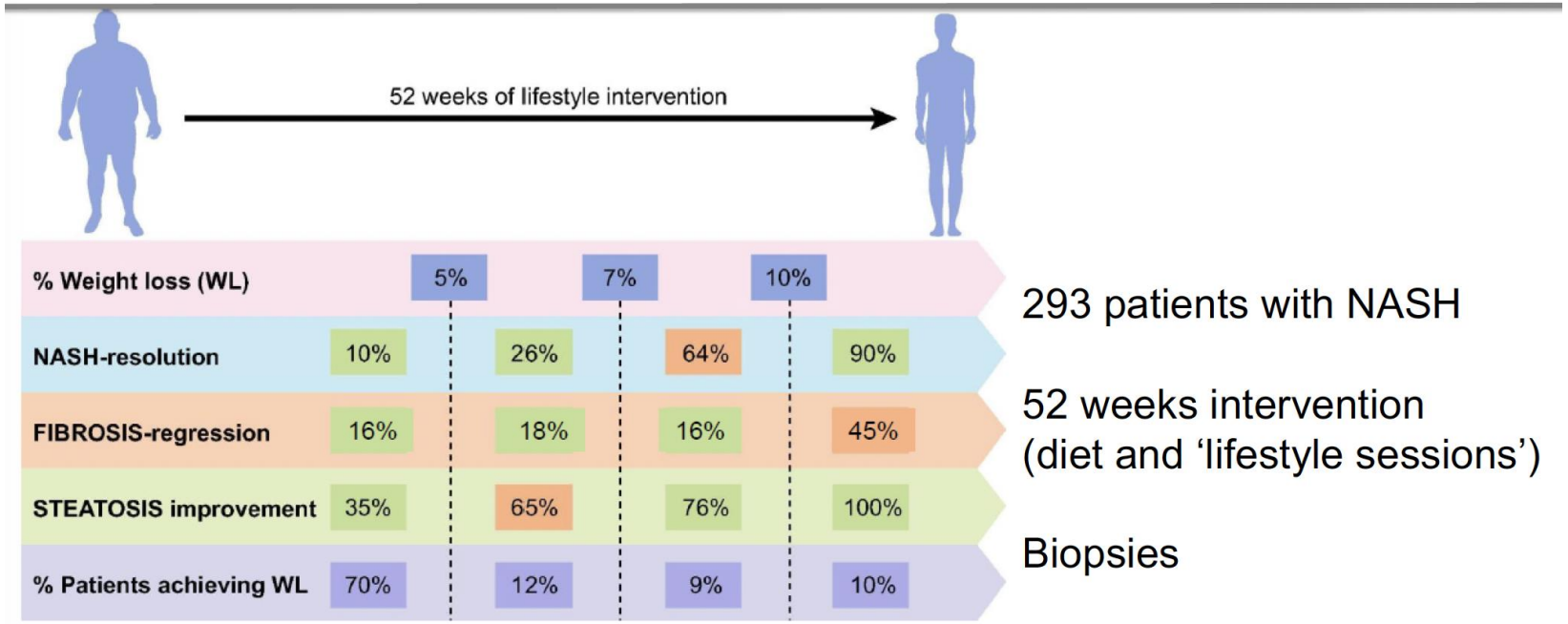
Diet

Beverages

Screens

Sleep

Weight loss



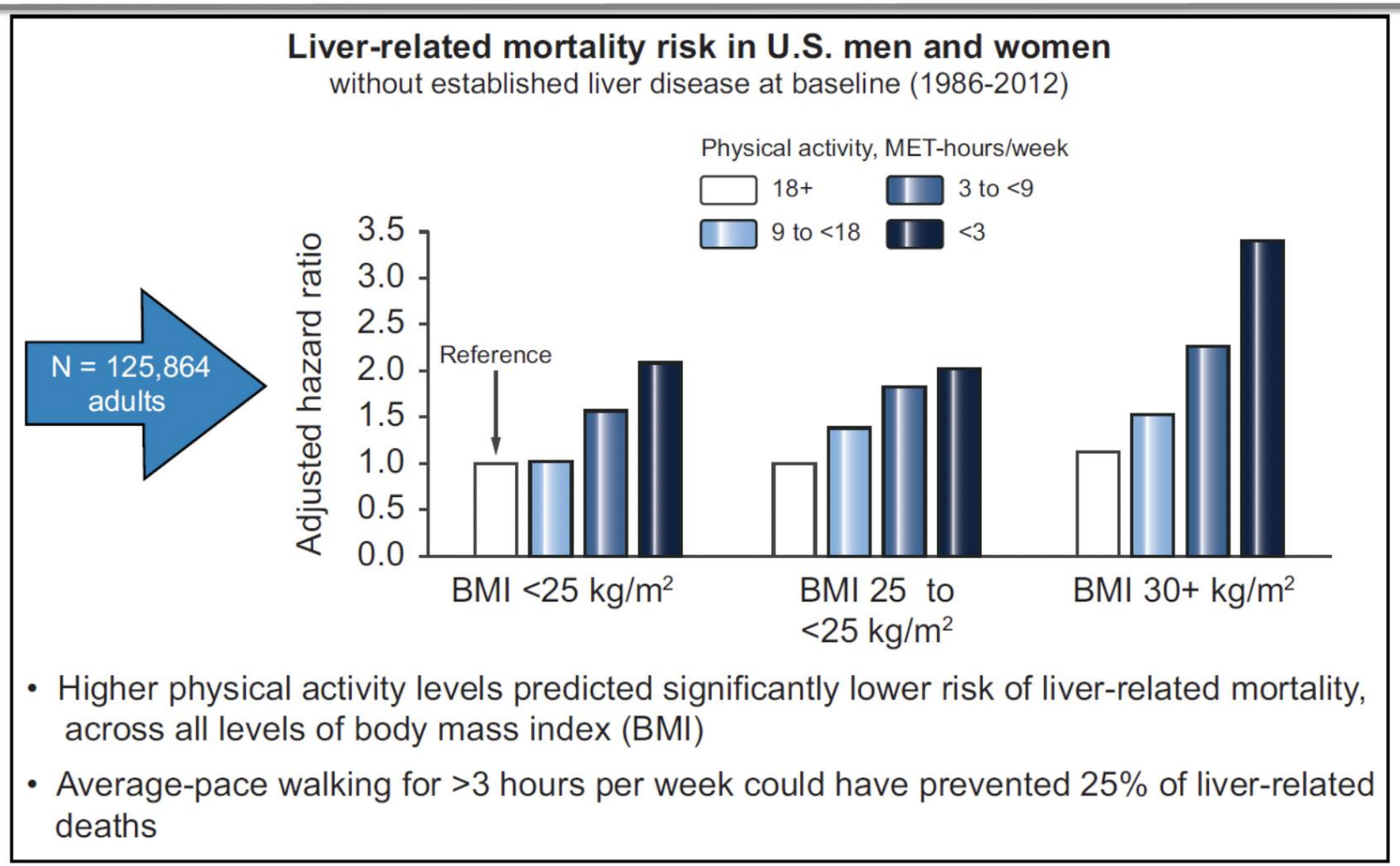
293 patients with NASH

52 weeks intervention
(diet and 'lifestyle sessions')

Biopsies

Vilar-Gomez et al, *Gastroenterology*, 2015
Romero-Gomez et al, *J Hep*, 2017

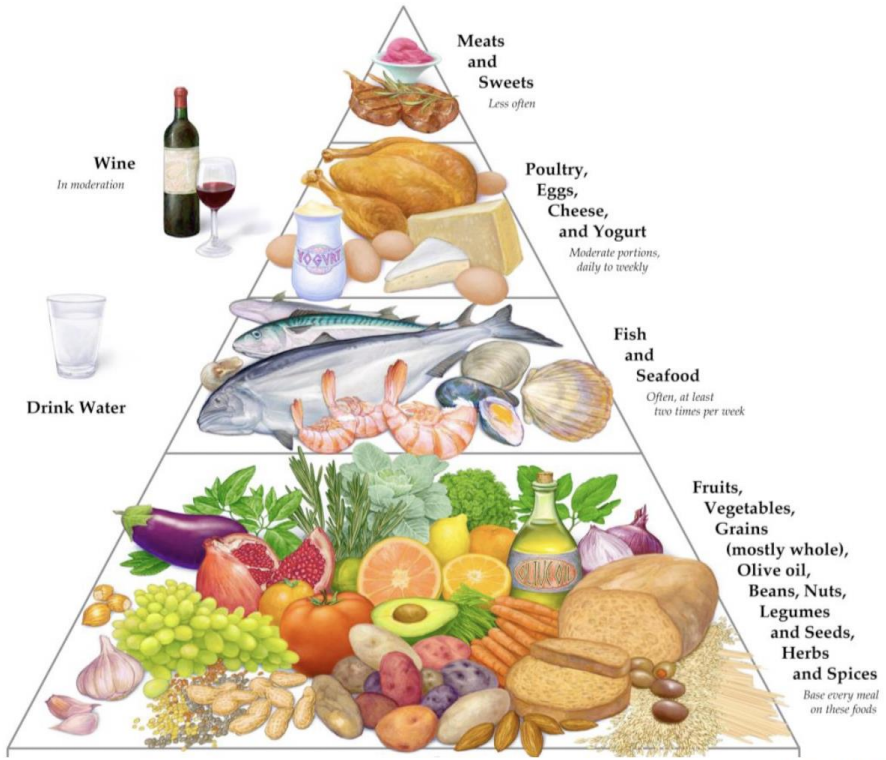
Physical activity and Liver mortality



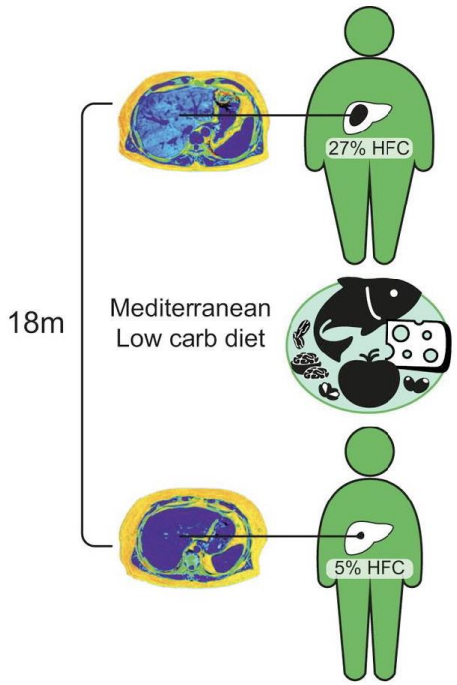
- Higher physical activity levels predicted significantly lower risk of liver-related mortality, across all levels of body mass index (BMI)
- Average-pace walking for >3 hours per week could have prevented 25% of liver-related deaths

Simon TG, J Hepatol 2020

Mediterranean Diet



www.mayoclinic.org

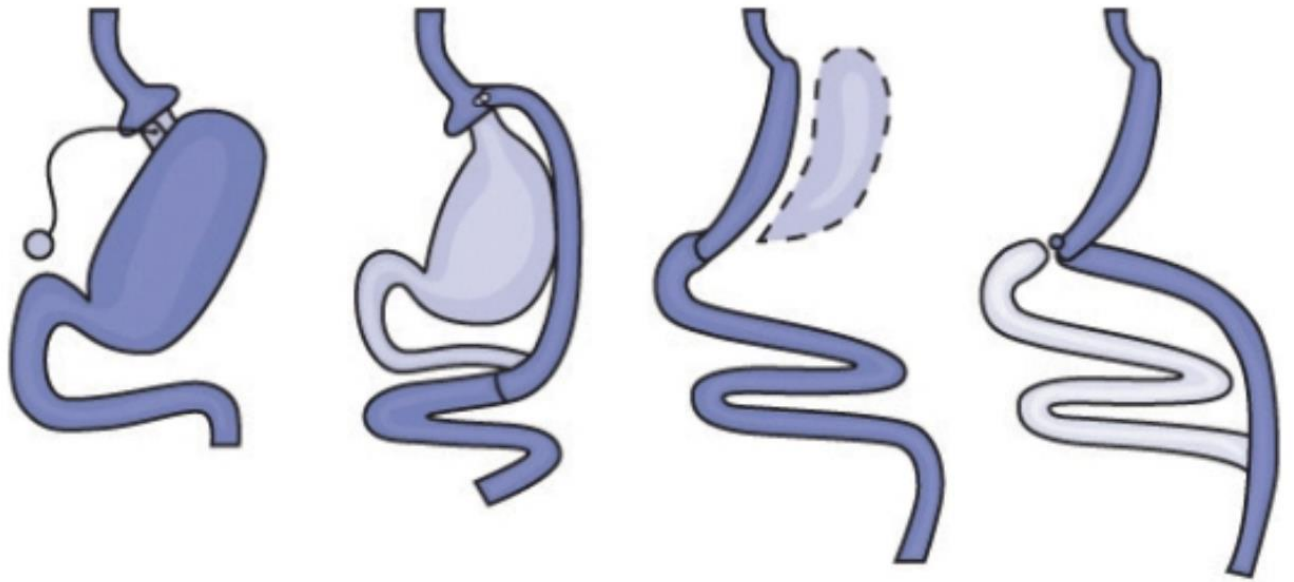


Gepner et al. J Hep 2019

Sugar Content in sodas

Courtoisie de Prof. M. Abdelmalek

Bariatric surgery



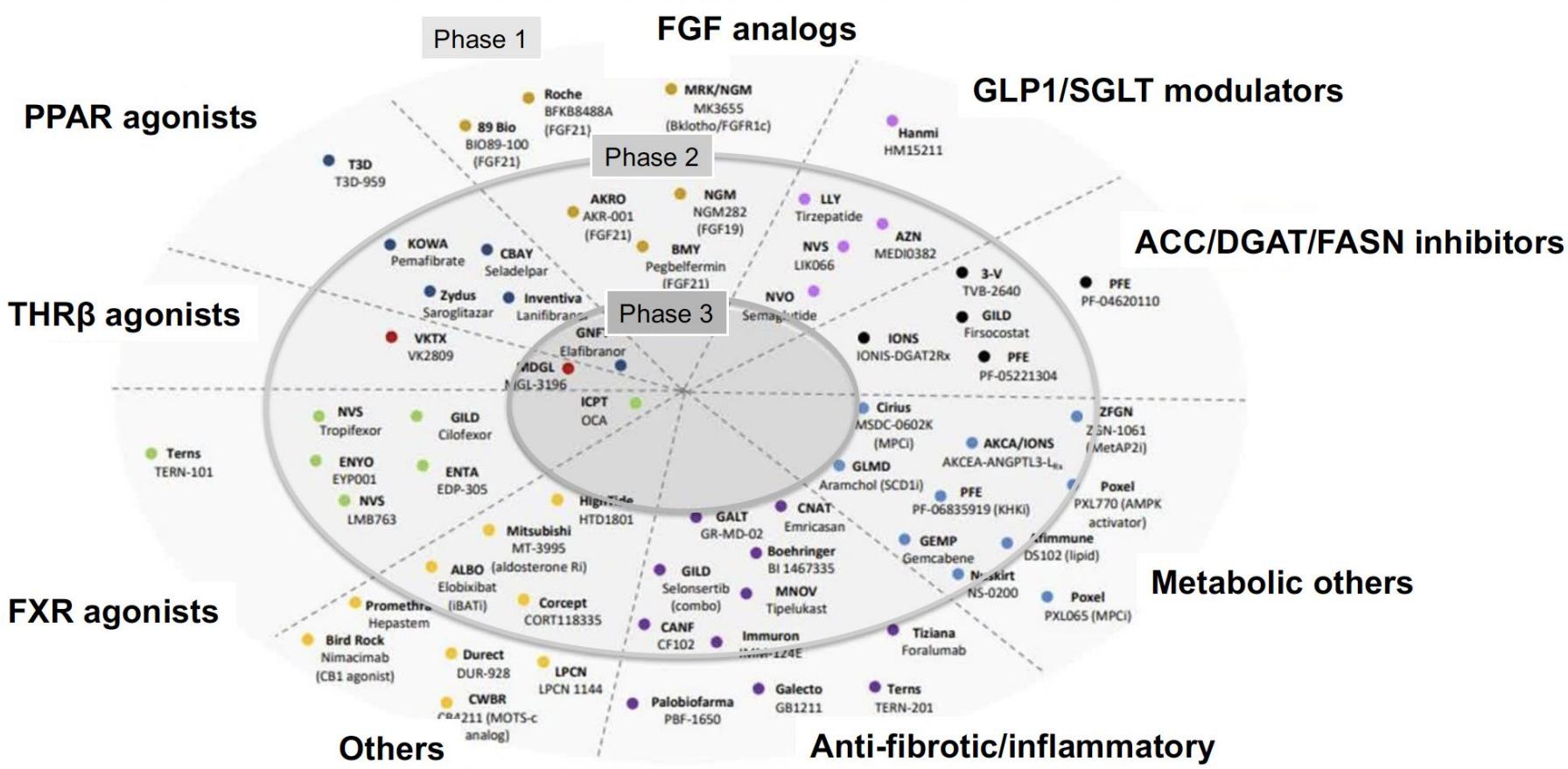
Adjustable Gastric Band (AGB)

Roux-en-Y Gastric Bypass (RYGB)

Vertical Sleeve Gastrectomy (VSG)

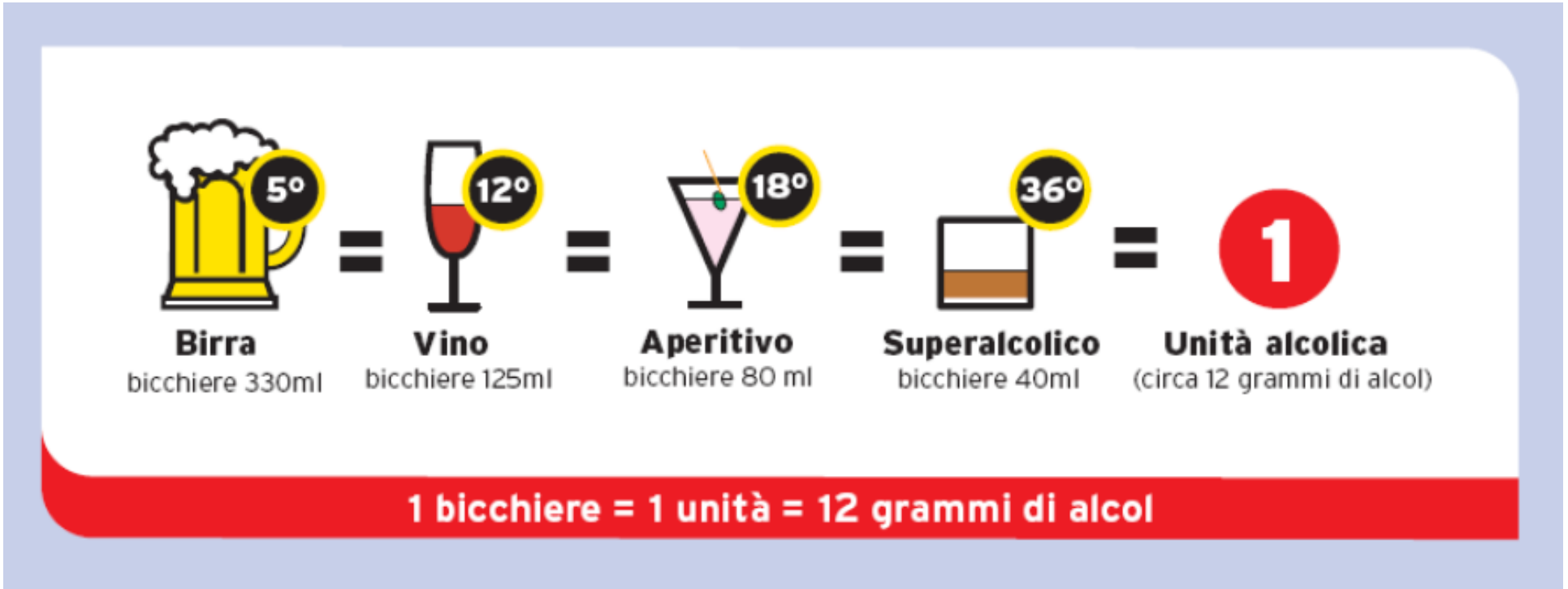
Biliopancreatic Diversion With a Duodenal Switch (BPD-DS)

Drug development in NASH



Lifestyles or drug ?

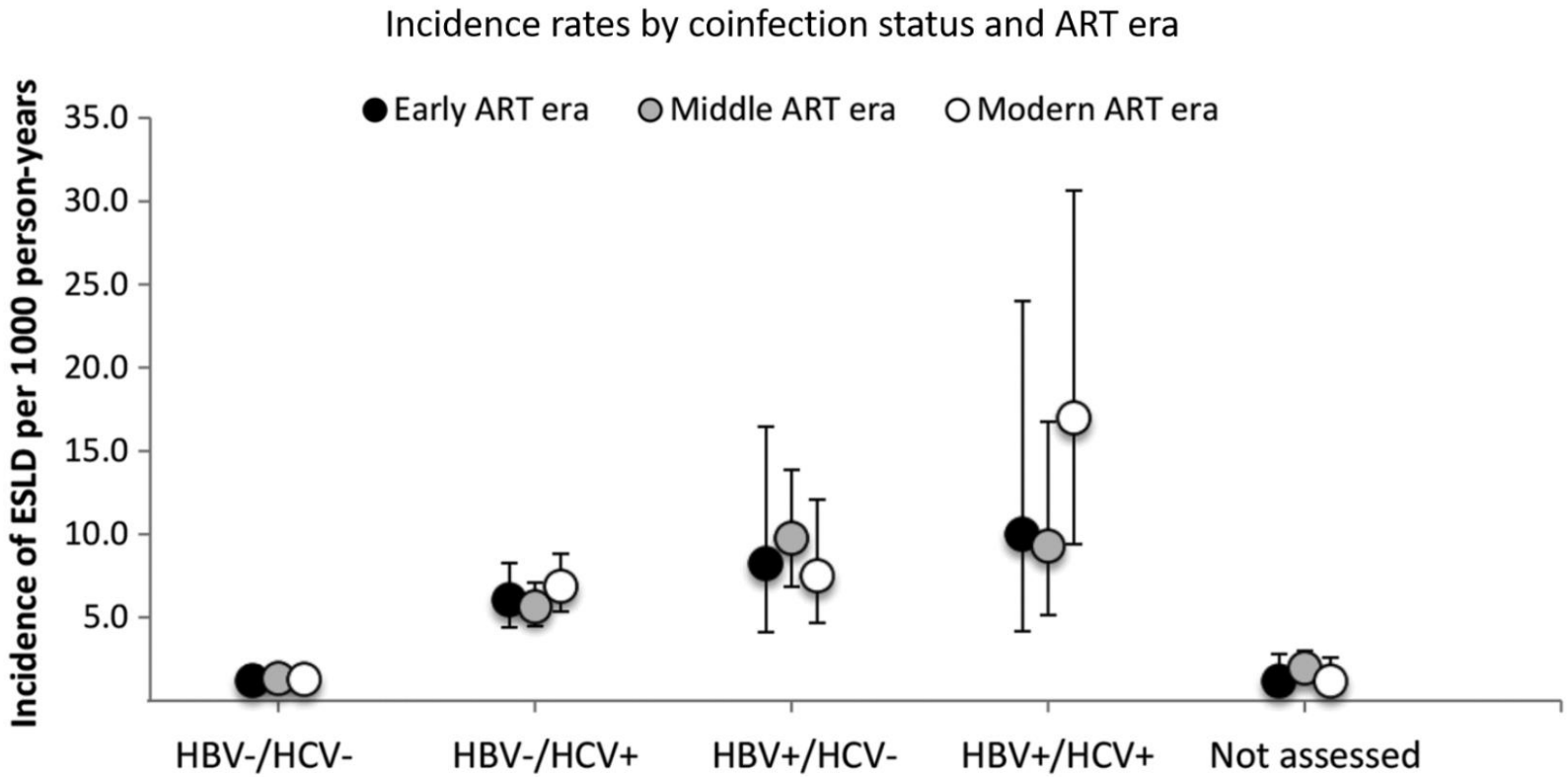
	Lifestyles	**Drug therapy**
Availability	Yes	Soon?
Cost	Cheap	Not cheap!
Side effects	Little	Likely
Acceptance	Poor	Good
Efficacy	Good	To be proven



Time to develop ALD = to amount of alcohol consumed

- Men : 60-80 gm/day for 10 years
- Women : 20-40 gm/day for 10 years

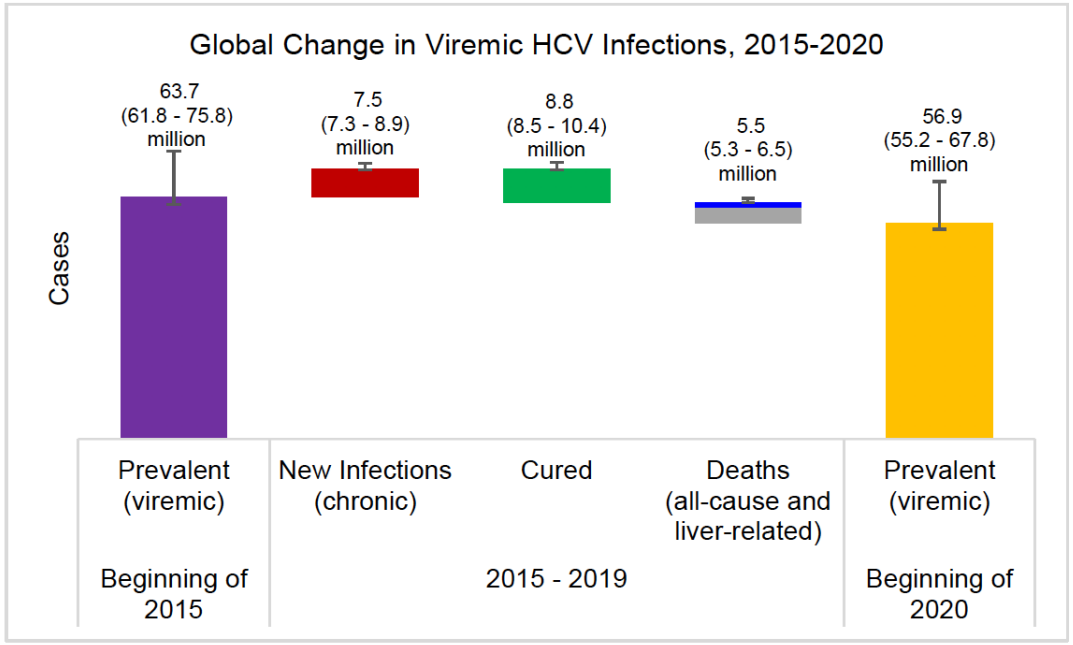
COINFEZIONE HCV



End-stage liver disease (ESLD) incidence rates and 95% confidence intervals by viral hepatitis coinfection status and antiretroviral therapy (ART) era, North American AIDS Cohort Collaboration on Research and Design, January 1996–December 2010. From Klein et al *Clin Infect Dis* 2016.

Updated HCV Epidemiology in 2020

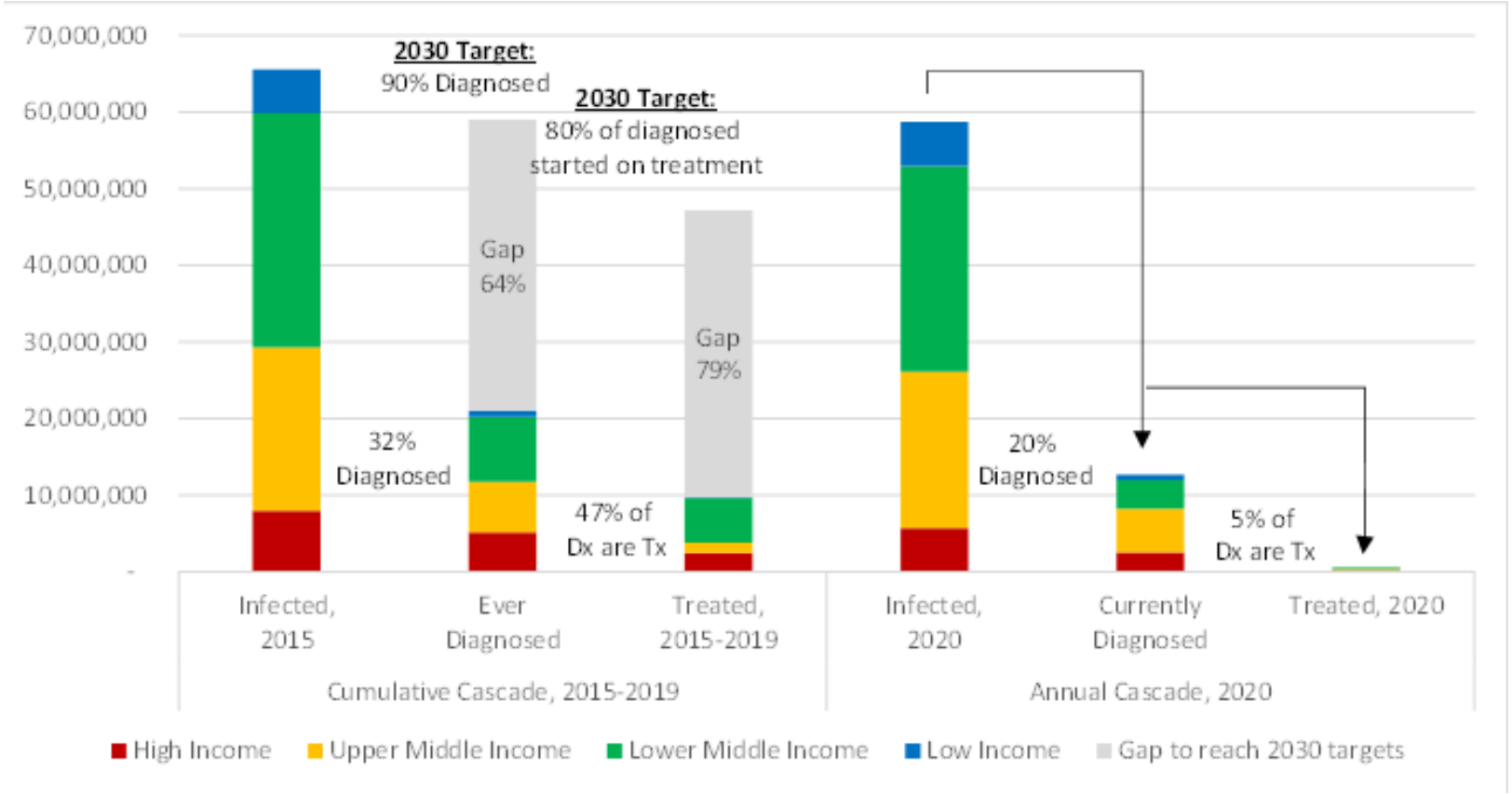
Viremic infections have declined since 2015, due to new/improved data, as well as mortality and cure



Updated estimates for Egypt, Brazil and Nigeria, as well as a new estimate for Democratic Republic of the Congo have contributed to a lower baseline prevalence in 2015

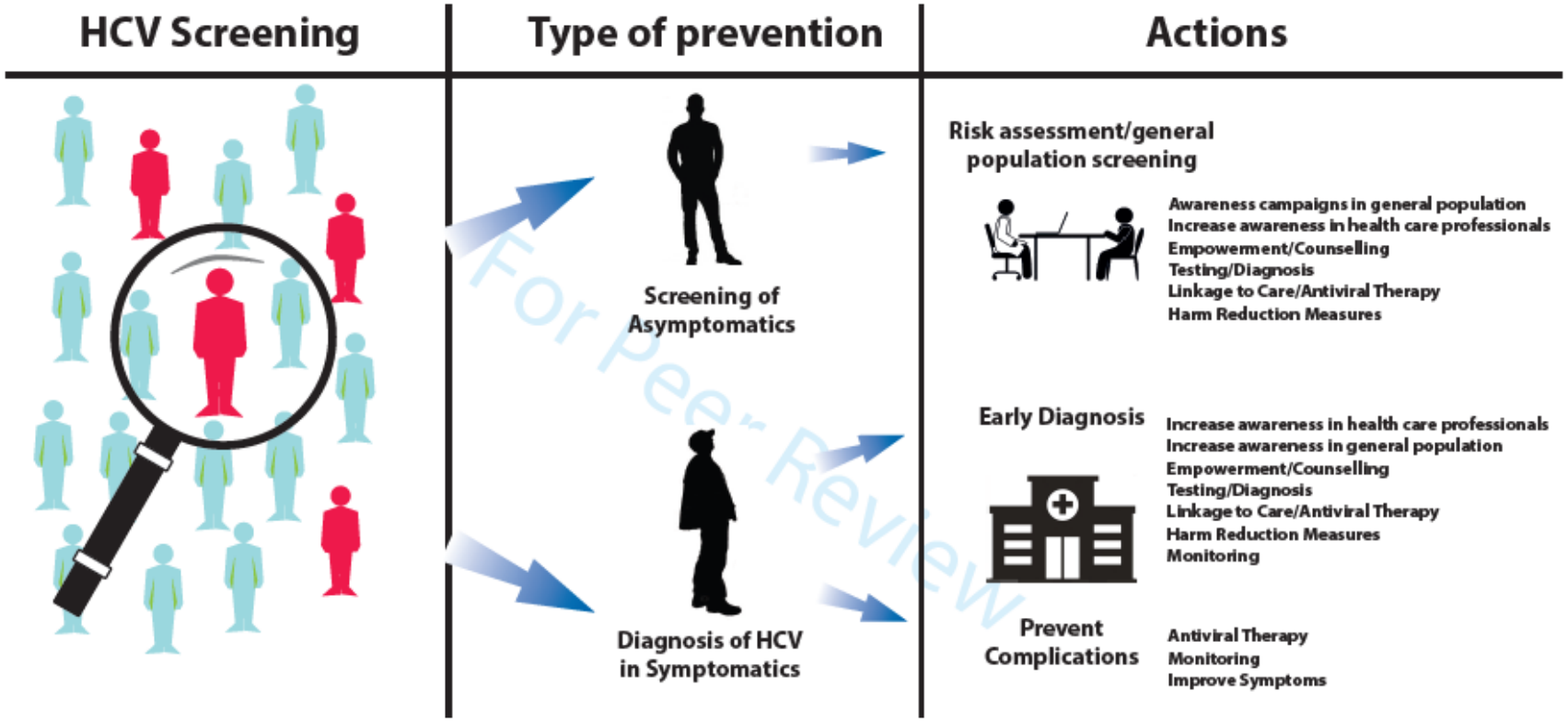
Blach S et al, LGH 2022

Updated HCV Epidemiology in 2020



Blach S et al, LGH 2022

HCV Screening:
Different Approaches Lead to Different Results



Kondili L et al, Liver International in press

EASL HCV Treatment Algorithm for TN/TE Patients Without Cirrhosis or With Compensated Cirrhosis

Treatment recommendations for HCV-mono-infected or HCV/HIV coinfected adult (aged ≥18 years) and adolescent (aged 12–17 years) patients with chronic HCV without cirrhosis or with CC* including TN and TE[†]

		Treatment-naïve		Treatment experienced	
		G/P	SOF/VEL	G/P	SOF/VEL
GT 1a, 1b, 2, 4, 5, and 6	**Without cirrhosis**	8 weeks	12 weeks	8 weeks	12 weeks
	With compensated cirrhotic	8 weeks	12 weeks	12 weeks	12 weeks
GT 3	**Without cirrhosis**	8 weeks	12 weeks	12 weeks	12 weeks
	With compensated cirrhotic	8–12 weeks[‡]	12 weeks with weight-based RBV[§]	16 weeks	12 weeks with weight-based RBV[§]

- *Child-Pugh A; [†]TE to pegIFN + RBV, pegIFN-α + RBV + SOF or SOF + RBV; [‡]In TN patients infected with GT3 with CC, treatment with G/P can be shortened to 8 weeks, but more data are needed to consolidate this recommendation; [§] If resistance testing is formed, only patients with the NS5A Y93H RAS at baseline should be treated with SOF/VEL + RBV or with SOF/VEL/VOX, whereas patients without the Y93H RAS should be treated with SOF/VEL alone.

CC, compensated cirrhosis; EASL, European Association for the Study of the Liver; G/P, glecaprevir/pibrentasvir; GT, genotype; pegIFN, pegylated interferon; RAS, resistance-associated substitution; RBV, ribavirin; SOF, sofosbuvir; TE, treatment experienced; TN, treatment-naïve; VEL, velpatasvir.

1. EASL. *J Hepatol* 2020 Nov;73(5):1170-1218. doi: 10.1016/j.jhep.2020.08.018. Epub 2020 Sep 15. 2. Maviret (GLE/PIB) US Prescribing Information.

Disease Severity Impacts the PK of PIs

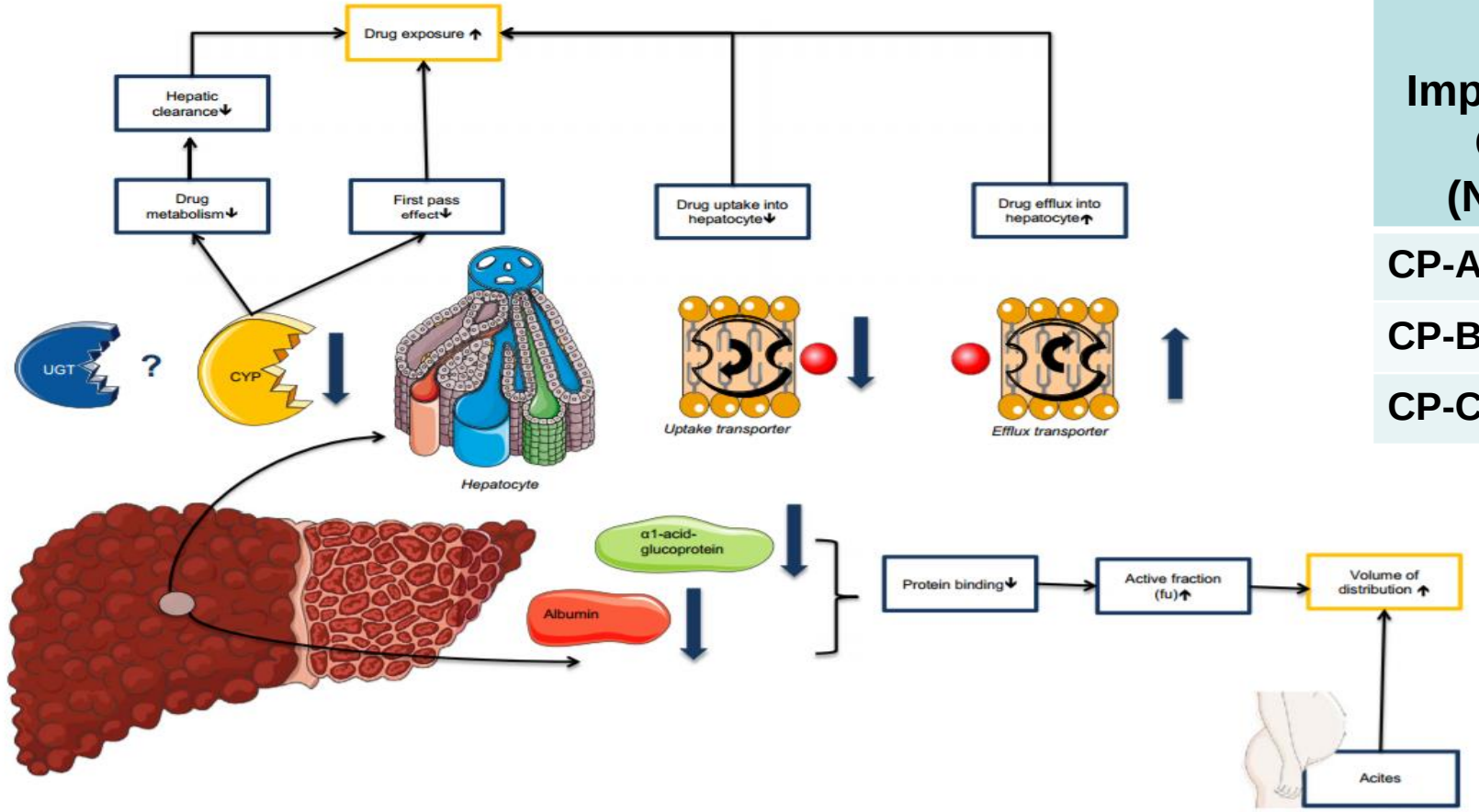


Fig. 2 Overview of the pathophysiological changes in patients with liver cirrhosis that influence drug metabolism and therefore the pharmacokinetics of drugs. *CYP* cytochrome P450, *UGT* uridine diphosphate-glucuronosyltransferase, ↓ indicates decrease, ↑ indicates increase

Impact of Hepatic Impairment on GZR PK (Non-HCV)	
CP-A	↑ 70%
CP-B	↑ 5-fold
CP-C	↑ 12-fold

SMPC Zepatier

Drug Saf (2016) 39:589–611

Liver INTERNATIONAL

ORIGINAL ARTICLE

Real-world effectiveness and safety of direct-acting antivirals in patients with cirrhosis and history of hepatic decompensation: Epi-Ter2 Study

Aleksandra Berkan-Kawiń
Zdunek, Krzysztof Tomas
Iwona Buczyńska, Monika
Jakub Klapaczyński, Włod
Aleksander Garlicki, Mare
Białkowska-Warzecha, Ol
... See fewer authors

First published: 02 March

Liver INTERNATIONAL

RESEARCH LETTER

Sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus retreatment in decompensated cirrhosis

Sonalie Patel, Michelle T. Martin, Steven L. Flamm

First published: 30 September 2021 | https://doi.org/10.1111/liv.15075

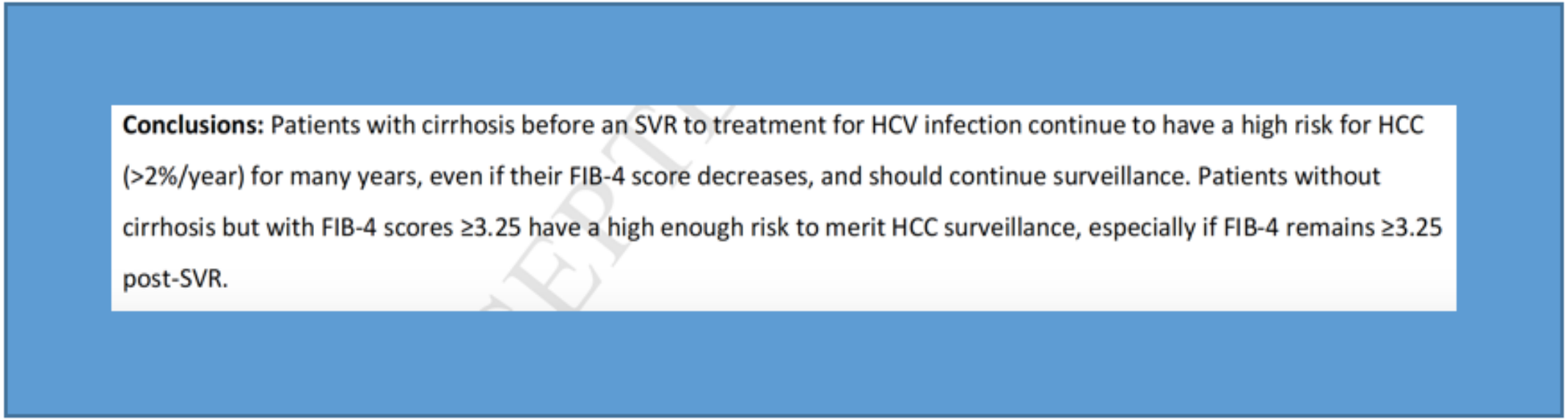
TABLE 1 Patient characteristics

Patient	1	2	3	4	5	6
Age (years)	82	63	57	56	62	52
Gender	Male	Male	Female	Male	Female	Male
BMI (kg/m^2)	30.6	22.5	29.2	37.6	29.3	34.3
Genotype/subtype	1b	3a	1a	1a	1a	3a
CTP Class (points)	B (8)	B (8)	B (7)	B (8)	B (9)	C (10)
Week 4						
HCV RNA (IU/ml)	Not detected	Not detected	126	Not detected	Not detected	Not detected
CTP CLass (points)	B (8)	B (7)	A (6)	B (7)	B (8)	B (7)
MELD-Na	15	14	11	10	15	16
Week 8						
HCV RNA (IU/ml)	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
CTP class (points)	B (8)	B (7)	A (6)	B (7)	B (7)	B (7)
MELD-Na	16	17	11	13	15	13
Week 12 (end of treatment)						
HCV RNA (IU/ml)	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
CTP class (points)	B (8)	B (7)	A (6)	B (7)	B (7)	B (7)
MELD-Na	17	13	12	12	14	17
HCV RNA (IU/ml)	Not detected	Not detected	Not detected	886,538	Not detected	Not detected
CTP class (points)	B (7)	B (7)	A (5)	B (7)	B (7)	B (9)
MELD-Na	12	11	9	11	14	14

Increased Risk of HCC Persists up to 10 Years After Virus Eradication in Patients with Advanced HCV

- 29,033 VA patients with an SVR to DAA and 19,102 with an SVR to IFN
- During 5.4 yr follow-up, 1509 incident HCCs were identified

Conclusions: Patients with cirrhosis before an SVR to treatment for HCV infection continue to have a high risk for HCC (>2%/year) for many years, even if their FIB-4 score decreases, and should continue surveillance. Patients without cirrhosis but with FIB-4 scores ≥3.25 have a high enough risk to merit HCC surveillance, especially if FIB-4 remains ≥3.25 post-SVR.



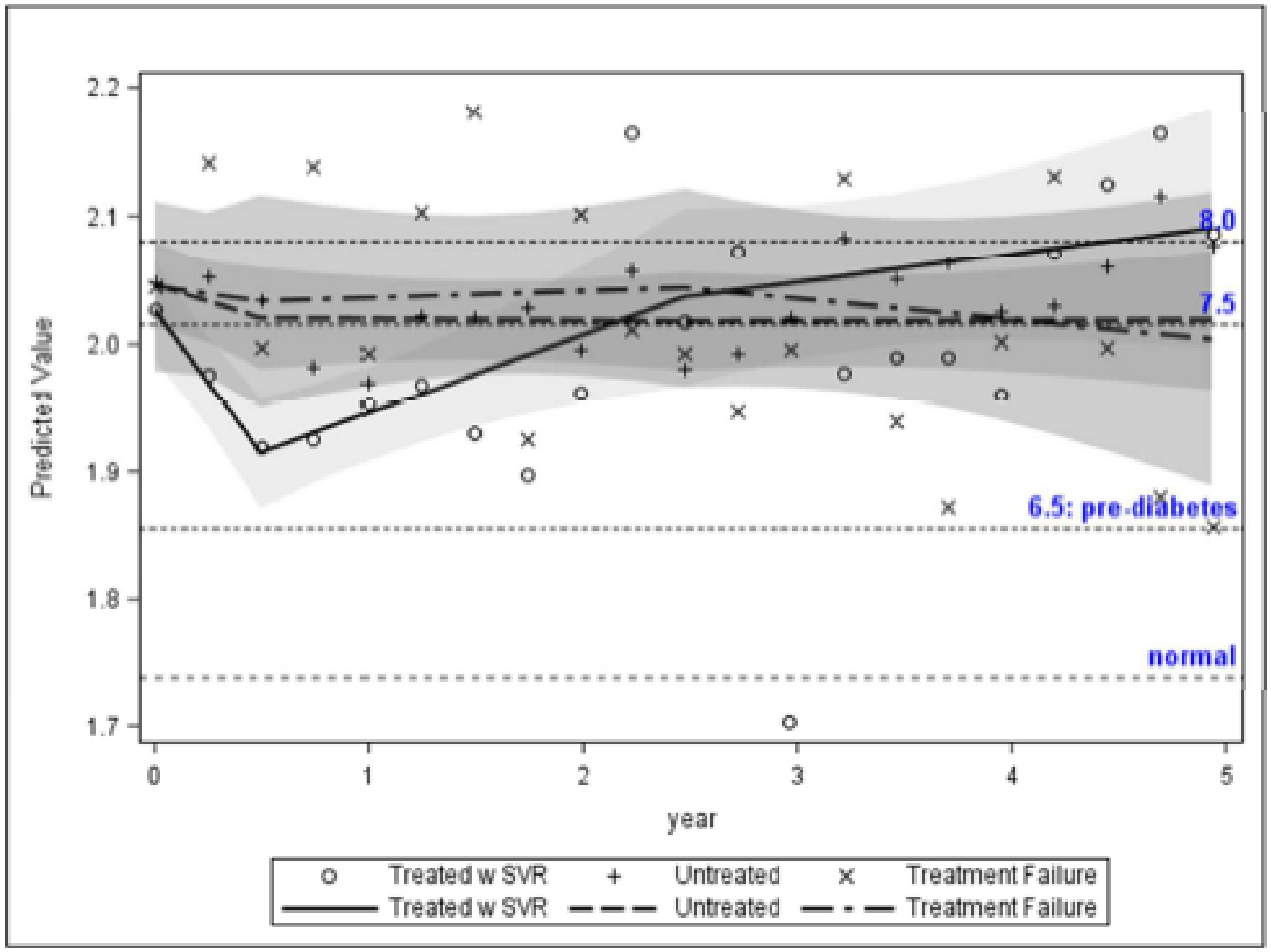
Ioannou GN et al Hepatology 2019

Who Should be Followed After an SVR?

- Patients with no to moderate fibrosis (METAVIR score F0-F2), with SVR and no ongoing risk behaviour should be discharged, provided that they have no other comorbidities (A1).

- Patients with advanced fibrosis (F3) or cirrhosis (F4) with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (A1).

SVR Does Not Improve Long Term Glycemic Control in HCV Patients



Lia Ji et al, Liver International 2019

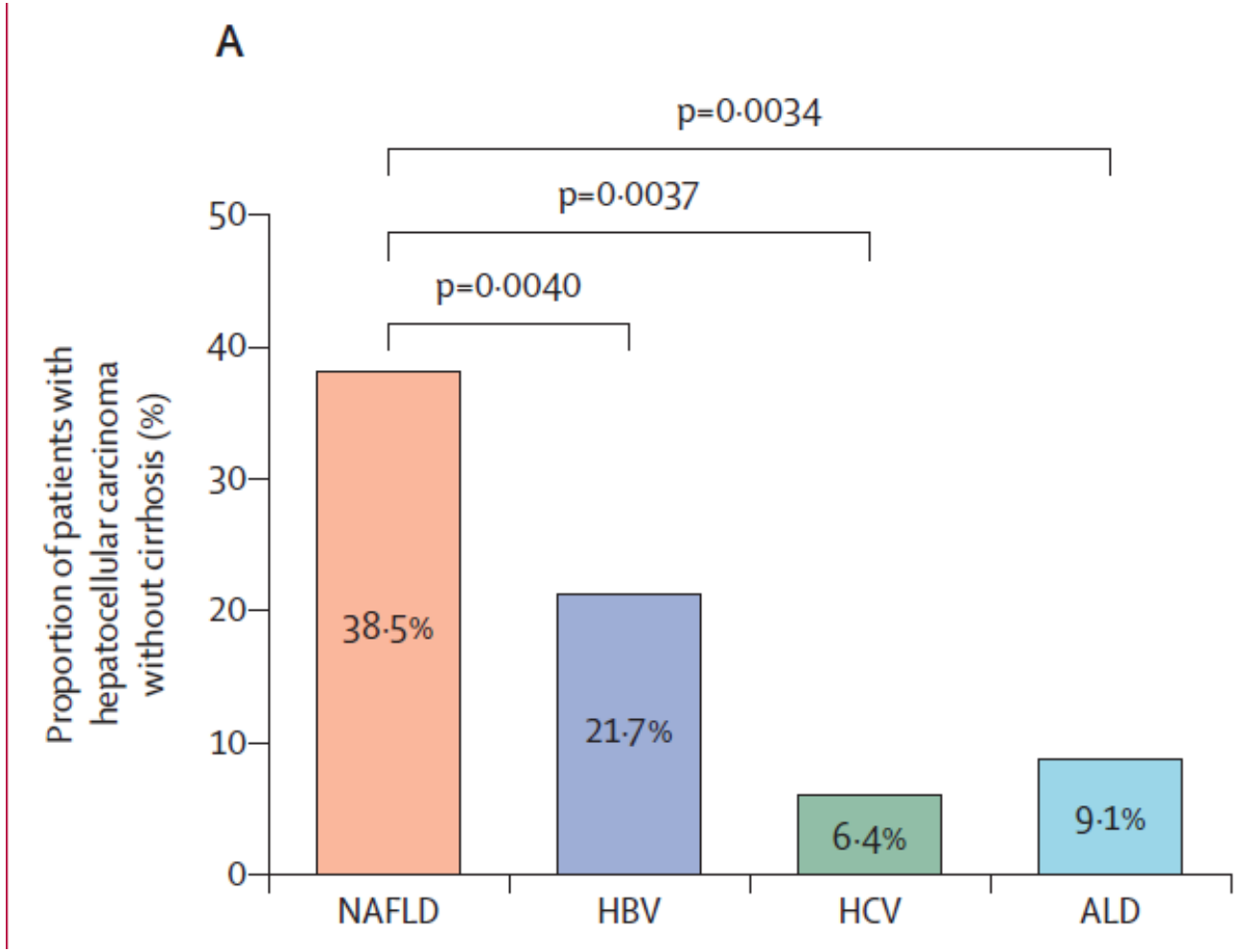
Diabetes and Obesity Impact on Repeated Elastography Measurements Following an SVR

TABLE 3. INDEPENDENT PREDICTORS OF LSM CHANGES AT 24-WEEK FOLLOW-UP AFTER THERAPY IN 748 PATIENTS WITH COUPLED EVALUATIONS

Term	Estimate	SEM	*P* Value
Sex, F	+0.008	0.016	0.63
Age, 10 years	+0.010	0.012	0.44
SVR, yes	−0.191	0.088	0.029
BMI, kg/m^2	+0.002	0.004	0.57
Diabetes, yes	+0.047	0.023	0.039

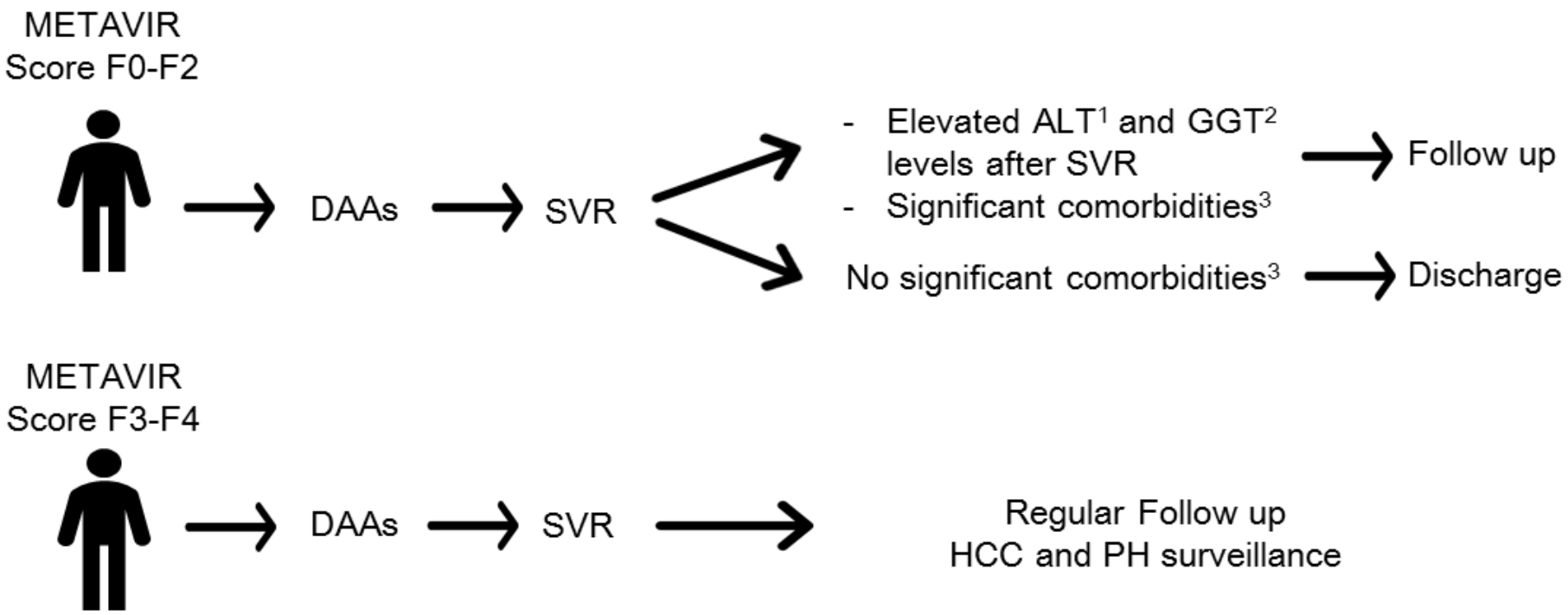
Valenti L et al, Hepatology Reports 2021

High Risk of HCC in NAFLD Without Cirrhosis



Tan et al, Lancet Oncology 2022

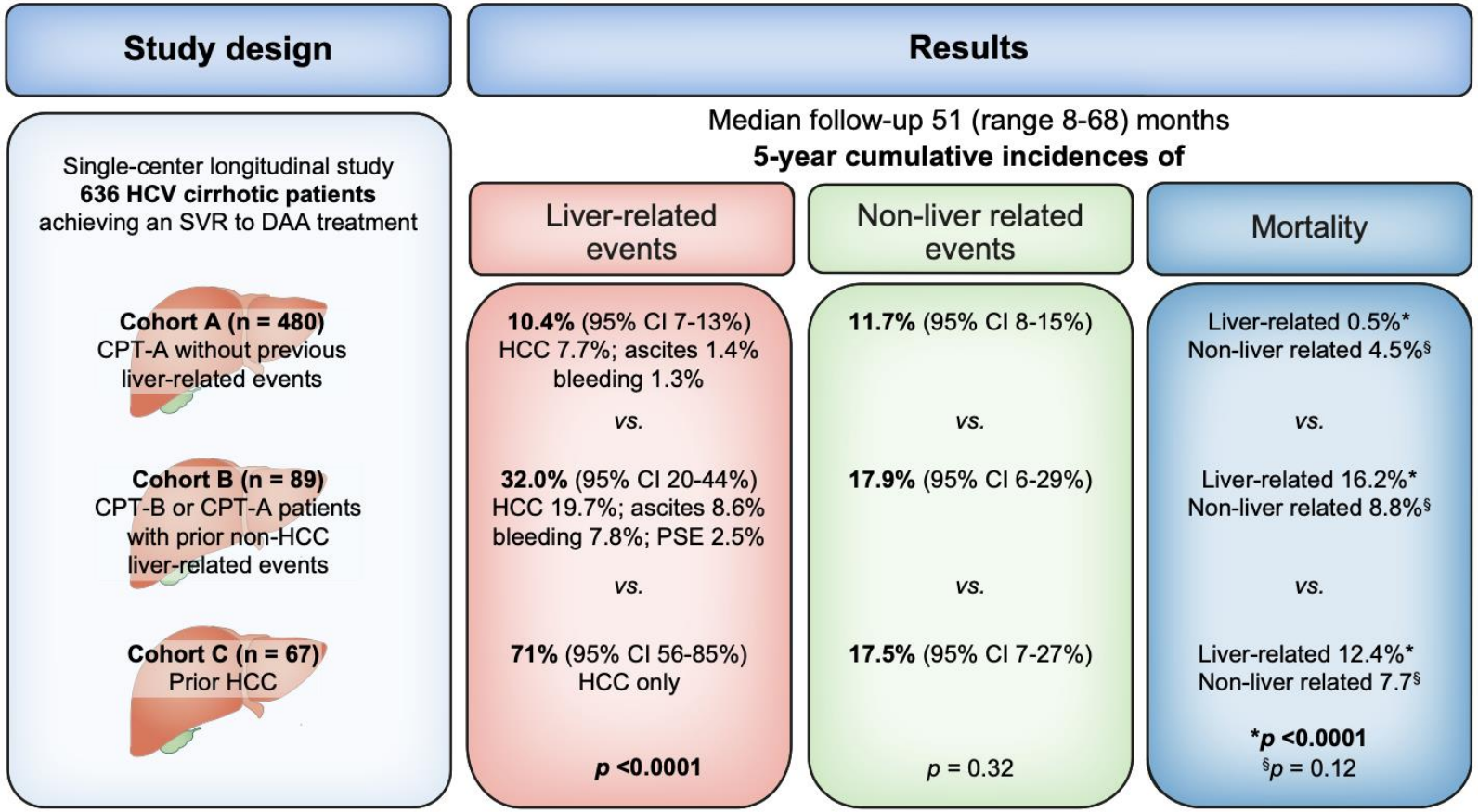
Who Should We Follow-up Post SVR?



1 elevated ALT levels: ≥ 35 U/L for females, ≥50 U/L for males 2. elevated GGT levels : 40 U/L for females, ≥ 60 U/L for males 3. Non alcoholic steato hepatitis, obesity, alcohol consumption and diabetes

Colapietro F, Aghemo A, Liver International 2020

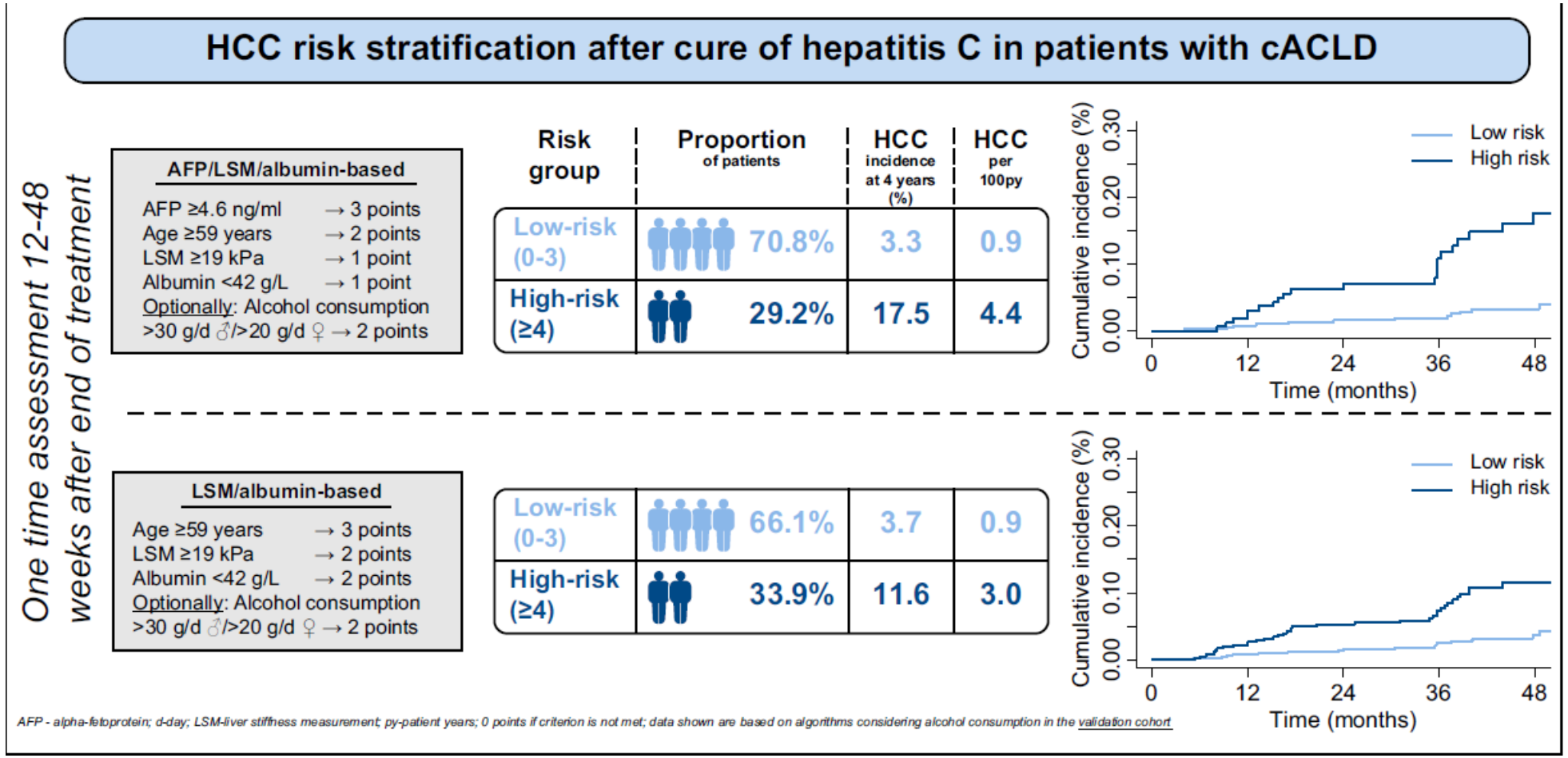
Who Should We Follow-up Post SVR?



SVR: Sustained virological response; DAA: direct-acting antivirals; CPT: Child-Pugh-Turcotte; HCC: hepatocellular carcinoma; PSE: porto-systemic encephalopathy

D'Ambrosio R et al, J Hepatol 2022

Who Should We Follow-up Post SVR?

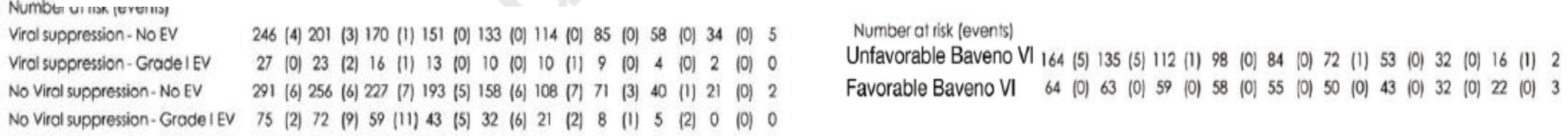


Semmler G et al, J Hepatol in press

Management of Portal Hypertension Following Viral Suppression

3.7 In the absence of co-factors, patients with HCV-induced cACLD who achieve SVR and show consistent post-treatment improvements with LSM values of <12kPa and PLT >150x10^9/L can be discharged from portal hypertension surveillance (LSM and endoscopy), as they do not have CSPH and are at negligible risk of hepatic decompensation. In these patients, hepatocellular carcinoma surveillance should continue until further data is available. (B.1) (New)

3.8 The Baveno VI criteria (i.e., LSM <20kPa and PLT >150x10^9/L) can be used to rule-out high-risk varices in patients with HCV- and HBV-induced cACLD who achieved SVR and viral suppression, respectively. (B.1) (New)



Thabut D et al, Gastroenterology 2019

Take home messages

- ✓ Fibrogenic pathways from HIV include direct effects on liver cells, immune activation from bacterial translocation, and altered immunity from T-cell exhaustion and death.
- ✓ Although HCV co-infection has declined, HBV and HDV are still main contributors to HIV related liver disease, and HEV is particularly common in Europe.
- ✓ NASH is highly prevalent in people with HIV and is associated with rapid fibrosis progression, with visceral fat related to lipodystrophy as a clinical predictor.
- ✓ Despite lowered risk of fibrosis progression with effective antiretroviral therapy, mechanisms of fibrogenesis are not completely reduced, and further studies in the possible contribution of contemporary antiretroviral therapy to fatty liver disease are needed.
- ✓ Emerging therapies include CCR5 inhibitors for modulation of hepatic fibrosis, tesamorelin for HIV associated nonalcoholic fatty liver disease, and bulevirtide and lonafarnib as potential cures for hepatitis D.