11

WORKSHOP
NAZIONALE CISAI

TORINO 2023

20 • 21 APRILE

Tollerabilità dei farmaci antinfettivi e co-morbilità associate all'infezione da HIV

Presidenti del Convegno
Paolo Bonfanti, Antonio Di Biagio, Giancarlo Orofino

FONDAZIONE ASIA

CISAI

11 WORKSHOP NAZIONALE CISAI TORINO 2023
20 • 21 APRILE

UNIVERSITAS STUDIORUM MUTINENSIS ET REGIENSIS
1175

UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

MAFLD: ultime evidenze

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Jovana Milic
Università di Modena e Reggio Emilia

Potenziale conflitto di interessi da dichiarare

Tipo di affiliazione o supporto finanziario	Sponsor
Speaker honorarium	Gilead
Speaker honorarium	ViiV

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MENU

- Definitions
- Why MAFLD would be more suitable?
- NAFLD/MAFLD in HIV
  - What are HIV specific risk factors?
  - What does EACS guidelines recommend?
  - NAFLD vs. MAFLD in HIV - implications of terminology change
  - Liver steatosis and liver fibrosis progression in PLWH
  - What is the role of ART in NAFLD natural history?
- Treatment for NAFLD/MAFLD/NASH
- Conclusions

Before we start…

REPRIEVE
Randomized Trial to Prevent Vascular Events in HIV

NIH National Institutes of Health
Turning Discovery Into Health

NEWS RELEASES

Tuesday, April 11, 2023

Daily statin reduces the risk of cardiovascular disease in people living with HIV, large NIH study finds

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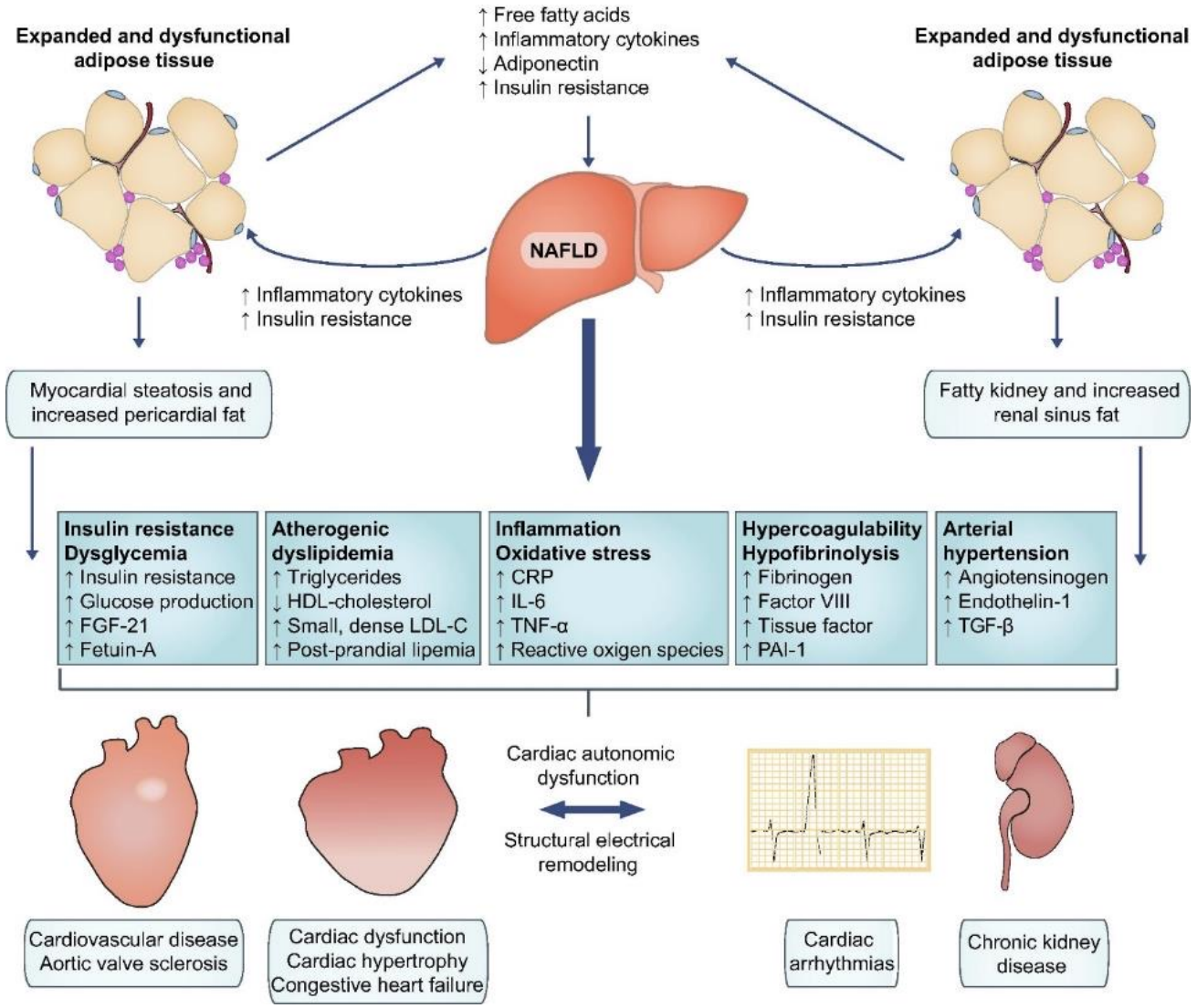
The study participants had no prior history of atherosclerotic cardiovascular disease and had comorbidities and laboratory values (including cholesterol and triglyceride levels) consistent **with low to moderate CVD risk — a population that would not normally be advised to take statins.**

(…)

At its most recent meeting, the board recommended that the study **should be stopped early** because the statin was already showing a clear benefit. **Participants who took pitavastatin had a 35% lower risk for major cardiovascular events**, making it unethical to keep some participants on the placebo.

NAFLD as a multisystemic state involved in immuno-metabolic pathways of cardiometabolic and endocrine conditions



Byrne CD, Targher G. J Hepatol 2015;62:S47–64

Non-Alcoholic Fatty Liver Disease (NAFLD)

Spectrum of NAFLD

Often associated with components of the metabolic syndrome:

NAFLD is defined as:

- hepatic steatosis involving > 5% of hepatocytes
- often associated with components of metabolic syndrome
- exclusion of both secondary causes and of alcoholic fatty liver disease (defined as a daily alcohol consumption ≥ 30 g for men and ≥ 20 g for women)

Non-Alcoholic SteatoHepatitis (NASH)

- Early NASH: no or mild (F0-F1) fibrosis
- Fibrotic NASH: significant (≥ F2) or advanced (≥ F3, bridging) fibrosis
- NASH-cirrhosis (F4)
- HCC (can occur in the absence of cirrhosis and histological evidence of NASH)

Most common concurrent diseases

- AFLD-alcoholic fatty liver disease
- Drug-induced fatty liver disease
- HCV-associated fatty liver (GT 3)

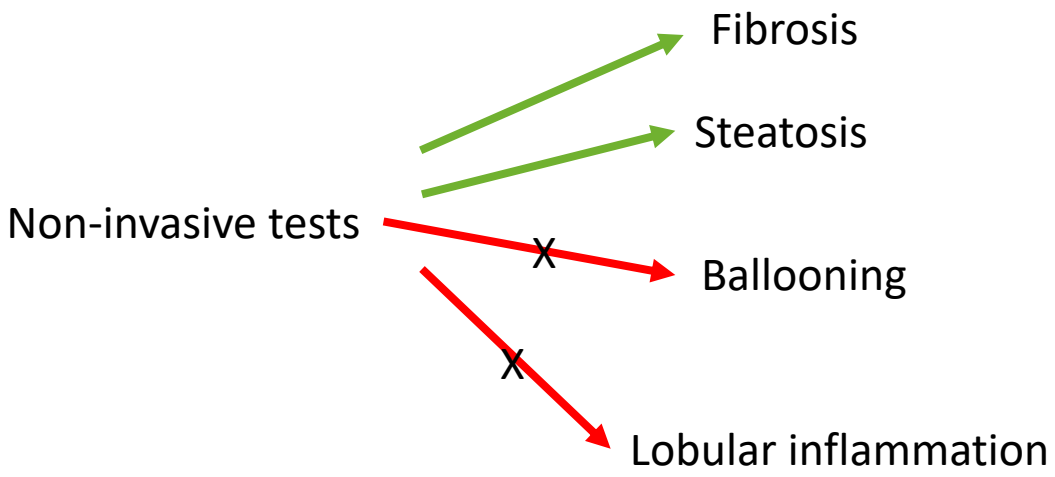
Diagnosis

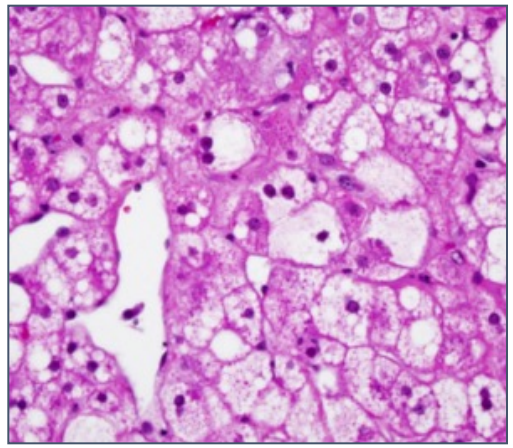
- Ultrasound is the preferred first-line diagnostic procedure for imaging of NAFLD
- Whenever imaging tools are not available or feasible, serum biomarkers and scores are an acceptable alternative for the diagnosis
- Where available and in experienced centres, transient elastography with controlled attenuation parameter could be used to diagnose HIV-associated NAFLD, although no optimal cut-off has been established yet
- A quantitative estimation of liver fat can only be obtained by MRS as well as MRI-PDFF. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting.
- NASH has to be diagnosed by a liver biopsy showing steatosis, hepatocyte ballooning and lobular inflammation

NASH: a histological diagnosis

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis

Recommendations		
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1



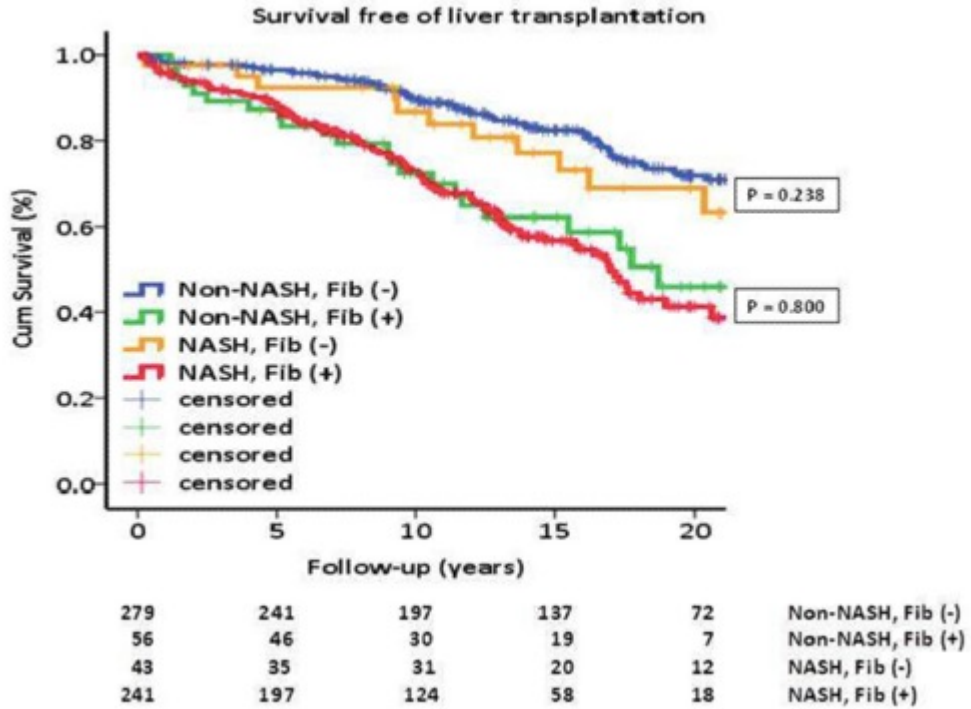


EASL–EASD–EASO CPG NAFLD. J Hepatol 2016

Gastroenterology
Volume 149, Issue 2, August 2015, Pages 389-397.e10

Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

Paul Angulo [1], David E. Kleiner [2] ✉, Sanne Dam-Larsen [3], Leon A. Adams [4], Einar S. Bjornsson [5], Phunchai Charatcharoenwitthaya [6], Peter R. Mills [7], Jill C. Keach [8], Heather D. Lafferty [7], Alisha Stahler [8], Svanhildur Haflidadottir [9], Flemming Bendtsen [10]

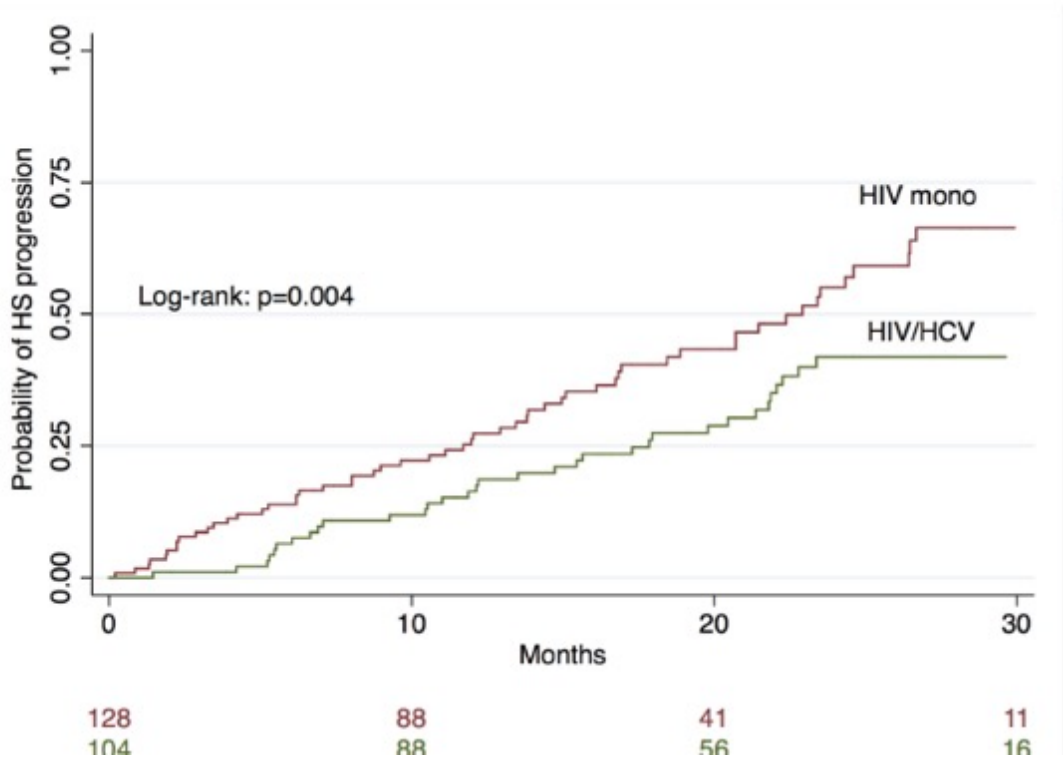


ELSEVIER
Journal of Hepatology
Volume 67, Issue 4, October 2017, Pages 801-808

Research Article

Hepatic steatosis progresses faster in HIV mono-infected than HIV/HCV co-infected patients and is associated with liver fibrosis

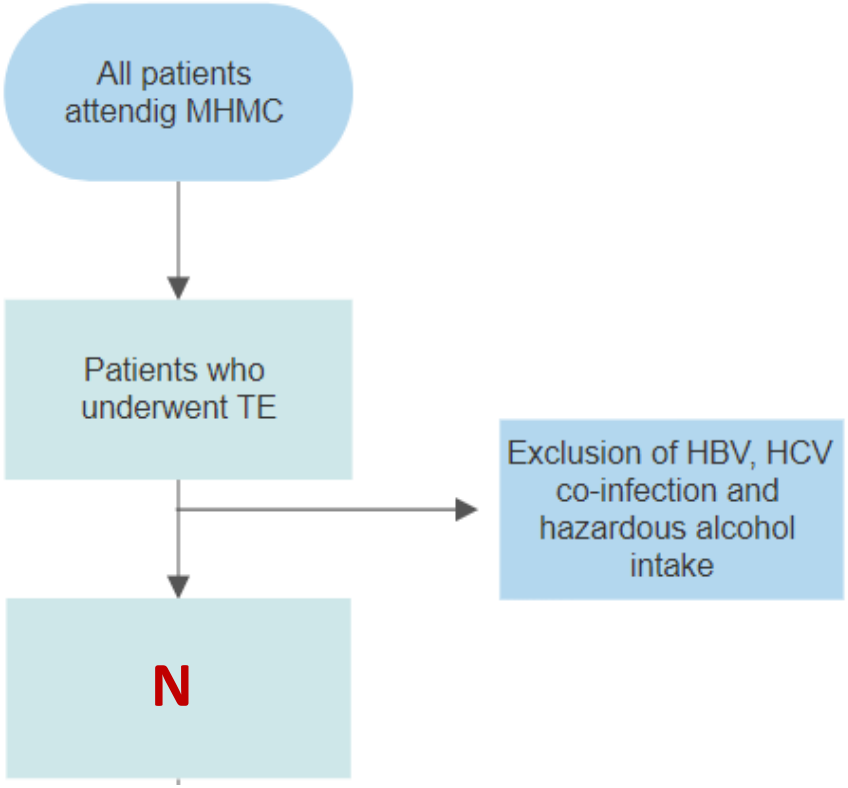
Thomas Pembroke [1, 2], Marc Deschenes [1], Bertrand Lebouché [1], Amine Benmassaoud [1], Maida Sewitch [1], Peter Ghali [1], Philip Wong [1], Alex Halme [1], Elise Vuille-Lessard [1], Costa Pexos [1], Marina B. Klein [1], Giada Sebastiani [1] ✉



NAFLD vs. MAFLD

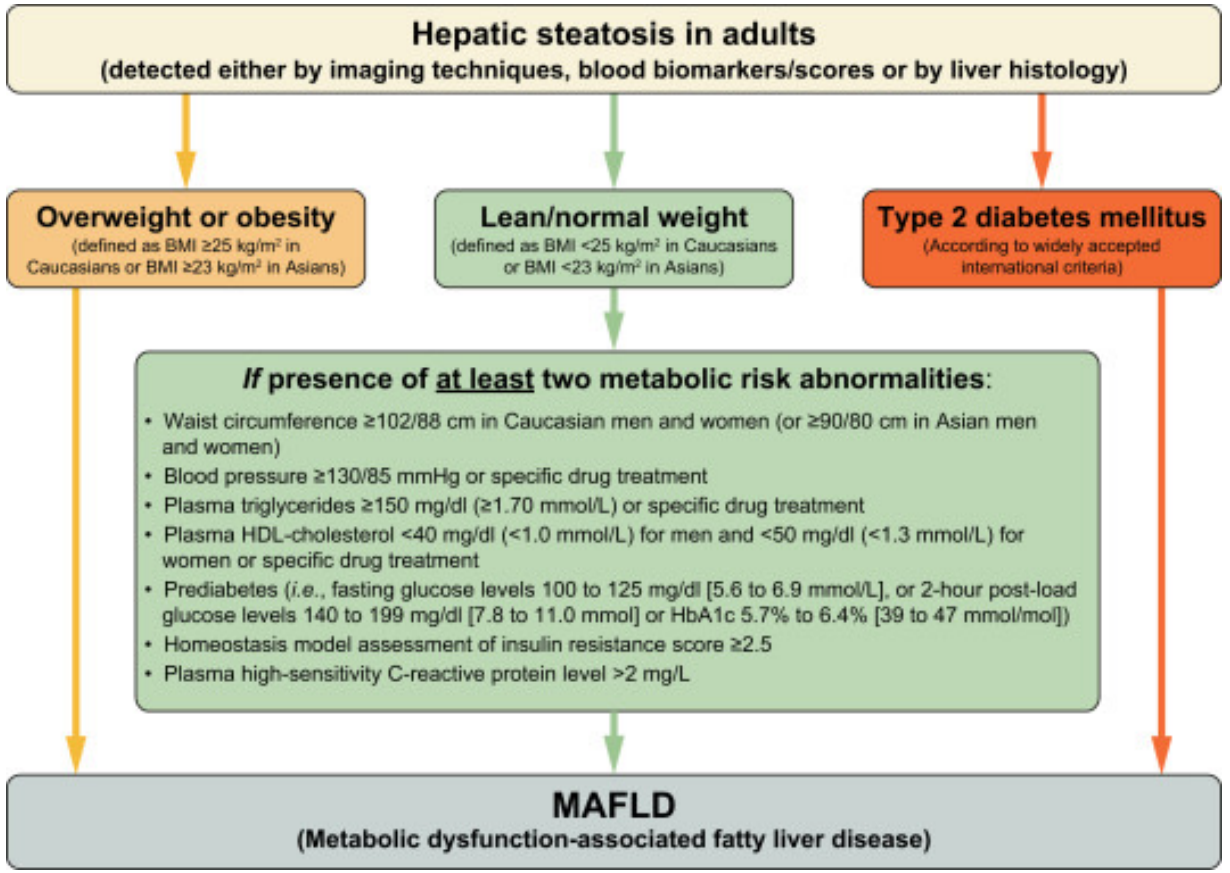
NAFLD

(non-alcoholic fatty liver disease)



MALFD

(metabolic associated fatty liver disease)



Eslam M. JHepatol.2020;73(1):202-209

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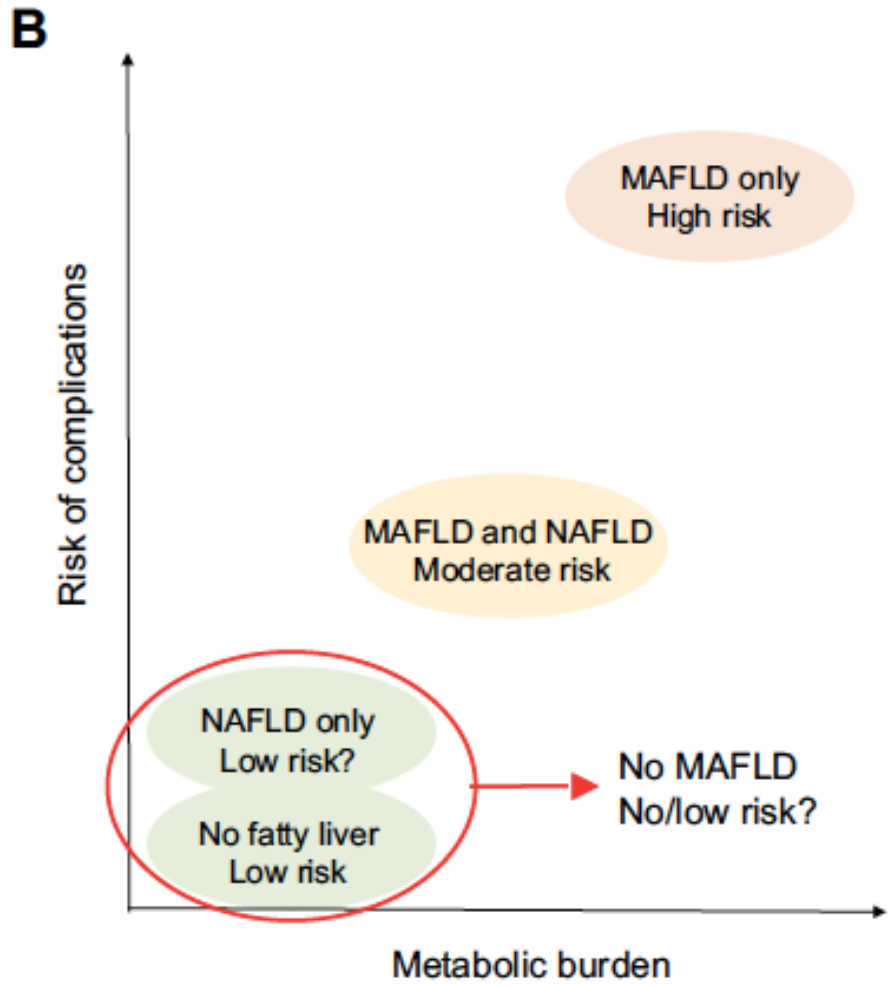
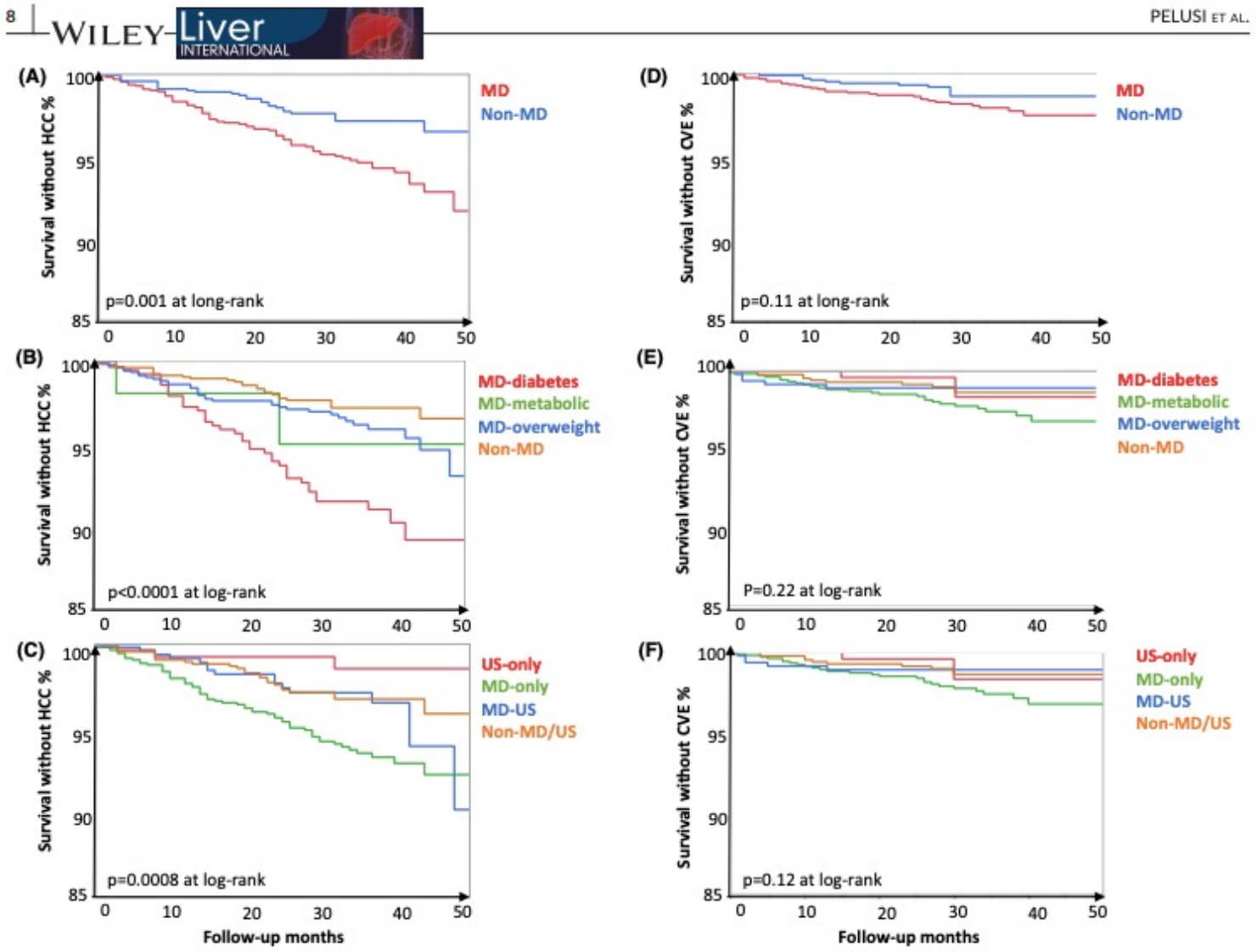
Prognosis of MAFLD *vs.* NAFLD and implications for a nomenclature change



Wong VW, Lazarus JV.. J Hepatol. 2021;75(6):1267-1270.

Metabolic dysfunction and not just fatty liver associated with HCC

- 2611 Italian patients cured of chronic HCV infection with direct antiviral agents and advanced liver fibrosis, without HBV/HIV, transplantation and negative for hepatocellular carcinoma (HCC) history
- Age 61.4 ± 11.8 years
- 63.9% males
- Median follow-up 34 (24–40 months).



Pelusi S, NAVIGATORE-Lombardia Network. Liver Int. 2023. doi: 10.1111/liv.15577.

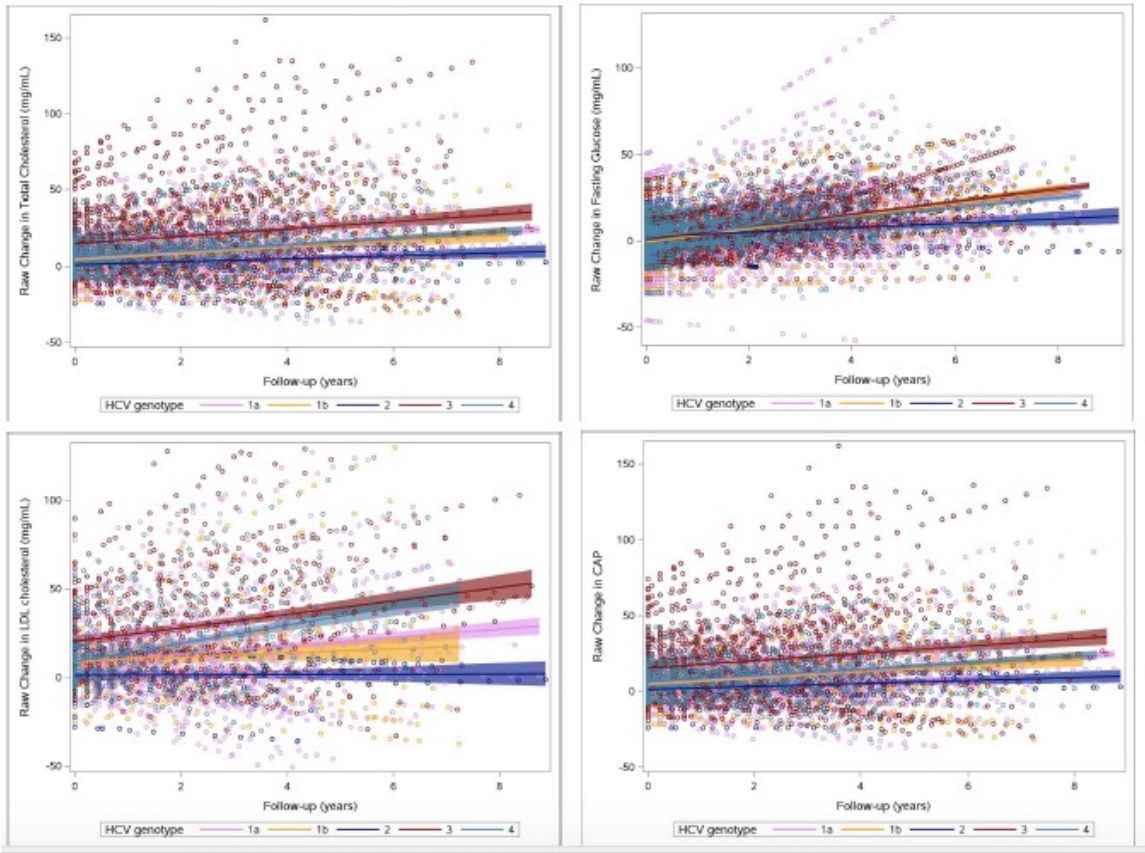
CAP and metabolic profile worsening post-SVR in HCV-HIV people as a sign of steatosis

615

Siribelli Alessia[2], Ceccarelli Daniele[2], Galli Laura[2], Morsica Giulia[2], Lolatto Riccardo[2], Bertoni Costanza[1], Castagna Antonella[1], Uberti-Foppa Caterina[1], Hasson Hamid[2]
1Vita-Salute University, Milan, Italy. 2Unit of Infectious Diseases, San Raffaele Hospital, Milan, Italy

In the HIV-HCV coinfected population who reached SVR after DAAs, a ***significant increase*** of ***CAP*** and ***lipid parameters*** was observed during a long-term follow-up.

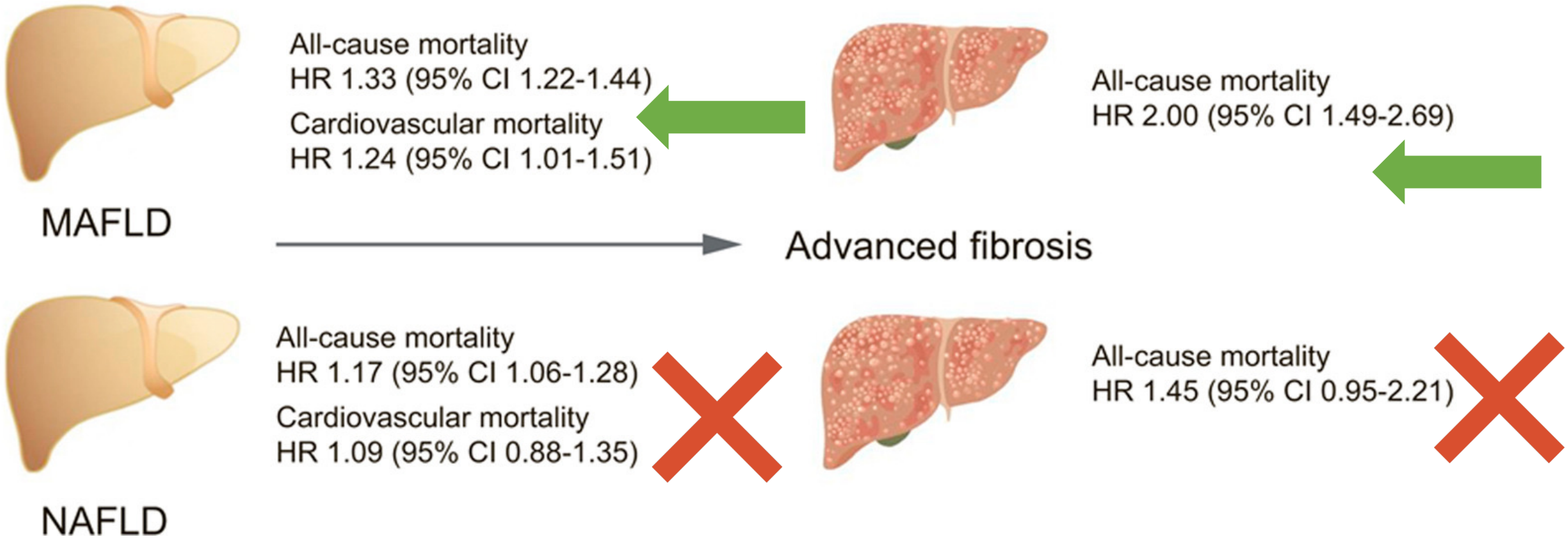
Figure 1. Mean annual percent changes (95% Confidence Interval) of CAP and metabolic parameters



Sirbelli A, poster 615, CROI 2023

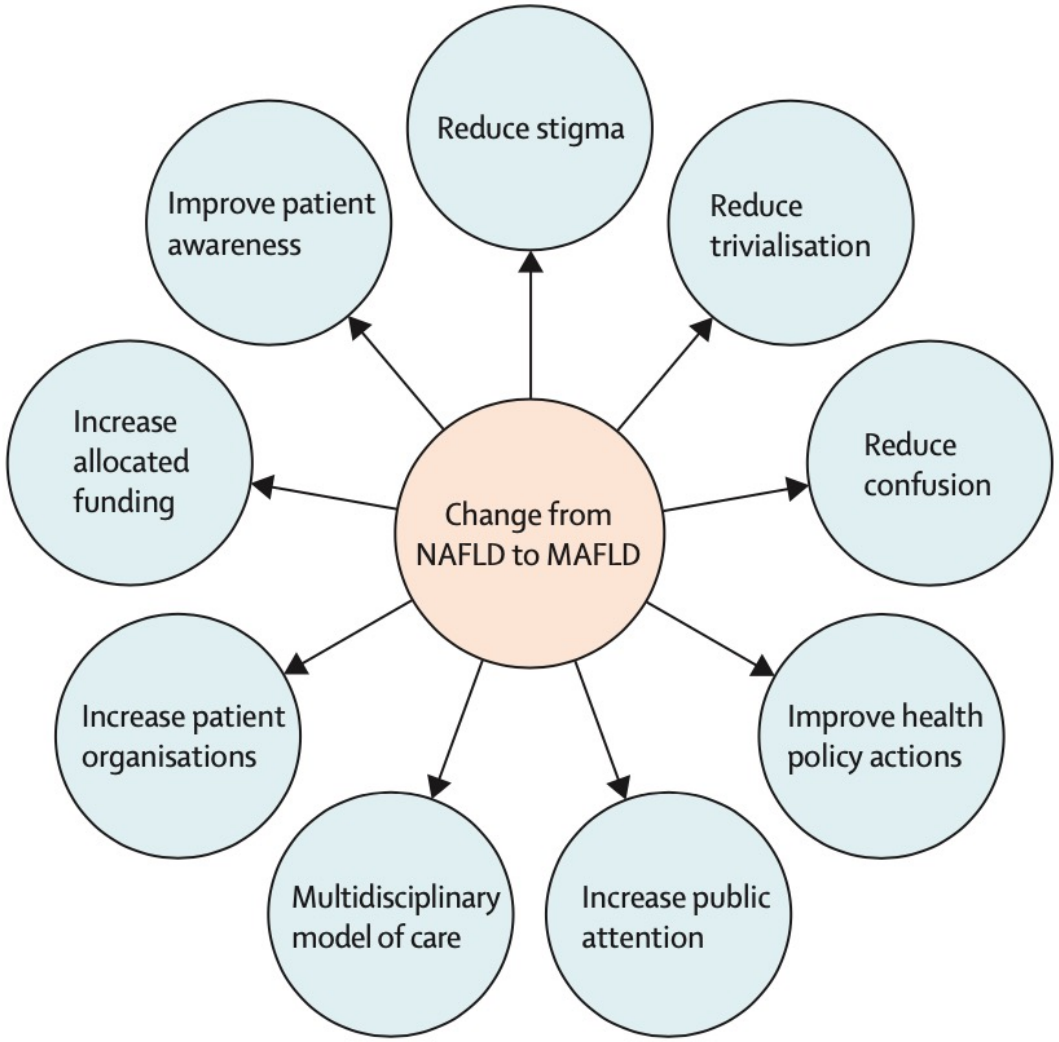
Increased all-cause mortality with metabolic dysfunction-associated fatty liver disease in the United Utates

US adults from the third National Health and Nutritional Examination Survey
23.2 years follow-up



Kim D, J Hepatol. 2021;75(6):1284-1291.

Implications for redefining fatty liver disease from a patient perspective



Shiha G et al, Lancet Gastroenterol Hepatol 2020

- For patients, policy makers, health planners, donors, and non-hepatologists, the new acronym MAFLD is clear, **squarely placing the disease as a manifestation of metabolic dysfunction** and improving understanding at a public health and patient level.

- The authors from **representative patient groups** are supportive of this change, particularly as the new acronym is meaningful to all citizens as well as governments and policy makers, and, above all, is **devoid of any stigma.**

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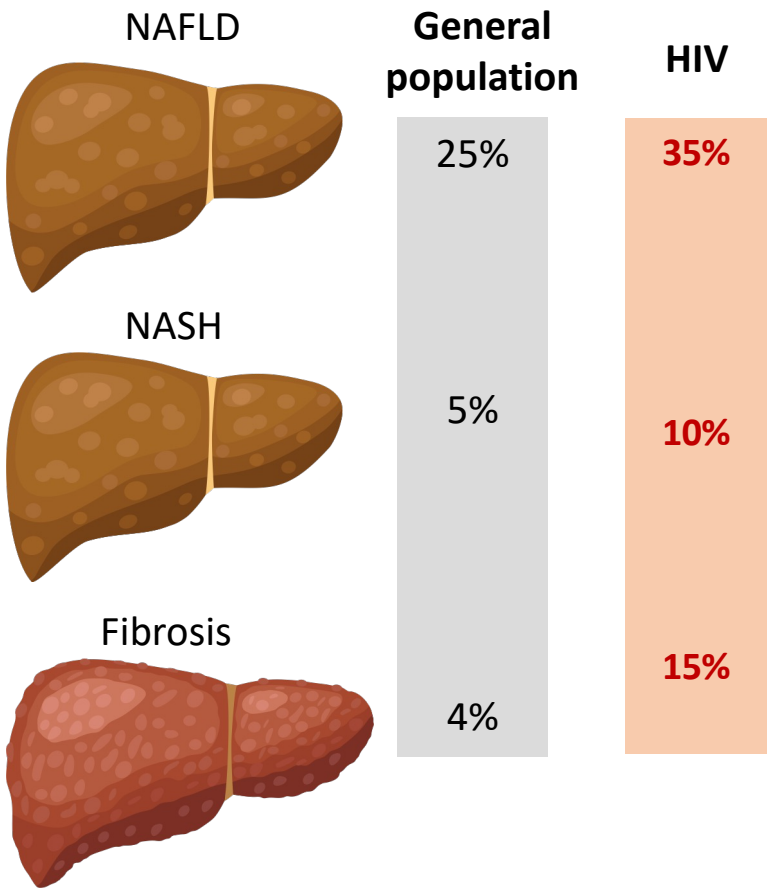
NAFLD in HIV

NAFLD is frequent in people living with HIV in absence of viral hepatitis coinfection



Prolonged ART Use
- Hepatotoxicity
- Oxidative stress
- Mitochondrial dysfunction

Metabolic Factors
- Abdominal obesity
- Diabetes
- Dyslipidemia
- Hypertension

People with HIV

HIV Direct Effects
- Hepatocyte apoptosis
- Kupffer cell infection
- HSC activation
- Immune activation

Patient-Related Risk Factors
- Age/Sex/Ethnicity
- Diet (fructose), lack of physical exercise
- Gut dysbiosis

Factors Unique to HIV **Classical Factors**

1. Younossi. J Hepatol. 2019;70:531. 2. Cervo. Curr HIV/AICS Rep. 2020;17:601.
3. Pembroke. J Hepatol. 2017;67:801-808. 4. Kabbany. Am J Hepatol. 2017;112:581.

PRACTICE GUIDANCE

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease

Rinella, Mary E.[1]; Neuschwander-Tetri, Brent A.[2]; Siddiqui, Mohammad Shadab[3]; Abdelmalek, Manal F.[4]; Caldwell, Stephen[5]; Barb, Diana[6]; Kleiner, David E.[7]; Loomba, Rohit[8]

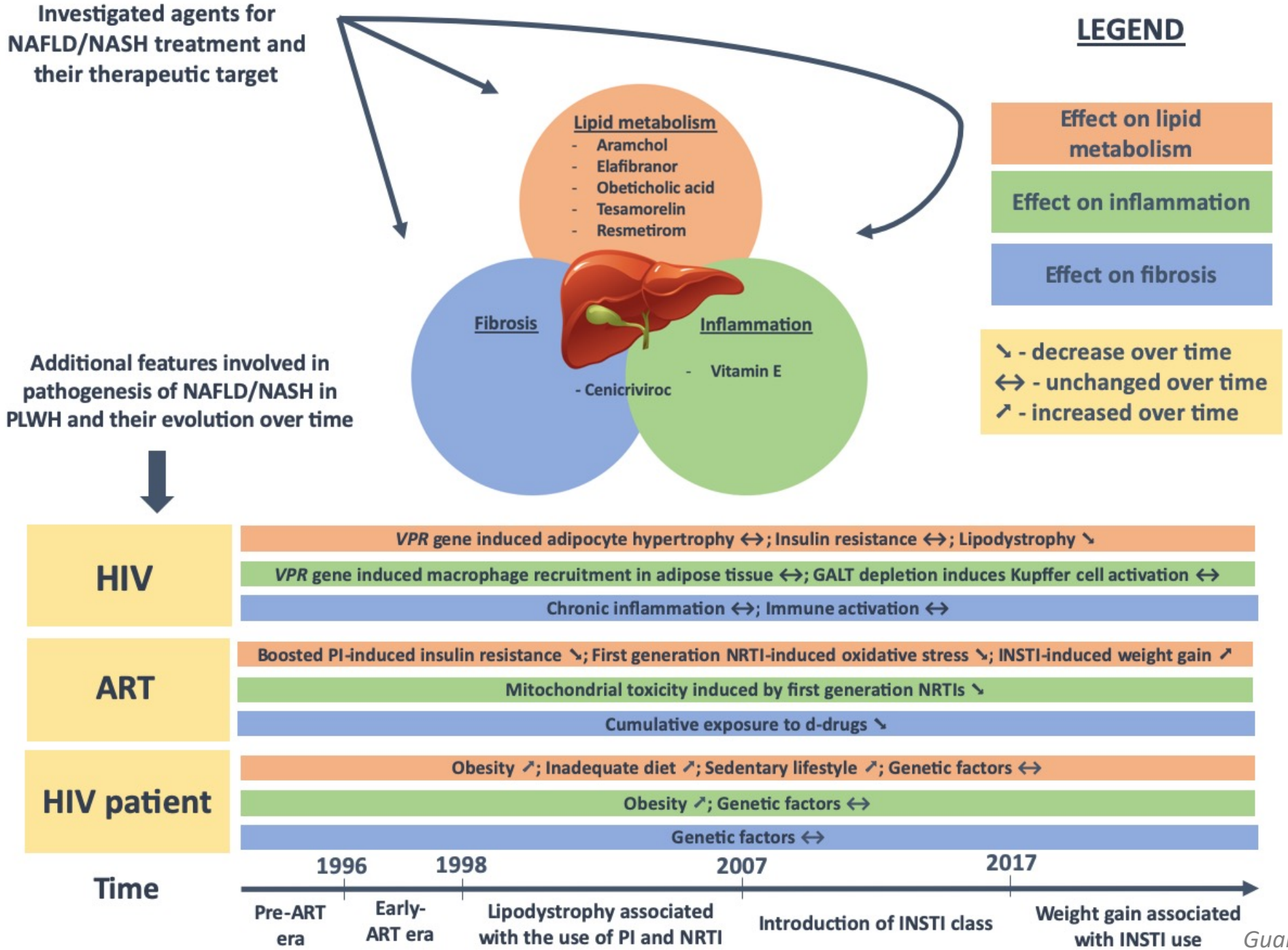
Author Information

Hepatology 77(5):p 1797-1835, May 2023. | *DOI:* 10.1097/HEP.0000000000000323

GENERAL RECCOMENDATIONS

- General population-based screening for NAFLD is not advised
- High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis
- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4
- In patients with pre-DM, T2DM, or 2 or more metabolic risk factors (or imaging evidence of hepatic steatosis) primary risk assessment with FIB-4 should be repeated every 1–2 years

PLWH are not identified as the population at risk!!!



Guaraldi G. Hepatology 2020

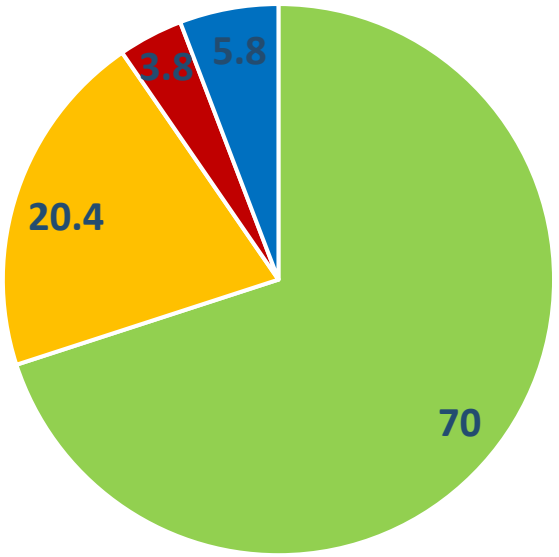
Prevalence, Predictors, and Severity of Lean Nonalcoholic Fatty Liver Disease in Patients Living With Human Immunodeficiency Virus

Adriana Cervo, Jovana Milic, Giovanni Mazzola, Filippo Schepis, Salvatore Petta, Thomas Krahn, Bertrand Lebouche, Marc Deschenes, Antonio Cascio, Giovanni Guaraldi, Giada Sebastiani ✉

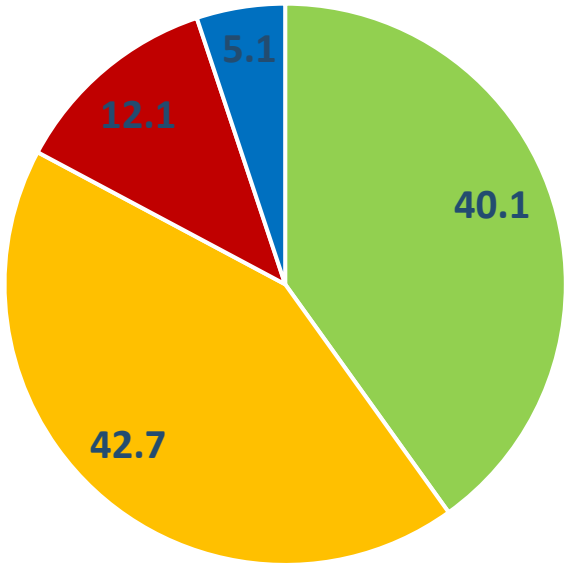
Clinical Infectious Diseases, Volume 71, Issue 10, 15 November 2020, Pages e694–e701,

- 1511 HIV mono-infected patients: 54.7% lean
- Prevalence of NAFLD and liver fibrosis in lean patients were **13.9%** and **5.5%**, respectively.
- NAFLD affected 24% lean vs. 59% overweight/obese patients (p<0.001)

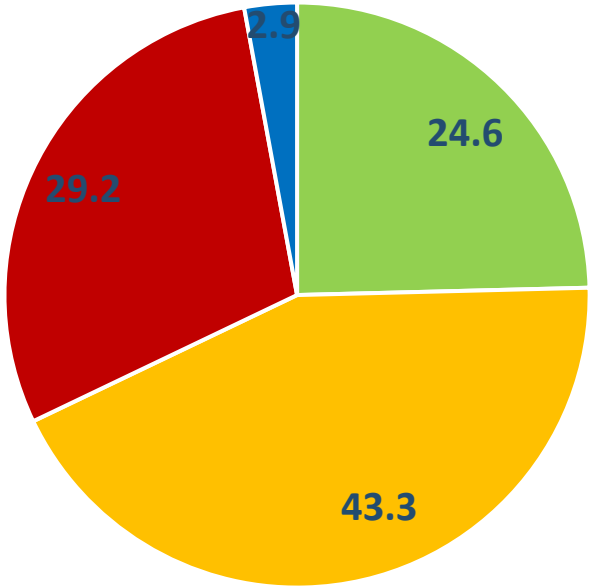
Lean (n=867, 57.4%)



Overweight (n=473, 31.3%)



Obese (n=171, 11.3%)



No NAFLD-No Fibrosis

NAFLD without fibrosis

NAFLD with fibrosis

Fibrosis without NAFLD

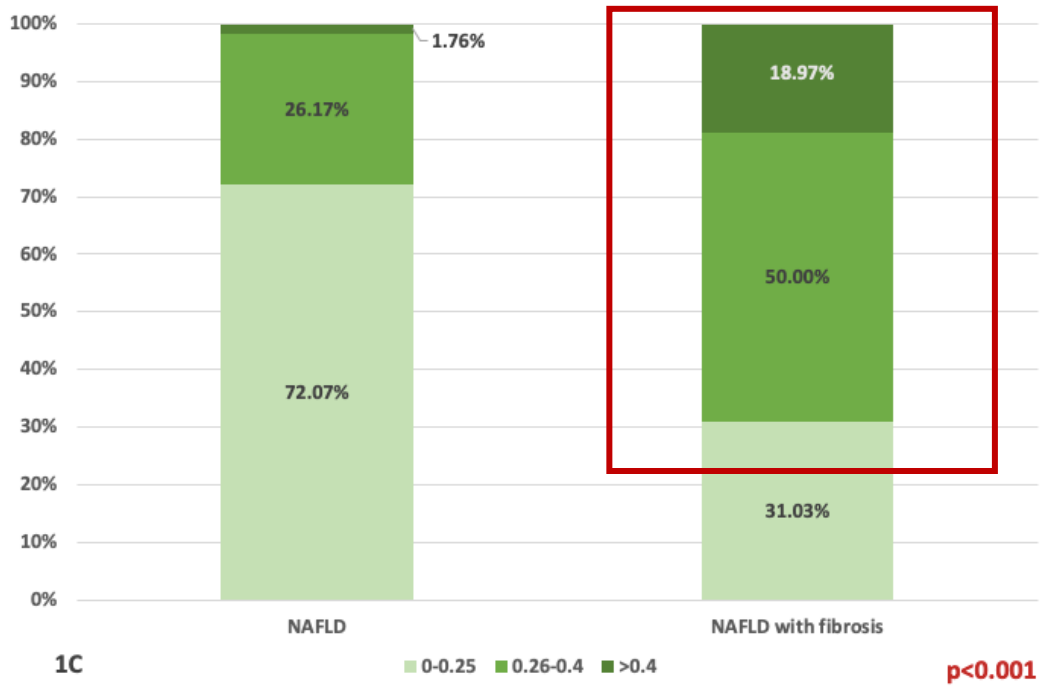
CLINICAL SCIENCE

Liver steatosis and nonalcoholic fatty liver disease with fibrosis are predictors of frailty in people living with HIV

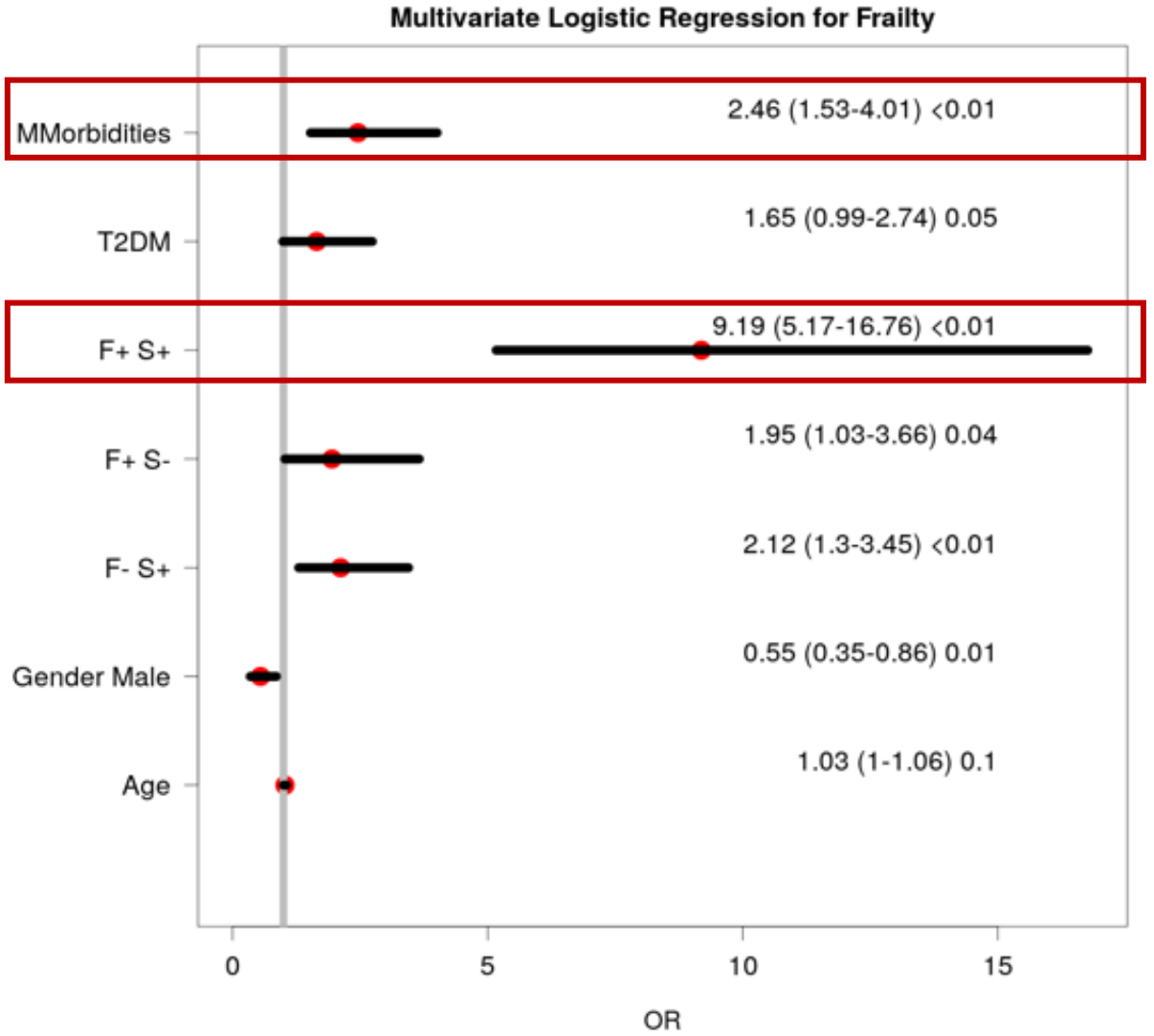
Milic, Jovana[a,b]; Menozzi, Valentina[c]; Schepis, Filippo[d]; Malagoli, Andrea[a]; Besutti, Giulia[b]; Franconi, Iacopo[a]; Raimondi, Alessandro[a]; Carli, Federica[a]; Mussini, Cristina[a]; Sebastiani, Giada[e]; Guaraldi, Giovanni[a] Author Information

AIDS: November 01, 2020 - Volume 34 - Issue 13 - p 1915-1921
doi: 10.1097/QAD.0000000000002650

Almost 70% of PLWH with NAFLD with fibrosis are frail.



NAFLD with fibrosis predicts frailty three times better than multimorbidity.



NAFLD with fibrosis as a multisystemic construct exceeds the construct of multimorbidity, defined as sum of single co-morbidities.

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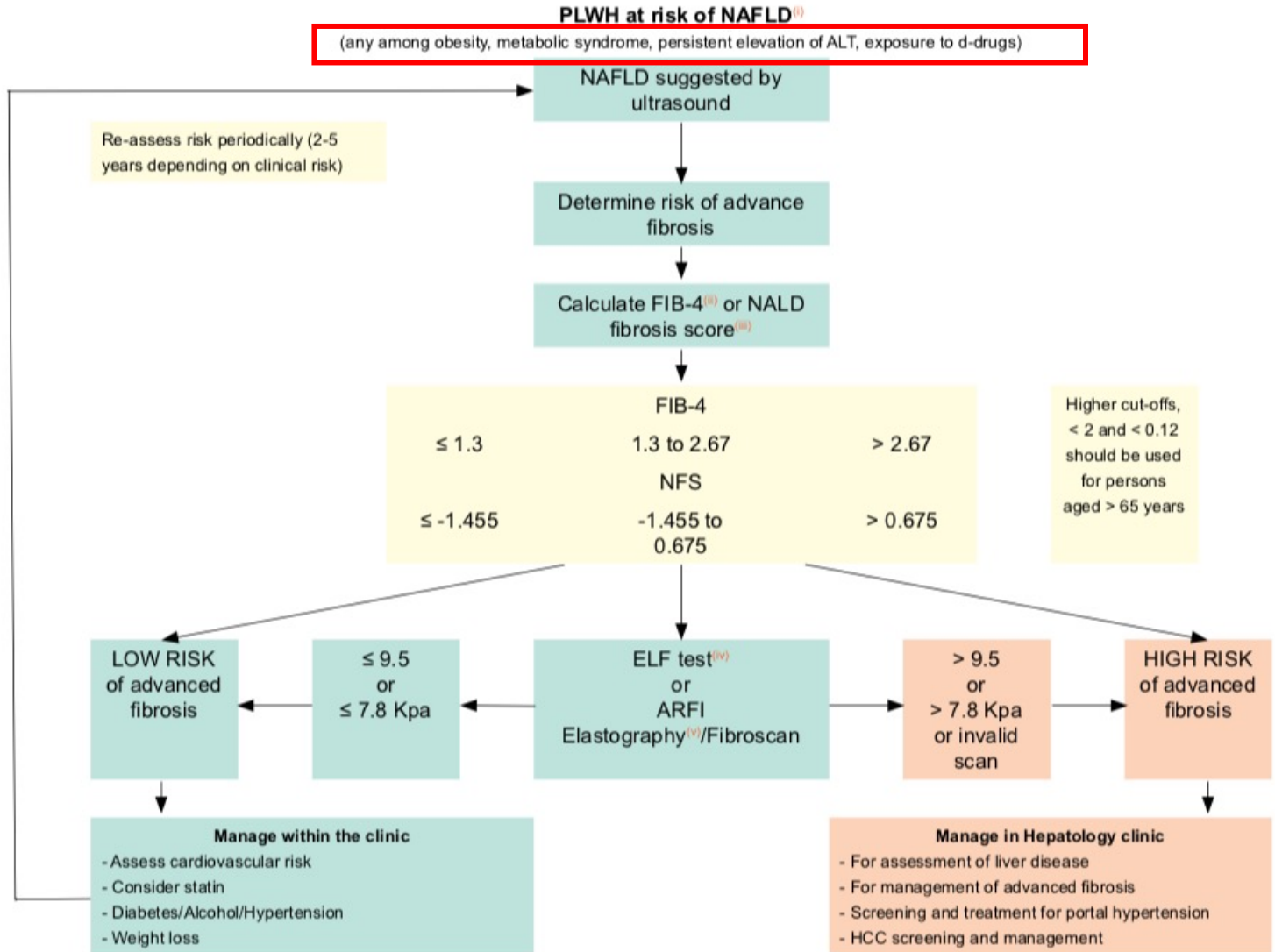
Diagnostic Flow-chart to Assess and Monitor Disease Severity in Case of Suspected NAFLD and Metabolic Risk Factors



These recommendations are largely inspired by the EASL–EASD–EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease: European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity [18]

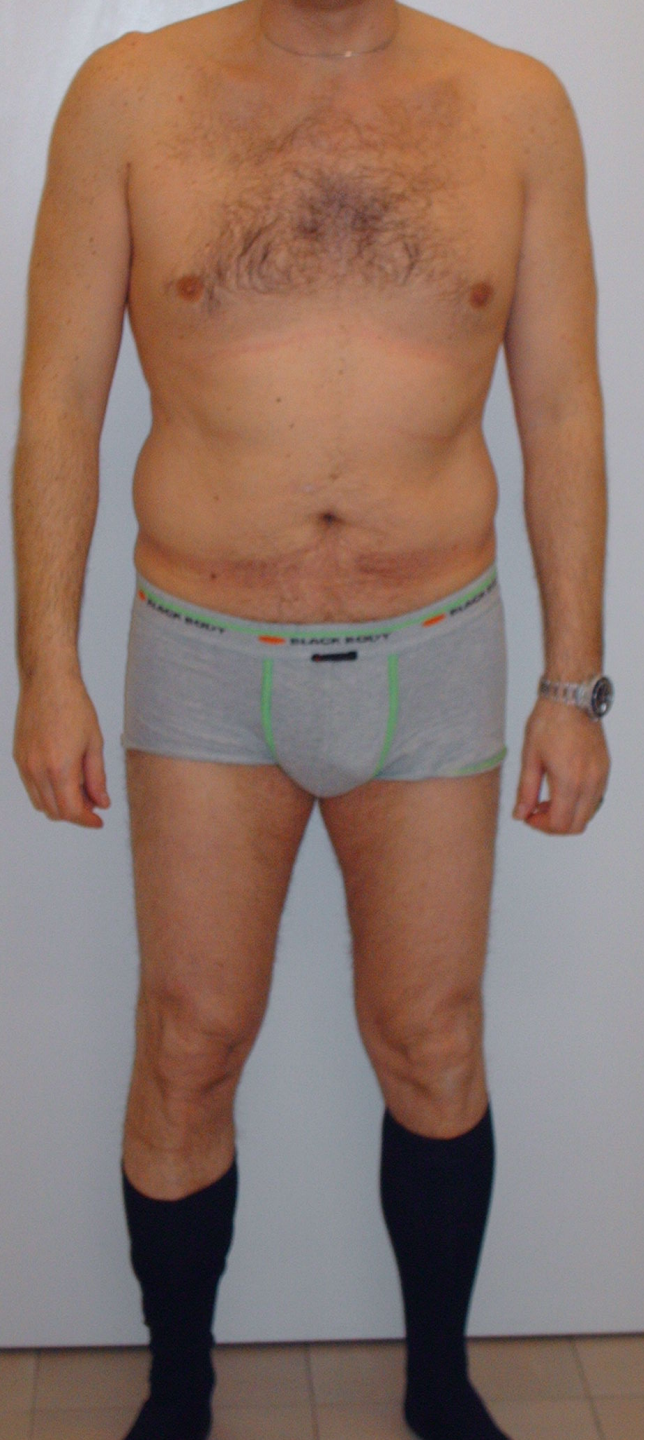
i NAFLD, Non-alcoholic fatty liver disease

ii FIB-4 = Age ([years] x AST [U/L]) / ([platelet [10^9/L]) x ALT [U/L])

iii NFS, Non-alcoholic fatty liver disease Fibrosis Score = -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x impaired fasting glucose/diabetes mellitus(iv) (yes=1/no=0) + 0.99 x AST/ALT ratio-0.013 x platelet (x10^9)-0.66 x albumin(g/dL)

iv ELF™ test, Enhanced Liver Fibrosis Test is a blood test that provides an estimate of liver fibrosis severity by measuring Hyaluronic Acid (HA), Amino-terminal propeptide of type III procollagen (PIIINP), Tissue inhibitor of metalloproteinase 1 (TIMP-1)

v ARFI elastography, Acoustic Radiation Force Impulse

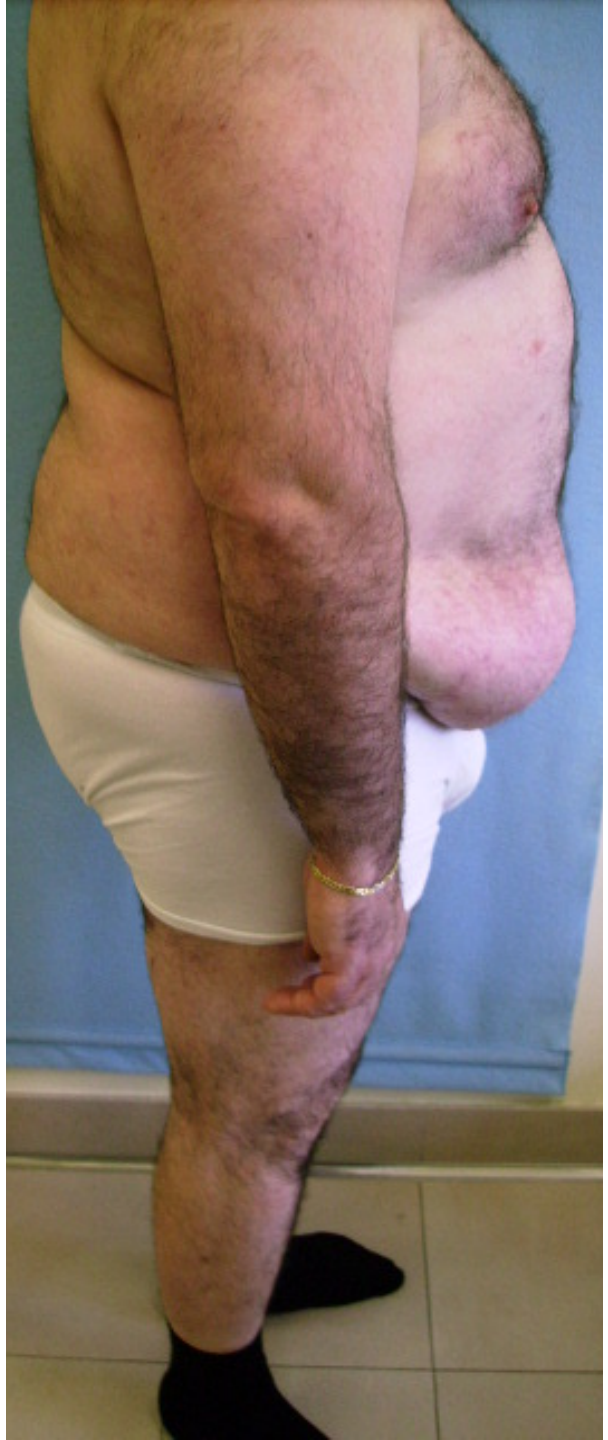


Male, 56 years

HIV history
- CDC A
- Nadir CD4 = 296 c/µL
- HIV duration: 13 years
- Current CD4 = 1285 c/µL
- CD4/CD8 = 1.7

HIV therapy
- DTG/3TC + MVC
- Exposure to d-drugs: NO

Anthropometrics and lifestyles
- BMI = 27 kg/m^2
- Waist = 94 cm
- No lipodystrophy
- Moderate physical activity
- Diet: 2100 Kcal
- Daily protein intake: 107g

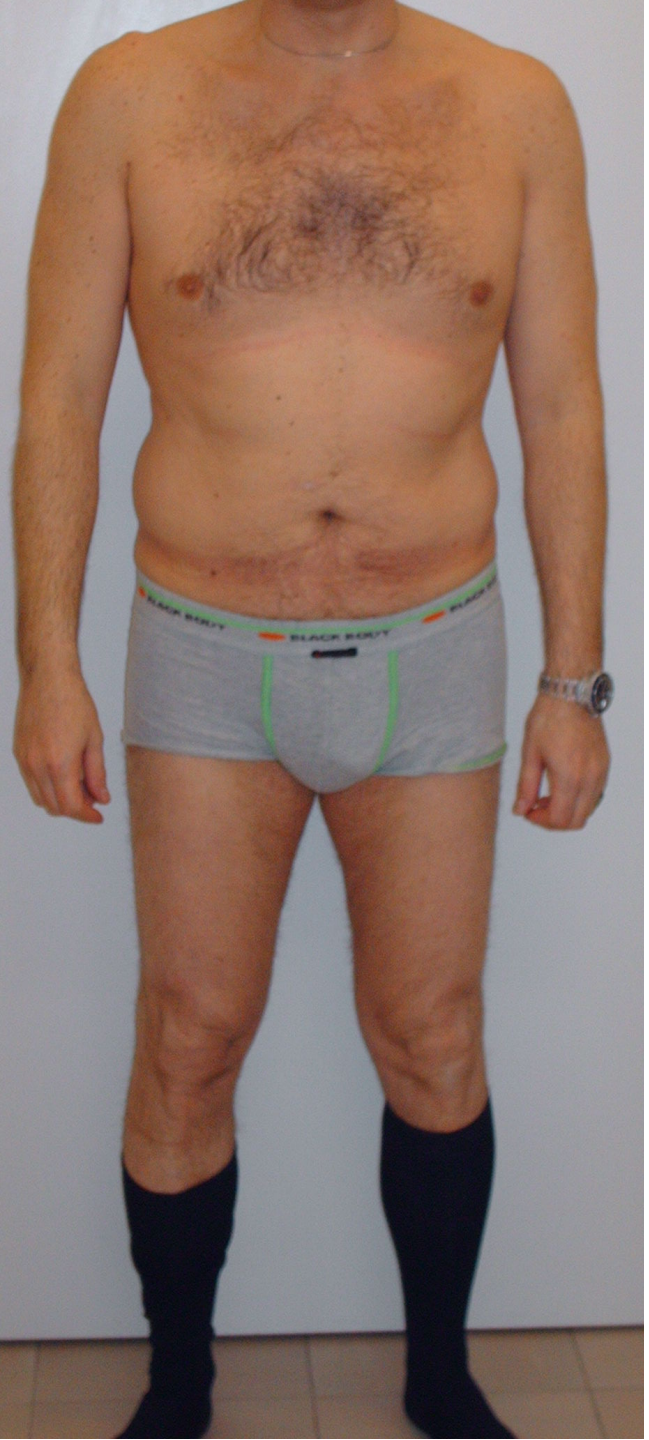


Male, 56 years

HIV history
- CDC A
- CD4 nadir = 342 c/µL
- HIV duration: 14 years
- Current CD4 = 651 c/µL
- CD4/CD8 = 0.76

HIV therapy
- DTG/3TC
- Exposure to d-drugs: NO

Anthropometrics and lifestyles
- BMI = 38.8 kg/m^2
- Waist = 128 cm
- Central adiposity
- Moderate physical activity
- Diet: 2050 Kcal
- Daily protein intake: 77g



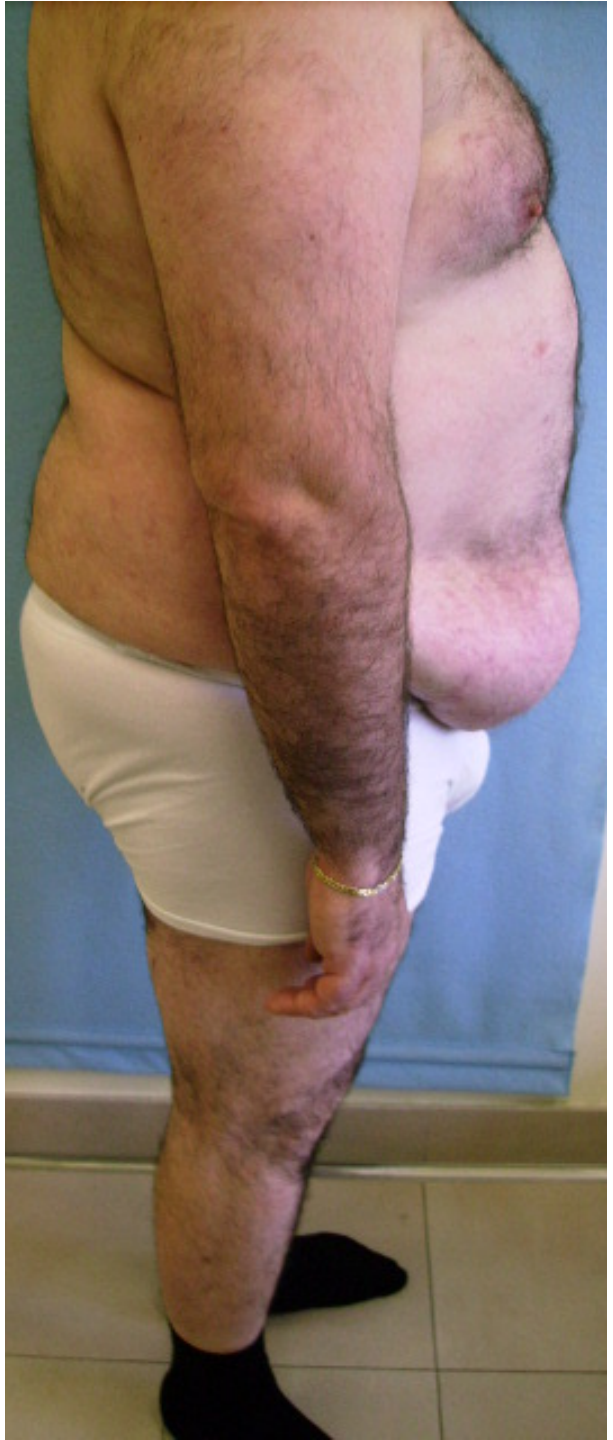
Male, 56 years

Co-morbidities

- Hypertension
- Dyslipidaemia
- NAFLD

Geriatric assessment and PROs

- Frailty index = 0.03
- Quality of life = 84.7%
- Self-rated health = 9/10



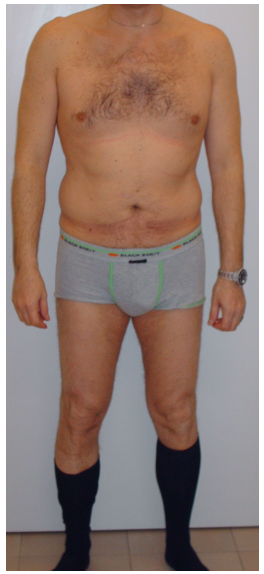
Male, 56 years

Co-morbidities

- Hypertension
- Dyslipidaemia
- Diabetes mellitus
- Obesity
- NAFLD

Geriatric assessment and PROs

- Frailty index = 0.26
- Quality of life = 100%
- Self-rated health = 10/10



AST = 20
ALT = 21
Dyslipidaemia, HTN

PLWH at risk of NAFLD[i]

(any among obesity, metabolic syndrome, persistent elevation of ALT, exposure to d-drugs)

NAFLD suggested by ultrasound

↓

Determine risk of advance fibrosis

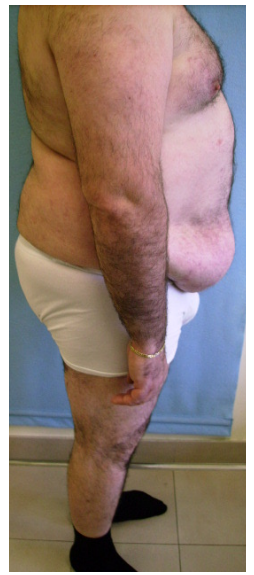
↓

Calculate FIB-4[ii] or NALD fibrosis score[iii]

↓

FIB-4		
≤ 1.3	1.3 to 2.67	> 2.67
NFS		
≤ -1.455	-1.455 to 0.675	> 0.675

AST = 30
ALT = 26
Obesity, diabetes



FIB-4 = 0.98
NFS = 0.344

Stiffness = 4.8 kPa
(F0F1 fibrosis)
CAP = 298 dB/m
(severe steatosis)

FIB-4 = 1.45
NFS = 2

Stiffness = 17 kPa
(F4 – cirrhosis)
CAP = 364 dB/m
(severe steatosis)

LOW RISK of advanced fibrosis ← ≤ 9.5 or ≤ 7.8 Kpa ← ELF test[iv] or ARFI Elastography[v]/Fibroscan → > 9.5 or > 7.8 Kpa or invalid scan → HIGH RISK of advanced fibrosis

↓

Manage within the clinic
- Assess cardiovascular risk
- Consider statin
- Diabetes/Alcohol/Hypertension
- Weight loss

Management
- **ASCVD 6.6%**
- **Weight loss**

↓

Manage in Hepatology clinic
- For assessment of liver disease
- For management of advanced fibrosis
- Screening and treatment for portal hypertension
- HCC screening and management

Management
- **Referral to Hepatology**

MENU

- Definitions
- Why MAFLD would be more suitable?
- NAFLD/MAFLD in HIV
  - What are HIV specific risk factors?
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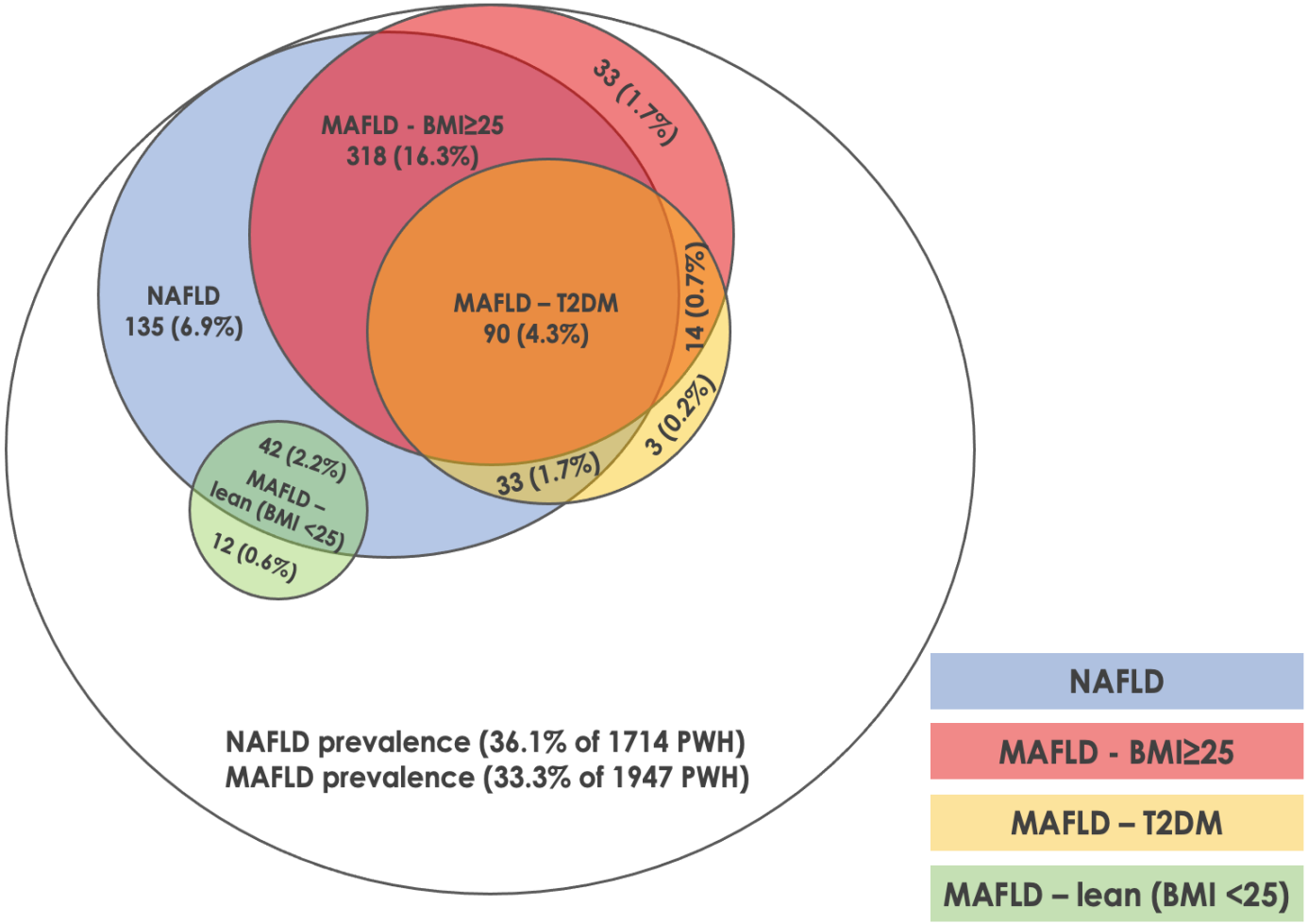
- Conclusions

From NAFLD to MAFLD: implications of change in terminology in PWH

Objective: **to characterize MAFLD in comparison to NAFLD and to determine prevalence and predictors of both conditions in PWH**

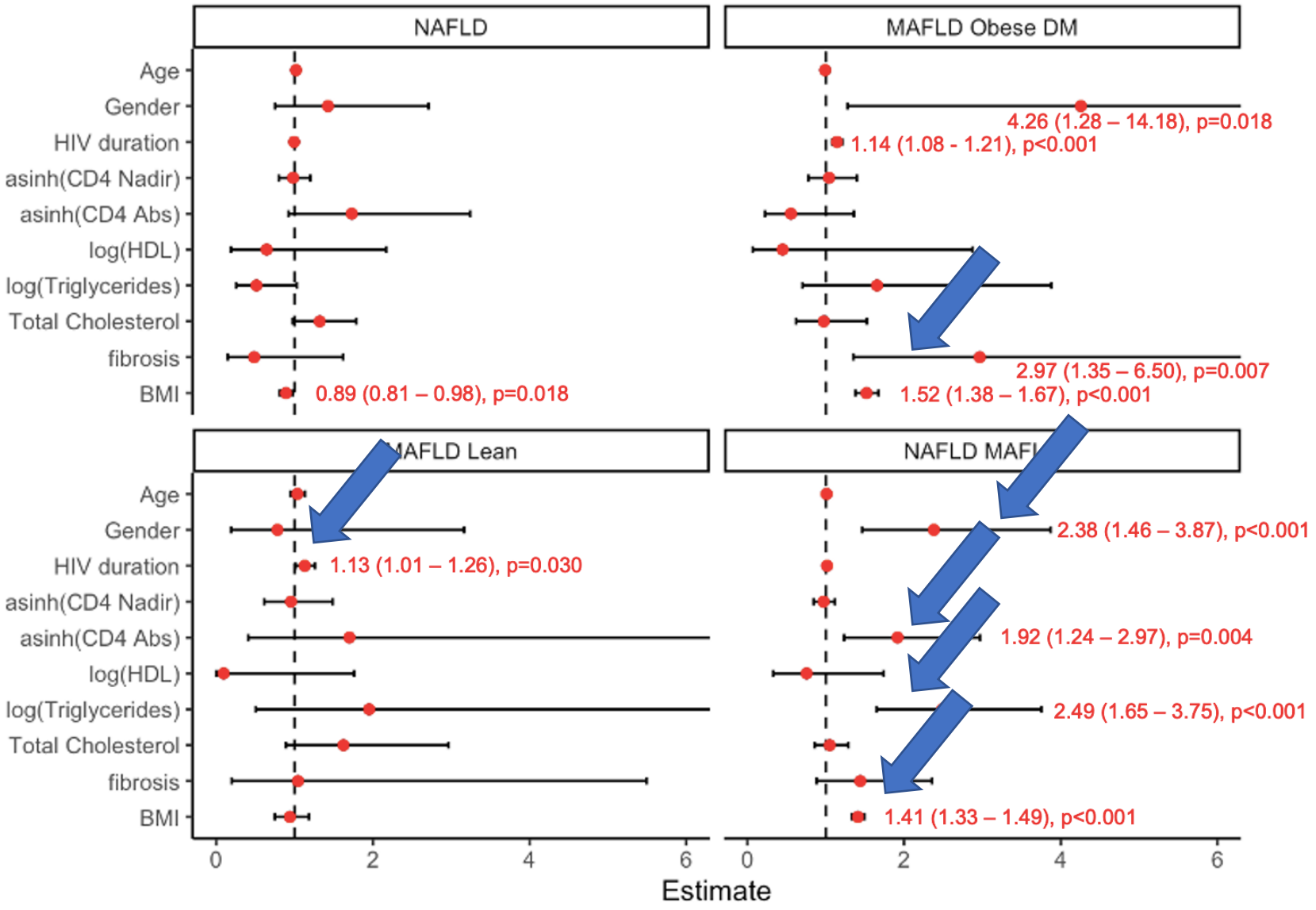
- **1947 PWH analysed**
- Prevalence of overweight and diabetes was 49.5% and 23.4%.
- **NAFLD** was diagnosed in 618/1714 (**36.1%)** PWH, after excluding PWH with significant alcohol intake (1.8%), HBV (1.2%), HCV (9.2%).
- **MAFLD** was diagnosed in 648 (**33.3%)** PWH.



Guaraldi G et al. CROI 2022 P.521 – cross sectional

From NAFLD to MAFLD: implications of change in terminology in PWH

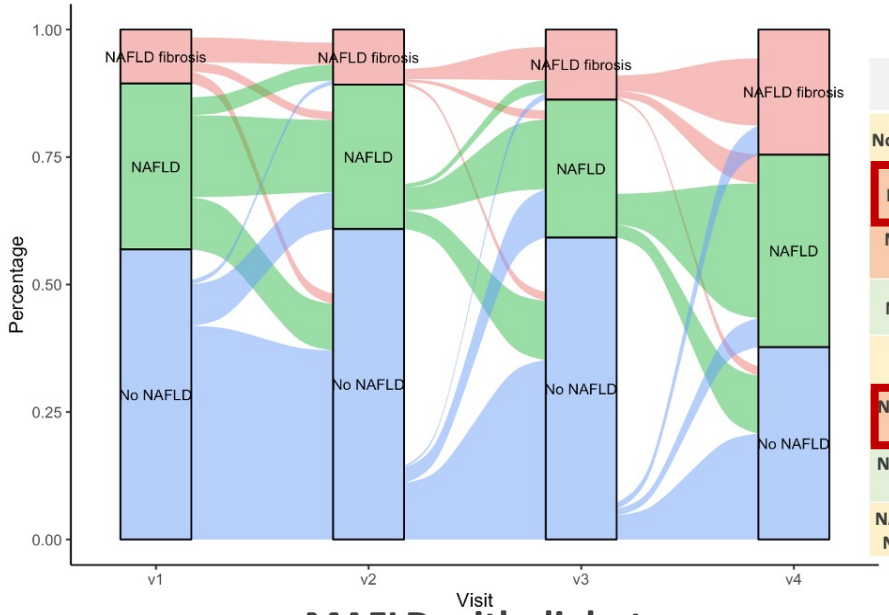
- Liver fibrosis was associated with MAFLD with diabetes or BMI>25 kg/m2.
- Longer time since HIV diagnosis was associated with lean MAFLD and MAFLD with BMI >25 kg/m2.
- Male sex, higher CD4 cell count and triglycerides were associated with NAFLD/MAFLD overlap.



Guaraldi G et al. CROI 2022 P.521 – cross sectional

The pathway of NAFLD vs MAFLD toward significant fibrosis

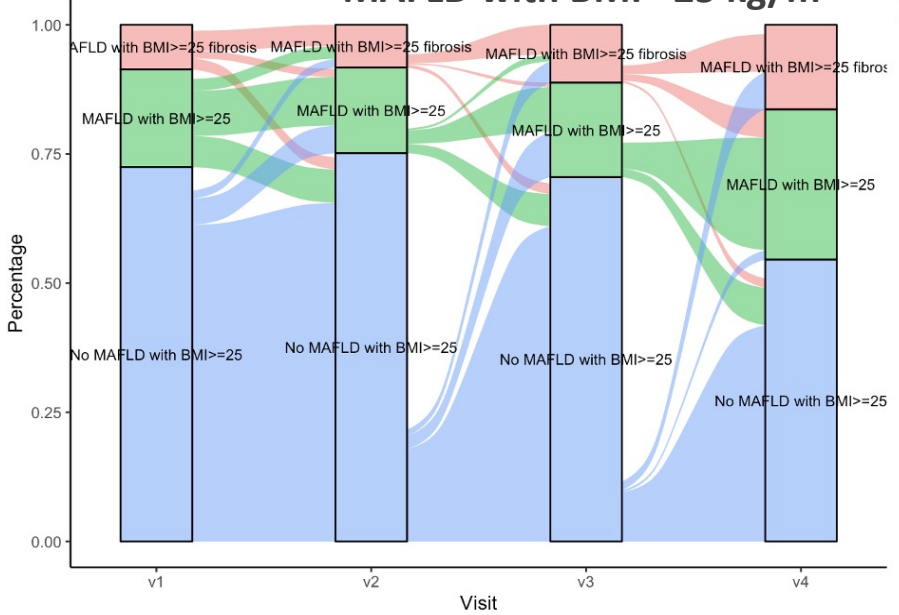
A NAFLD



Probability of state transition for NAFLD

Path	Estimates
No NAFLD - No NAFLD	80.3%
No NAFLD - NAFLD	17%
No NAFLD – NAFLD with fibrosis	2.6%
NAFLD – no NAFLD	36.4%
NAFLD - NAFLD	53.4%
NAFLD – NAFLD with fibrosis	10.2%
NAFLD with fibrosis - NAFLD	21.3%
NAFLD with fibrosis – NAFLD with fibrosis	58.5%

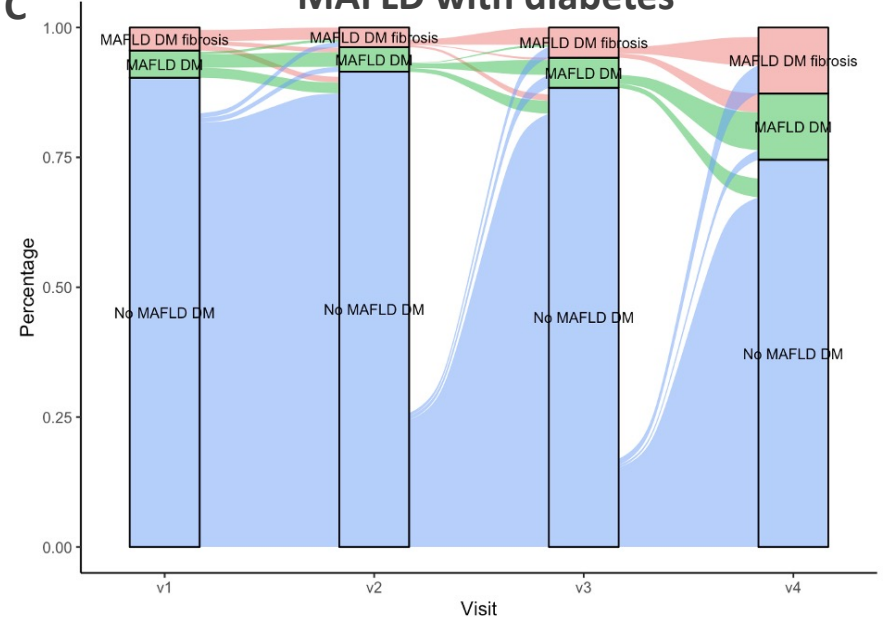
B MAFLD with BMI >25 kg/m²



Probability of state transition of MAFLD with BMI ≥ 25

Path	Estimates
No MAFLD - No MAFLD	88.3%
No MAFLD - MAFLD	8.2%
No MAFLD – MAFLD with fibrosis	3.5%
MAFLD – no MAFLD	35.7%
MAFLD - MAFLD	53.1%
MAFLD – MAFLD with fibrosis	10.5%
MAFLD with fibrosis - MAFLD	18.8%
MAFLD with fibrosis – MAFLD with fibrosis	55.2%

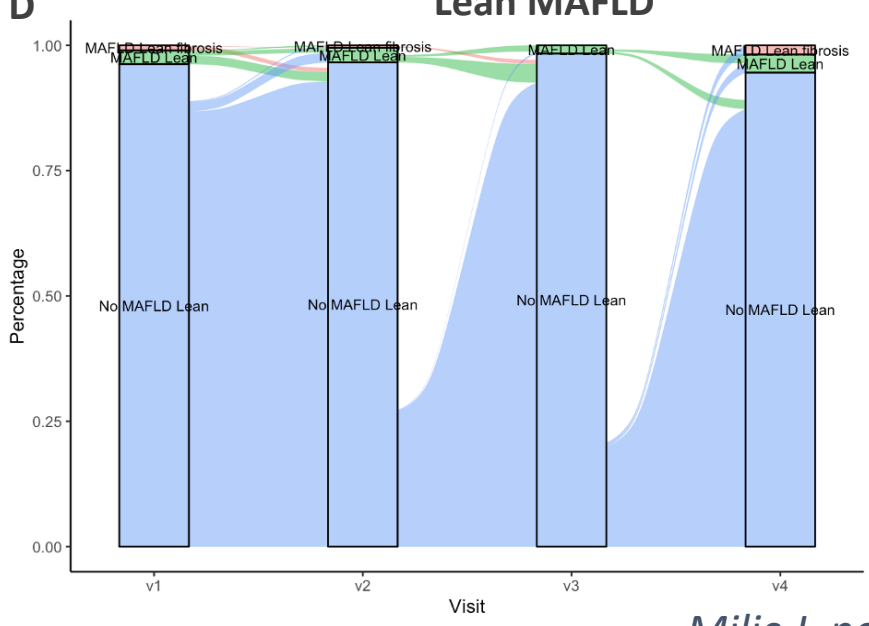
C MAFLD with diabetes



Probability of state transition of MAFLD with diabetes

Path	Estimates
No MAFLD - No MAFLD	96.9%
No MAFLD - MAFLD	1.5%
No MAFLD – MAFLD with fibrosis	1.6%
MAFLD – no MAFLD	40%
MAFLD - MAFLD	52.3%
MAFLD – MAFLD with fibrosis	7.7%
MAFLD with fibrosis - MAFLD	18.9%
MAFLD with fibrosis – MAFLD with fibrosis	58.5%

D Lean MAFLD



Probability of state transition of MAFLD with BMI <25 (lean)

Path	Estimates
No MAFLD - No MAFLD	98%
No MAFLD - MAFLD	1.7%
No MAFLD – MAFLD with fibrosis	0.3%
MAFLD – no MAFLD	65.8%
MAFLD - MAFLD	28.9%
MAFLD – MAFLD with fibrosis	5.3%
MAFLD with fibrosis - MAFLD	10%
MAFLD with fibrosis – MAFLD with fibrosis	0%

Milic J, poster 522 CROI 2022

FAST score predicts liver-related outcomes in people with HIV

Cohort

International cohort study
4 centers, 3 countries

1472 people with HIV (⊘hepatitis)
Age 26-76 years, 75% males
Median liver stiffness 4.9 kPa

Median follow-up 3.8 years

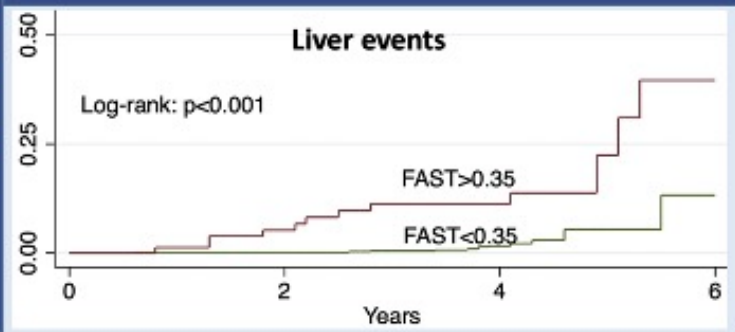
Outcomes

Clinical outcomes

Liver events
(8.9 per 1000 PY)

Extra-hepatic events
(33.7 per 1000 PY)

All-cause mortality
(3.4 per 1000 PY)



Key findings

Area Under the Curve

	Liver events	Extra-hepatic events
FAST	0.86	0.54
Stiffness	0.77	0.63
FIB-4	0.67	0.70
APRI	0.79	0.54

→ Clinical outcomes are frequent in people with HIV mono-infection

→ FAST predicts liver-related outcomes and can be used for risk stratification in clinical practice

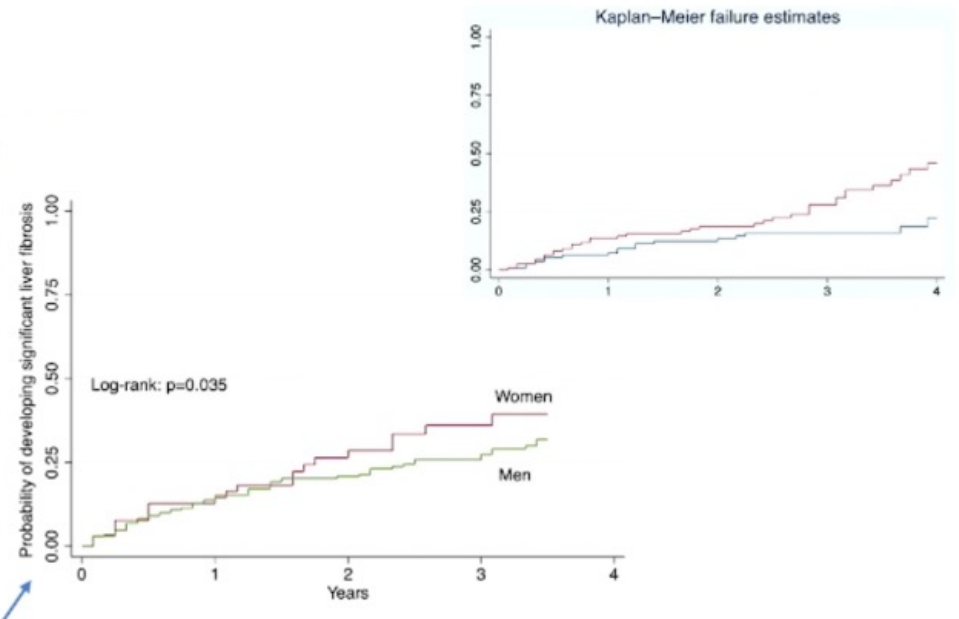
Sebastiani, et al. *Clinical Infectious Diseases.*

Clinical Infectious Diseases

Sex differences in MAFLD and liver fibrosis progression

Baseline characteristics

	Female	Male
Prevalence of MAFLD	17.7%	24.3%
Prevalence of liver fibrosis	10.7%	13.4%
Black ethnicity	48%	17%
ALT, U/L	26.4 ± 20.4	33.4 ± 22.5
HDL cholesterol, mmol/l	1.46 ± 0.57	1.11 ± 0.33
Triglycerides, mmol/l	1.69 ± 0.96	2.47 ± 2.63



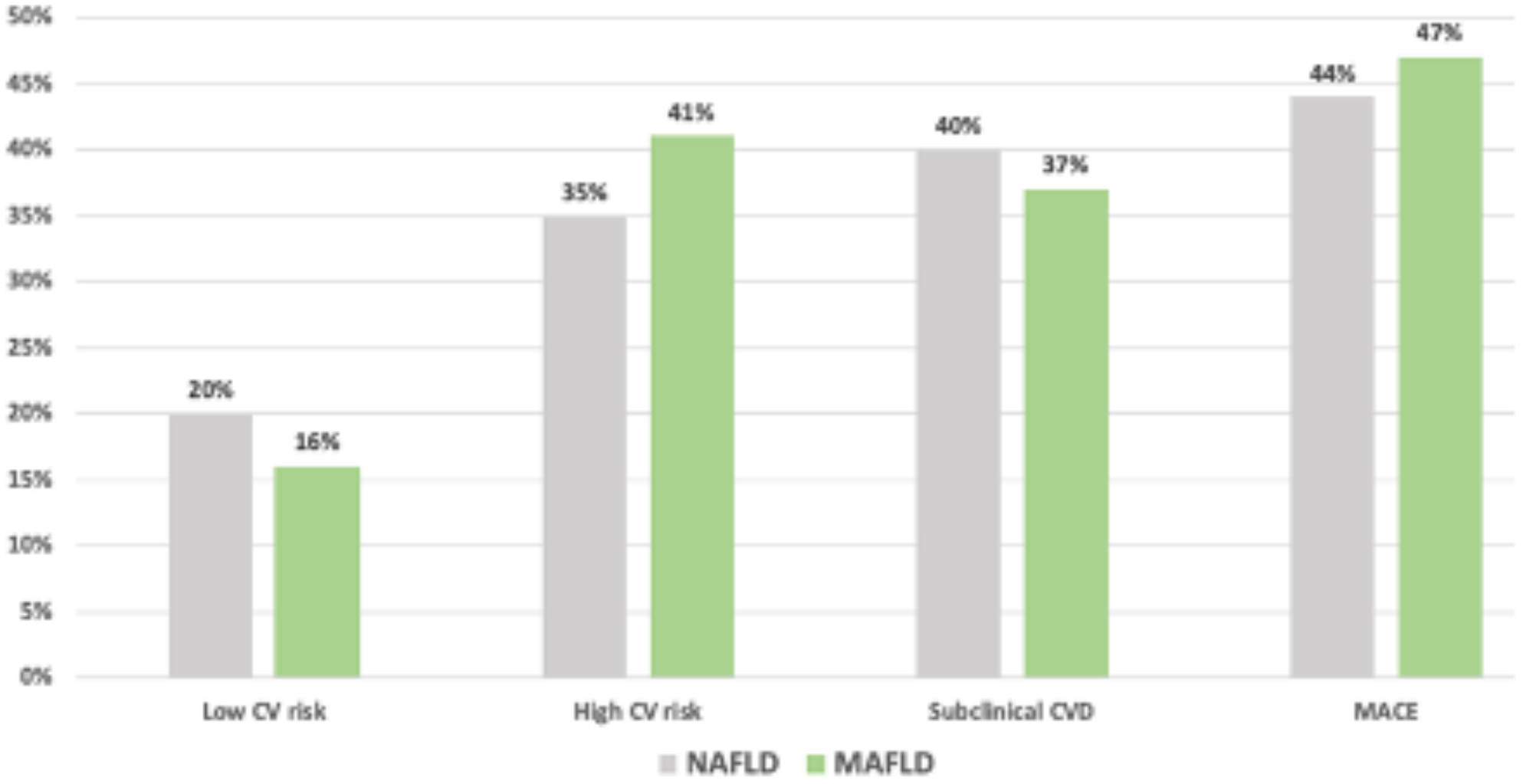
- Incidence of **MAFLD similar between women and men with HIV**
- Incidence of **liver fibrosis was higher in women** vs. men with HIV
  - 7.0 vs. 5.9 per 100 PY

particularly **after 50 years old**

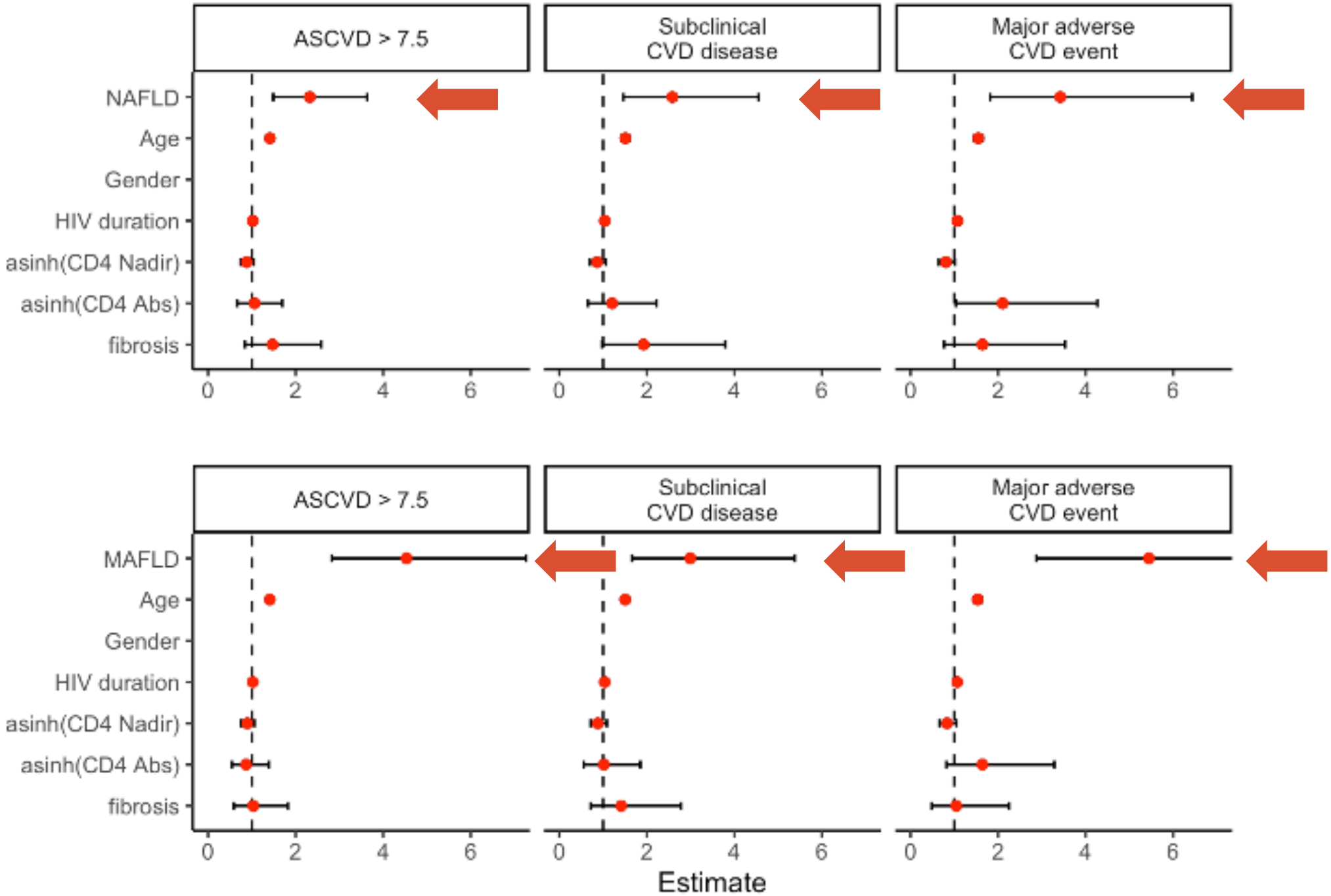
- On multivariable cox regression and after age adjustment: **MAFLD** (aHR 3.3, 95% CI 2.0-5.6) **and female sex** (aHR 2.2, 95% CI 1.3-3.5) **were independent predictors** of developing significant liver fibrosis while **CD4 cell count was protective** (aHR 0.99, 95% CI 0.99-0.99).

Kalawi D, poster 611, CROI 2023

NAFLD and MAFLD prevalence according to CV risk, subclinical CVD and MACE



Milic J, ICAR 2022


ASCVD > 7.5
Subclinical CVD disease
Major adverse CVD event
NAFLD
Age
Gender
HIV duration
asinh(CD4 Nadir)
asinh(CD4 Abs)
fibrosis
0
2
4
6
ASCVD > 7.5
Subclinical CVD disease
Major adverse CVD event
MAFLD
Age
Gender
HIV duration
asinh(CD4 Nadir)
asinh(CD4 Abs)
fibrosis
0
2
4
6
Estimate

MENU

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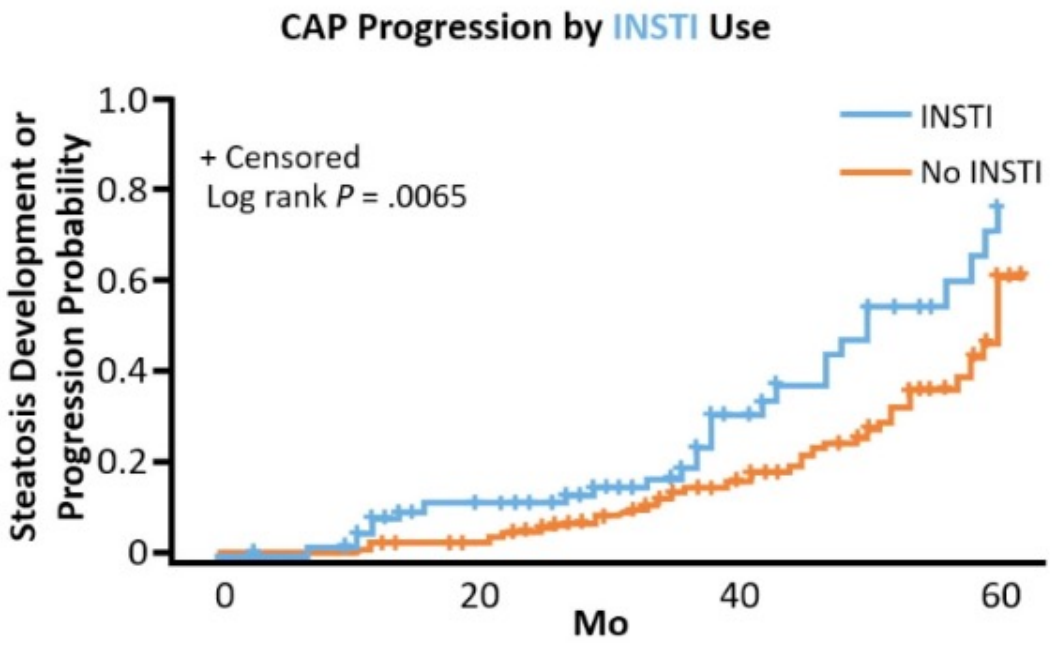
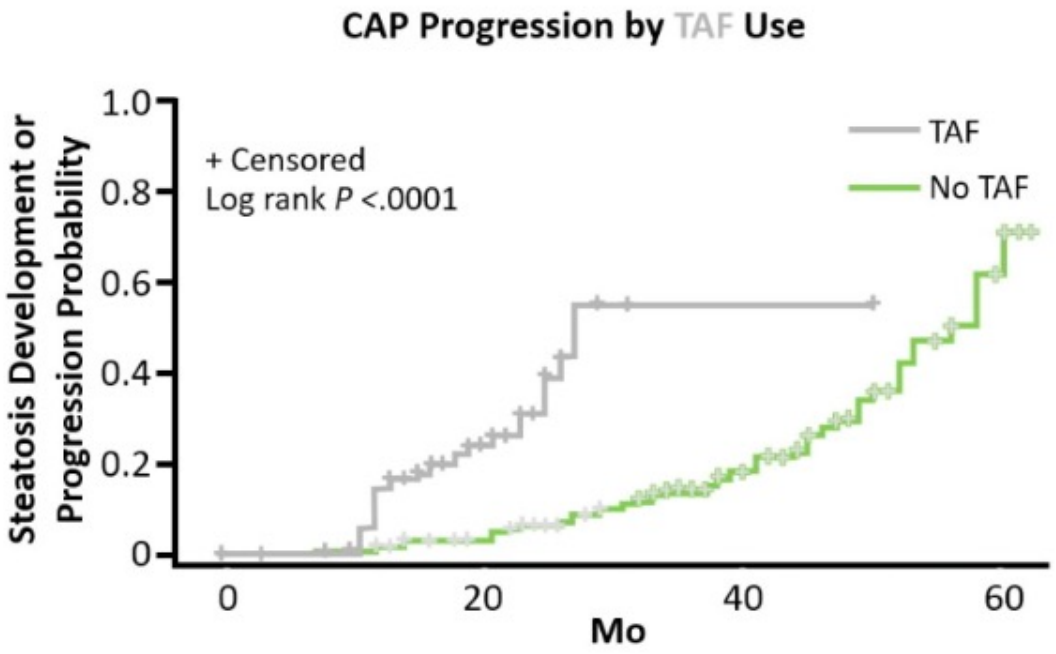
Effect of ART on steatosis progression?

- PWH (n = 301), serial transient elastography with CAP (follow-up 41.8 ± 14.8 mo)
- Individuals who received INSTI- and TAF-based cART demonstrated a faster steatosis development or progression

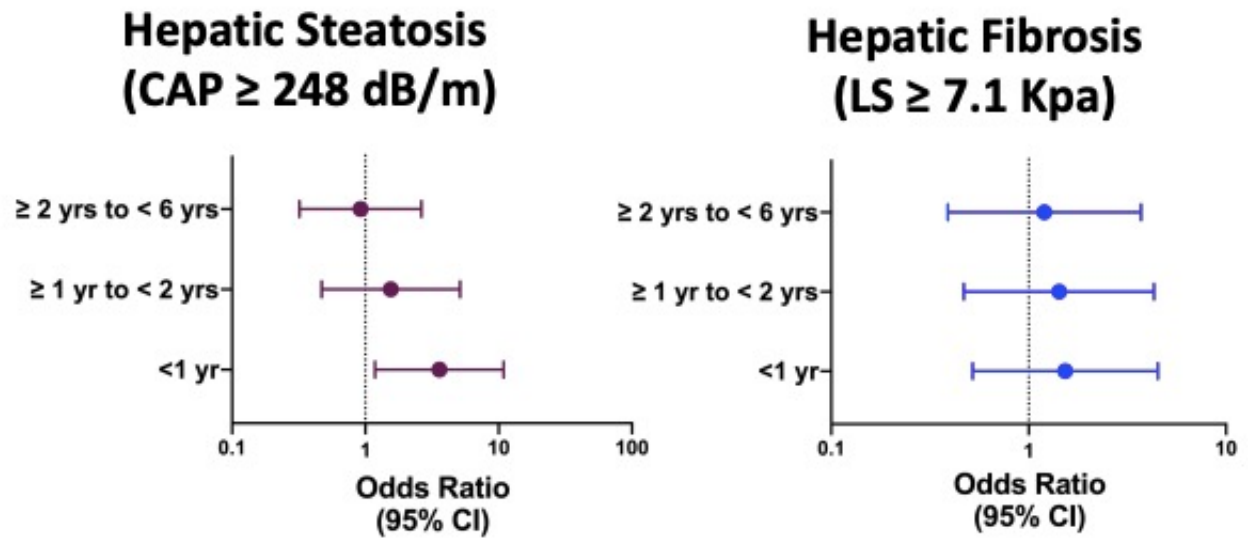




Bischoff. eClinicalMed. 2021;40:101116.

Effect of ART on liver fibrosis progression?

Figure 3. Model-adjusted odds of hepatic steatosis and moderate fibrosis in INSTI vs non-INSTI groups.
Women on INSTIs had a 3.6 greater odds of having hepatic steatosis within 1 year of switch compared to non-INSTI Controls.



- 257 WWH (123 INSTI, 134 Control) were included.
- Overall, mean age was 50 years (SD 8), BMI was 32 (8) kg/m2, CD4 count was 796 (305) cells/mm3.

Lahiri C, poster 610, CROI 2023

	Cox regression analysis of the liver fibrosis progression		
Predictors	**Hazard ratio**	**CI**	**p**
Current exposure to INSTI	1.47	0.61 – 3.52	0.389
Current exposure to TAF	0.85	0.39 – 1.87	0.683
Current exposure to NNRTI	0.83	0.32 – 2.18	0.704
Current exposure to PI	1.53	0.64 – 3.63	0.340
Male sex	1.08	0.43 – 2.71	0.863
Age at baseline	0.99	0.95 – 1.04	0.690
Nadir CD4 <200	0.56	0.27 – 1.17	0.120
Years since HIV diagnosis	1.05	1.00 – 1.10	0.064
Chronic hepatitis B virus infection	2.08	0.56 – 7.69	0.272
Chronic hepatitis C virus infection	1.08	0.45 – 2.57	0.868
MAFLD	**2.50**	**1.06 – 5.89**	**0.036**
BMI gain > 5%	**2.64**	**1.32 – 5.26**	**0.006**

- A total of 1183 PWH were included.
- Median age 52.9 years, 77% males, BMI was 24.1 kg/m2, median duration since HIV diagnosis 18 years).

Guaraldi G, poster 617, CROI 2023

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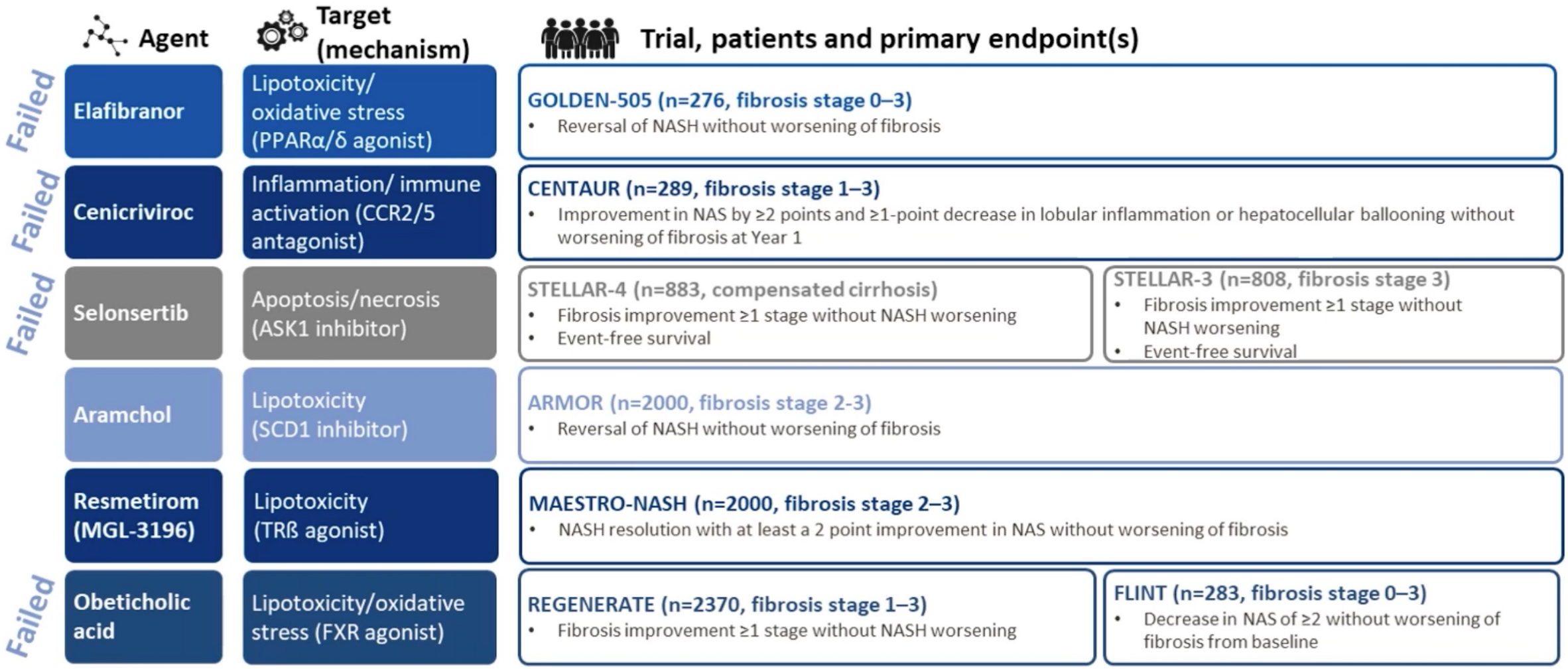
Potential drug-drug interactions between selected antiretrovirals and drugs to treat NASH

		Clinical trial phase	ATV/c	ATV/r	DRV/c	DRV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
NASH drugs	Aramchol	III															↔	↔	↔	↔	↔
	Cenicriviroc	III	↑	↑289%	↑	↑213%	↔	↓43%[a]	↓	↓	↔	↔	↔	↓29%	↑	↔	↔	↔	↔	↔	↔
	Elafibranor	III															↔	↔	↔	↔	↔
	Obeticholic acid*	III	↑	↑	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Resmetirom (MGL-3196)	III					↔	↔	↔	↔	↔	↔	↔	↔		↔	↔	↔	↔	↔	↔
	Tesamorelin		↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

We strongly advocate for the scientific community to include this group as a sub-population within studies.

Guaraldi G Hepatology 2020

NASH Agents in clinical development for the general population



FDA requires improvement of fibrosis without worsening of NASH or vice versa.
Steatosis per se it is not an approvable end point

Treatments for other conditions with favourable/limited success in NAFLD/NASH reduction

Medication	FDA indication	Patient population	Clinical benefits	Potential side effects	Cardiac benefit
Vitamin E (rrr-alpha) 800 IU daily[427,428]	NA	NASH without T2DM or cirrhosis	Liver related: improves steatosis, NASH resolution? No proven benefit on fibrosis	Hemorrhagic stroke, risk of prostate cancer?	No
Pioglitazone 30–45 mg po daily[429–431]	T2DM	NASH with and without T2DM	Liver related: improves steatosis, activity and NASH resolution, fibrosis improvement? Nonliver related: improves insulin sensitivity, prevention of diabetes, CV risk reduction and stroke prevention	Weight gain, risk of heart failure exacerbation, bone loss	Yes
Liraglutide[a] 1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)[432]	T2DM, obesity	NASH without cirrhosis	Liver: improves steatosis, no proven impact on fibrosis. Nonliver related: improvement in insulin sensitivity, weight loss, CV risk reduction, may slow progression of renal disease	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Semaglutide[b] 0.4 mg s.c. daily, 0.25–2.4 mg SQ weekly[433]	T2DM, obesity	NASH without cirrhosis	Liver related: improves steatosis, activity, and NASH resolution, no proven benefit on fibrosis, but may slow fibrosis progression. Nonliver related: improvement in insulin sensitivity, weight loss, improves CV and renal outcomes, stroke prevention	Gastrointestinal, gallstones (related to weight loss), pancreatitis	Yes
Tirzepatide[434,435]	T2DM	T2DM or obesity with NAFLD	Liver related: reduces steatosis on imaging. Nonliver related: improvement in insulin sensitivity, significant weight loss	Gastrointestinal, gallstones related to weight loss, pancreatitis	Unknown
SGLT-2i[436–438]	T2DM	T2DM and NAFLD	Liver related: reduction in steatosis by imaging. Nonliver related: may improve insulin sensitivity, improves CV and renal outcomes; benefit in heart failure, modest weight loss	Risk of genitourinary yeast infection, volume depletion, bone loss	Yes

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):p 1797-18352023.

NAFLD/NASH studies in PWH

Author and Year of Publication	Country/ Sample Size	Study Design	Diagnostic Method for NAFLD/NASH	Treatment	Mechanism	Main Finding
Matthews (2015)	USA/13	48-week RCT	MRS	Pioglitazone	PPARG	Decreased liver fat
Ajmera (2019)	USA/50	12-week RCT	MRS	Aramchol	SCD – 1	No reduction in liver fat
Sebastiani (2019)	Canada/27	24-week Open	Fibroscan	Vitamin E	Vitamin E	Reduced liver fat by CAP
Stanley (2019)	USA/61	48-week RCT	MRS/Biopsy	Tesamorelin	GHRH Agonist	Reduced liver fat Prevented fibrosis progression
Piconi (2019)	Italy/312	Retrospective	L/S by CT	Maraviroc	CCR2/5 Antag.	No effect on NAFLD

Guaraldi G Hepatology 2020

Take home messages

- MAFLD (vs. NAFLD) might be more suitable to stratify patients at higher risk for hepatic and extra-hepatic outcomes.
- HIV infection in an important (although not always recognized) risk factor for NAFLD/MAFLD/NASH.
- The highest risk of liver fibrosis progression is observed in PWLH with MAFLD with BMI >25.
- Sex differences should be considered and assessed in the natural history of NAFLD/MAFLD/NASH in PLWH.
- Role of ART od liver steatosis and liver fibrosis progression remains unclear.
- There is still no approved treatment for NAFLD/MAFLD/NASH, but a few clinical trials have promising results.

Acknowledgments

- Prof. Giovanni Guaraldi
- Prof. Cristina Mussini
- Prof. Giada Sebastiani
- Staff of Modena HIV Metabolic Clinic
- Informatics and statistics team
  - Dr. Stefano Renzetti
  - Prof. Stefano Calza
  - Dr. Federico Motta
  - Ing. Gian Luca Lonardi
- Office for clinical research and protocols
  - Dr. Barbara Beghetto
  - Dr. Giulia Nardini
  - Dr. Enrica Roncaglia
- All colleagues from Clinic for Infectious Diseases, Policlinico di Modena

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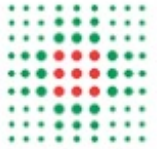

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