NAFLD en personas que viven con el VIH (PWH)

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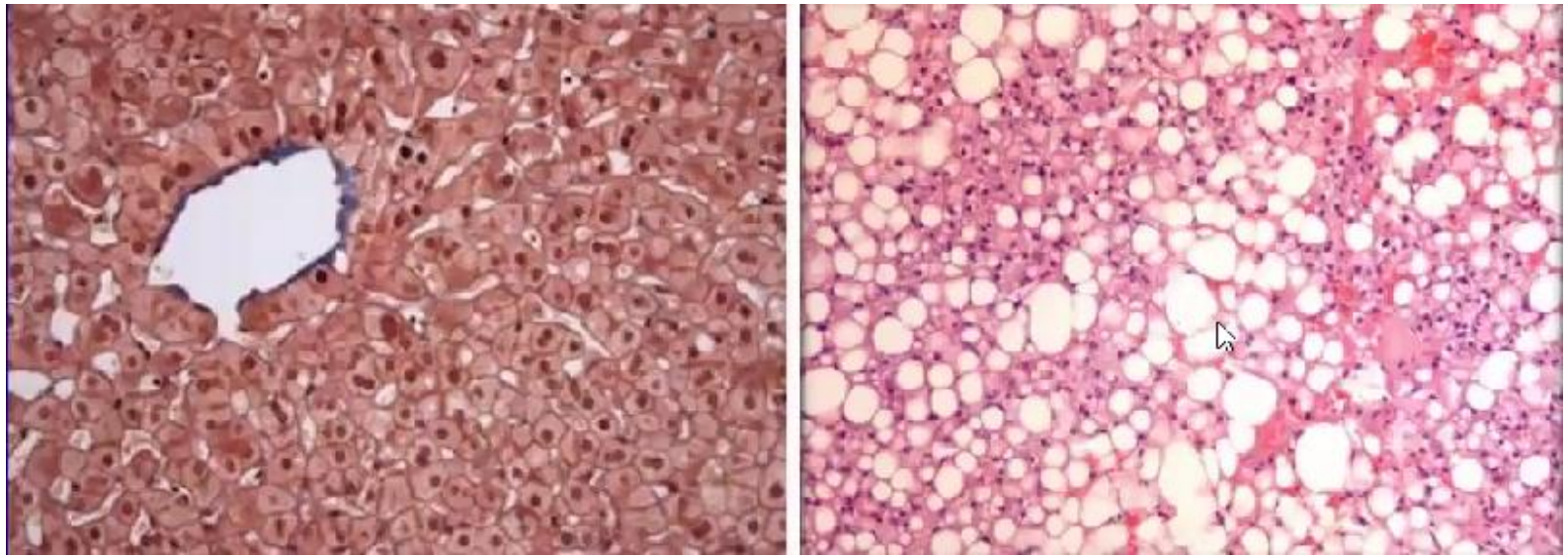
AGENDA

- ❑ Definion of hepatic steatosis and NALFD
- ❑ Define the impact of fatty liver on PWH
- ❑ Describe care interventions for PWH and fatty liver
- ❑ Describe the impact of antirretroviral treatment on NAFLD

Definition of Hepatic Steatosis

- **Hepatic steatosis is a histologic definition**
  >5% lipid deposition by liver weight

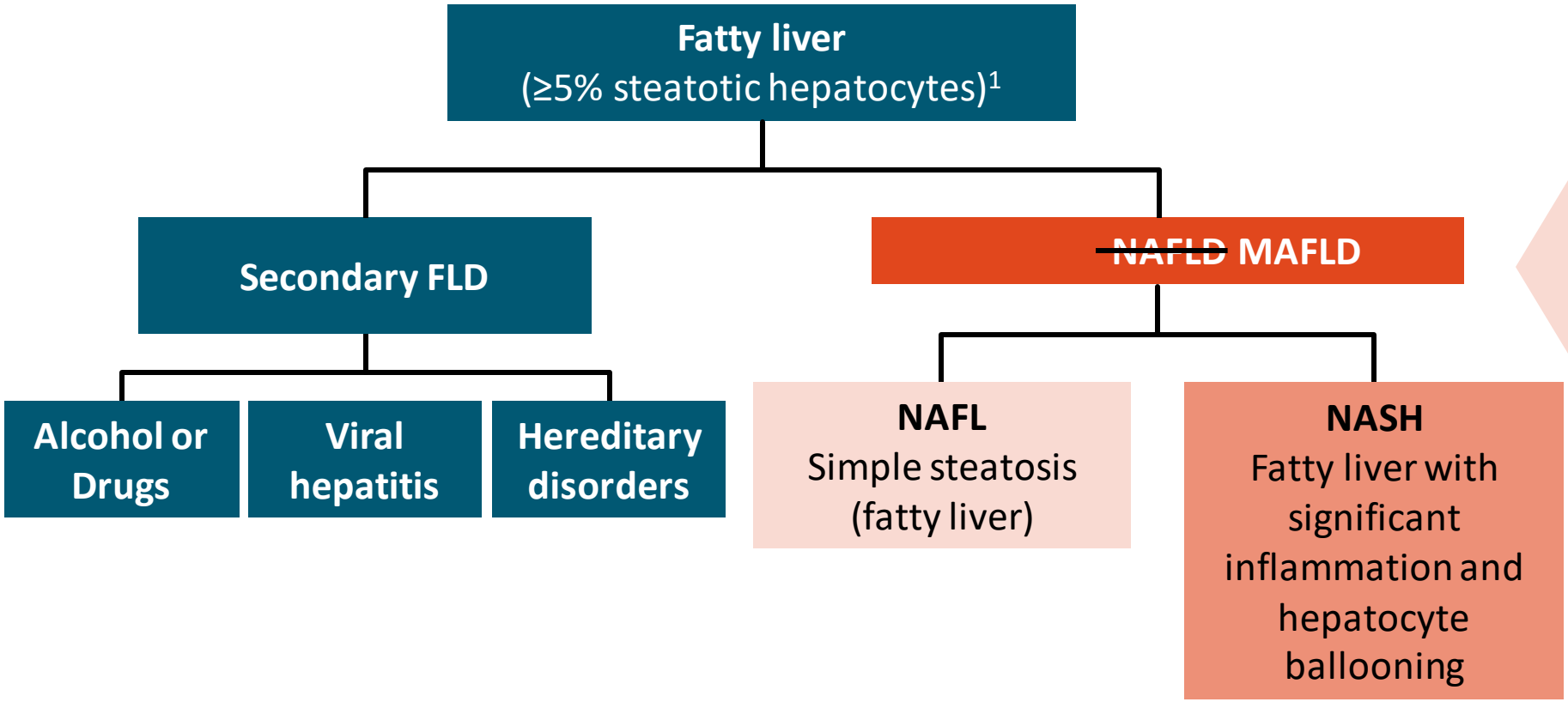
Nornal



Steatosis

RINELLA ME. *JAMA.* 2015;313(22):2263-2273.

NAFLD Definition

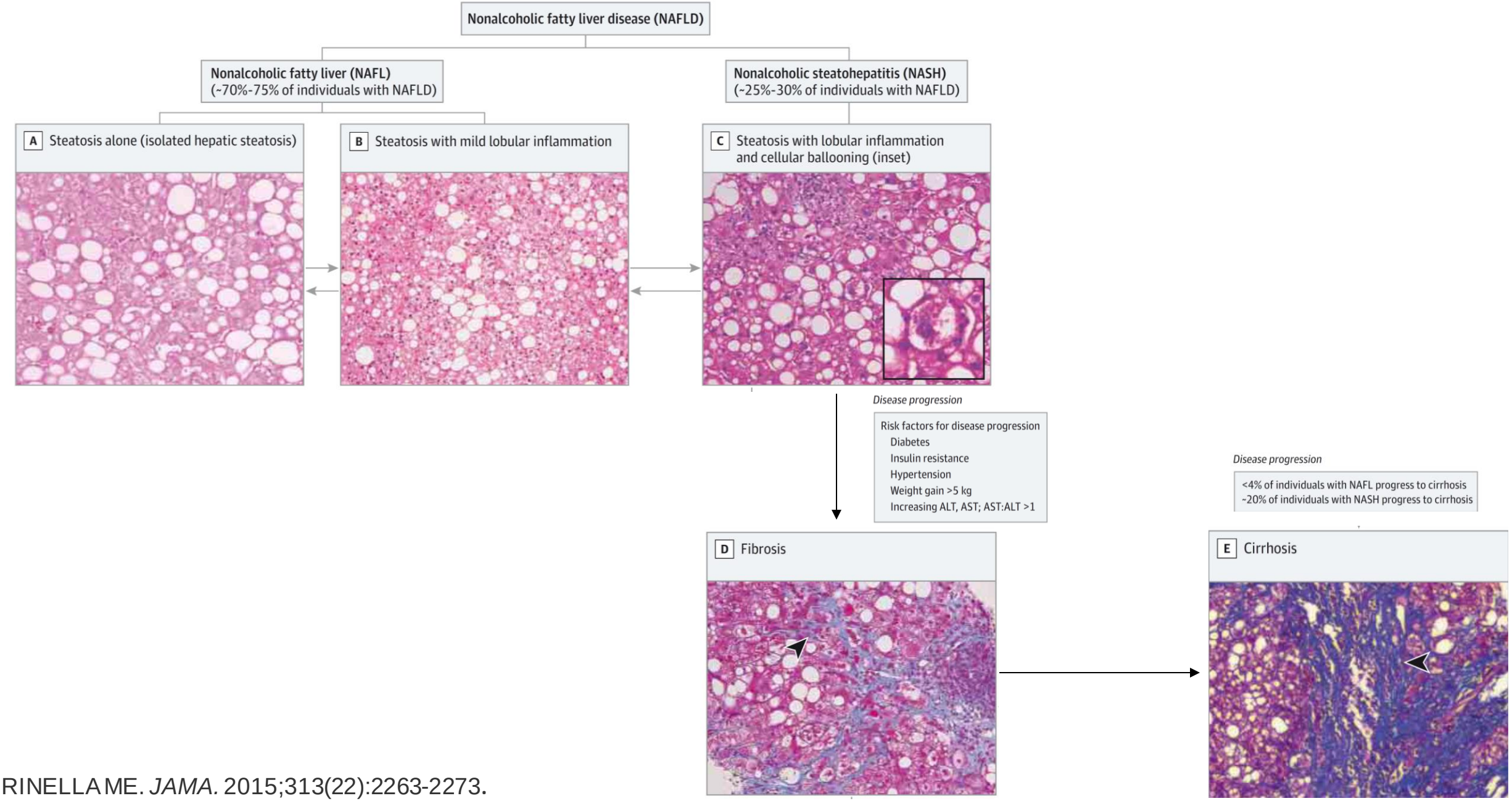


Metabolic abnormalities likely associated with NAFLD pathogenesis:

Insulin resistance
Obesity, diabetes, hypertension, dyslipidemia[1,2]

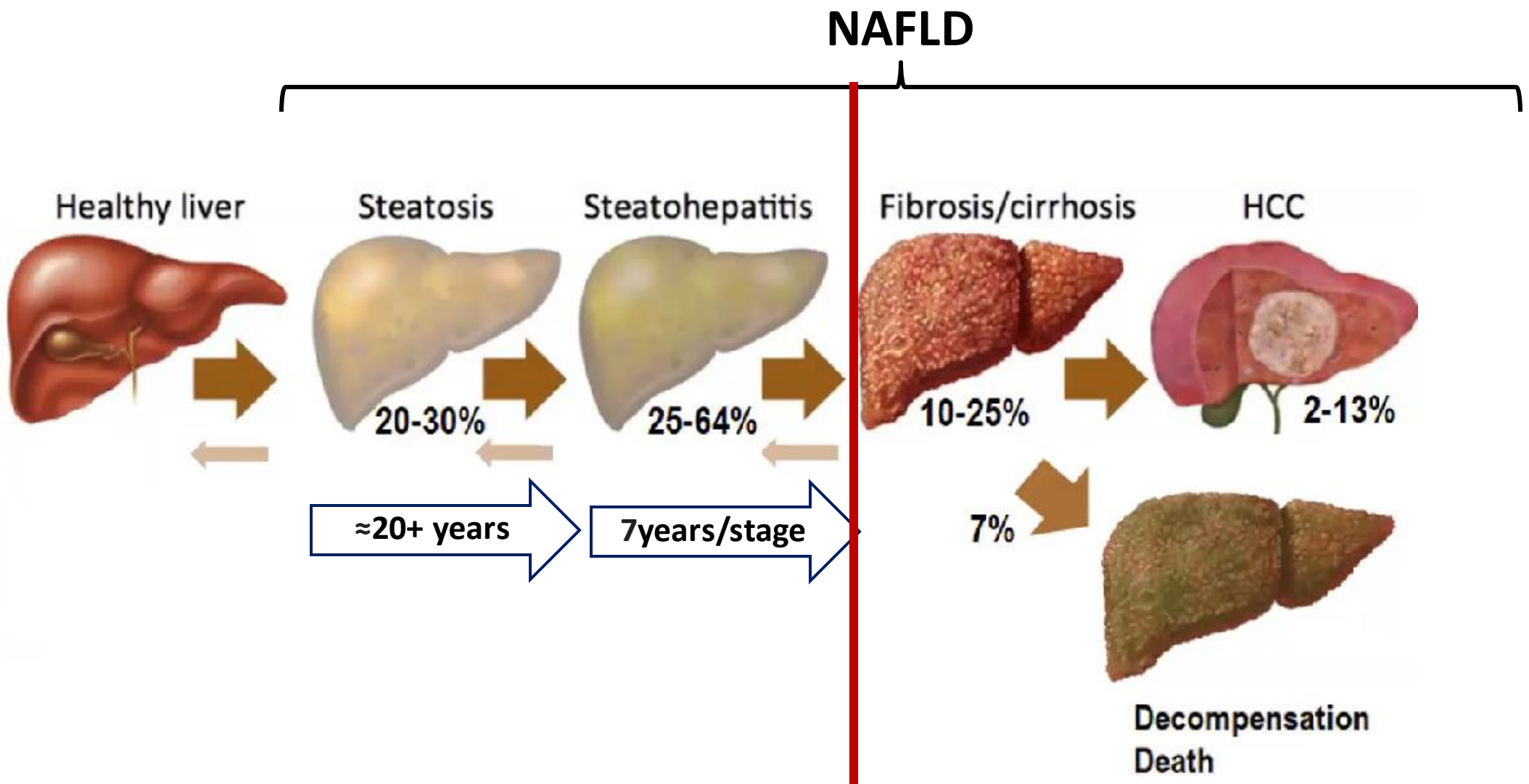
1. Chalasani. Hepatology. 2018;6:328. 2. Demir. J Dig Dis. 2015;16:541 (adapted from CCO)
2. Eslam M, J Hepatol. 2020 Jul;73(1):202-209

Histological Subtypes of NAFLD and Their Implications for Disease Progression



RINELLA ME. *JAMA.* 2015;313(22):2263-2273.

The spectrum of Fatty Liver Evolution



1. Younossi. J Hepatol. 2019;70:531. 2. Singh. April 24, 2014, p643-654.e9 Clinic. Gastro and Hep.
3. Benmassaoud. PLoS ONE. 2018;13:e0191985. 4. Kabbany. Am J Hepatol. 2017;112:581.

Tweet

CCO Infectious Disease Retweeted

CCO Infectious Disease
@CCO_InfDis

#POLL In your practice, how often do you perform noninvasive diagnostic tests to identify #HIV patients with NASH-related fibrosis?

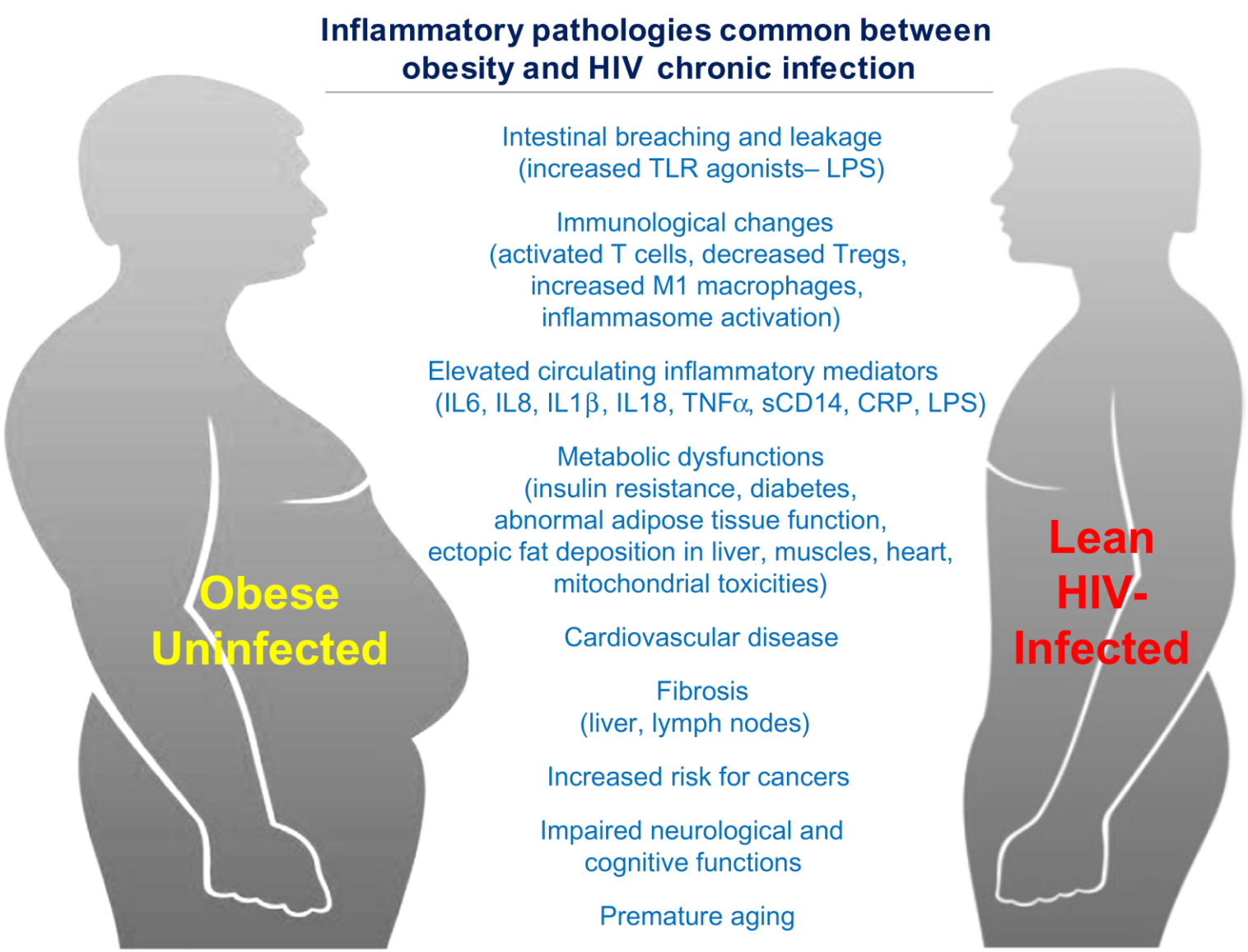
#IDTwitter #LiverTwitter #MedTwitter #NAFLD #NASH

Frequently	25.7%
Rarely	**40%**
Never	34.3%

35 votes · Final results

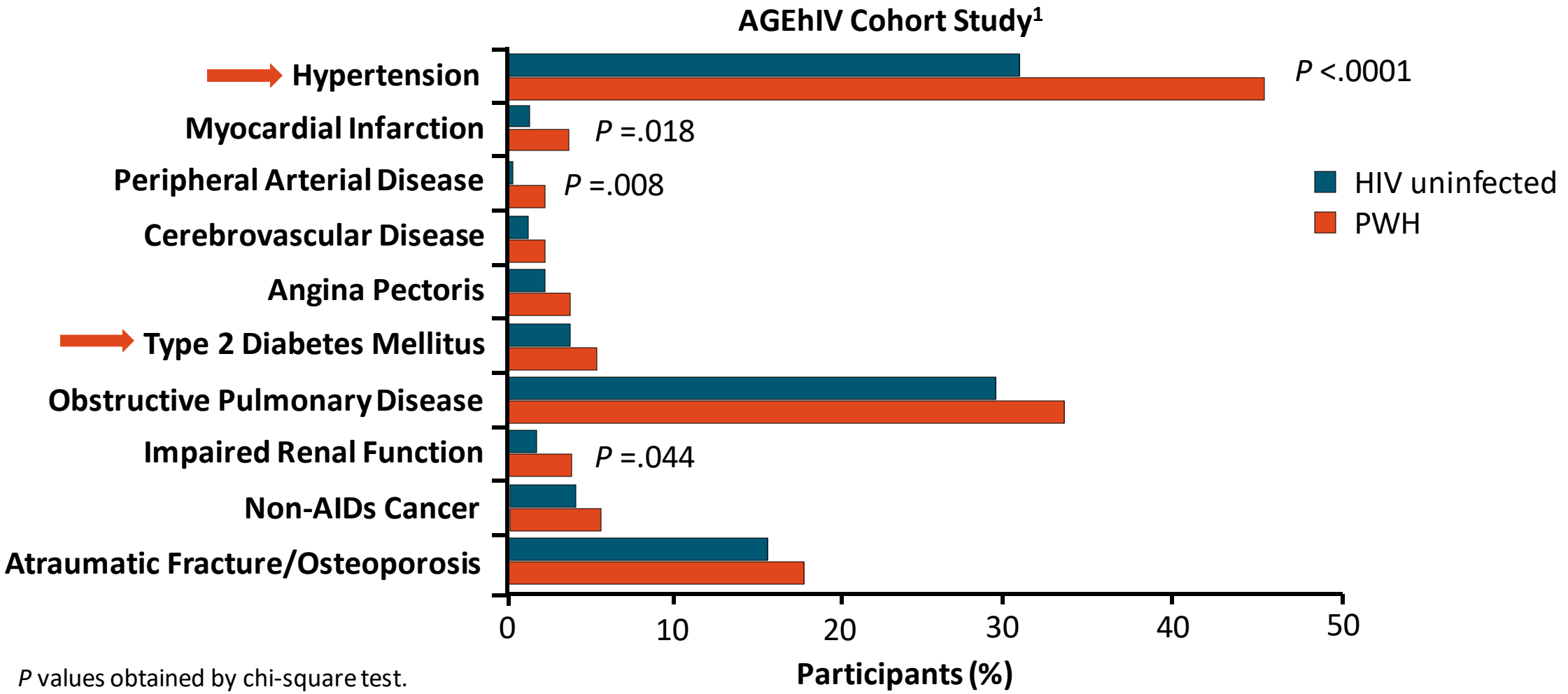
7:29 PM · Mar 23, 2022 · Twitter Web App

Similarities of chronic inflammation in obese uninfected and PWH



Lewis D et al, Translational Inflammation, 2019, Pages 111-131

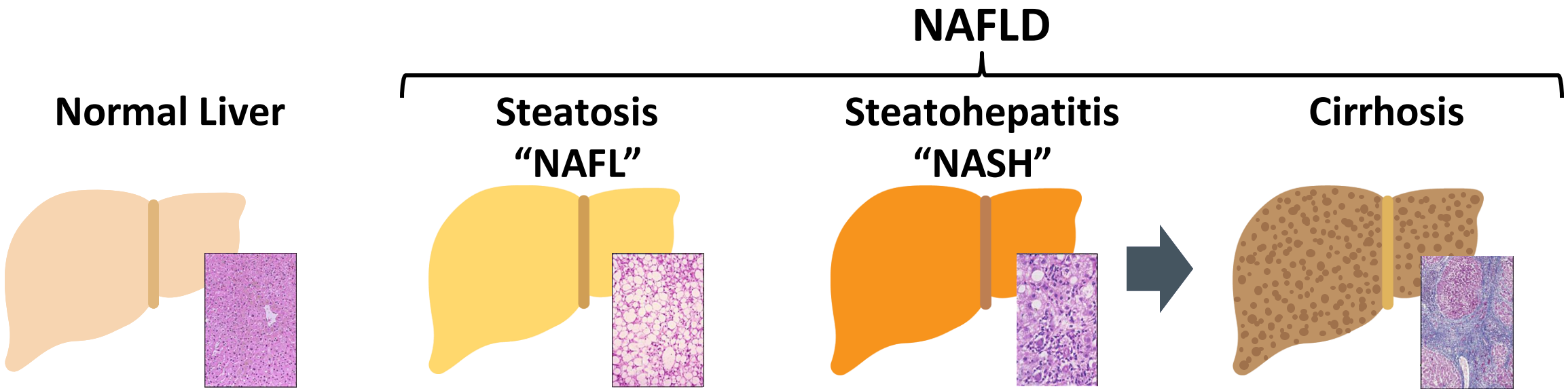
Prevalence of Age-Associated Metabolic Comorbidities in PWH



P values obtained by chi-square test.

1. Schouten. Clin Infect Dis. 2014;59:1787.

The NAFLD Continuum: NAFLD, NASH, Cirrhosis More Prevalent in PLWH

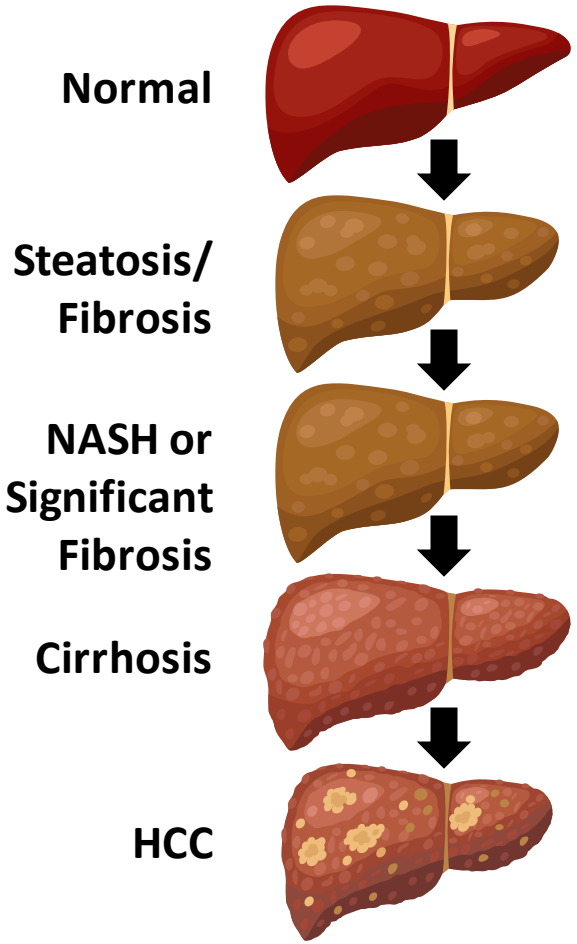


Worldwide prevalence:	**25%[1,2]**	**3% to 5%[1]**	**1% to 2% at risk***
Prevalence in HIV:	**13% to 65%[2]**	**10%[3]**	**2.3-6% at risk[2]**

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis.[4]

1. Younossi. J Hepatol. 2019;70:531. 2. Cervo. Curr HIV/AICS Rep. 2020;17:601.
3. Benmassaoud. PLoS ONE. 2018;13:e0191985. 4. Kabbany. Am J Hepatol. 2017;112:581.

Hypothetic Multifactorial Progression of Liver Disease in Aging Patients With HIV



Factors Unique to HIV

Prolonged ART Use
- Lipodystrophy
- Hepatotoxicity

HIV Direct Effects
- Hepatocyte injury/apoptosis
- Kupffer cell infection/activation
- Hepatic stellate cell activation (via HIV, gp120)

Universal Factors

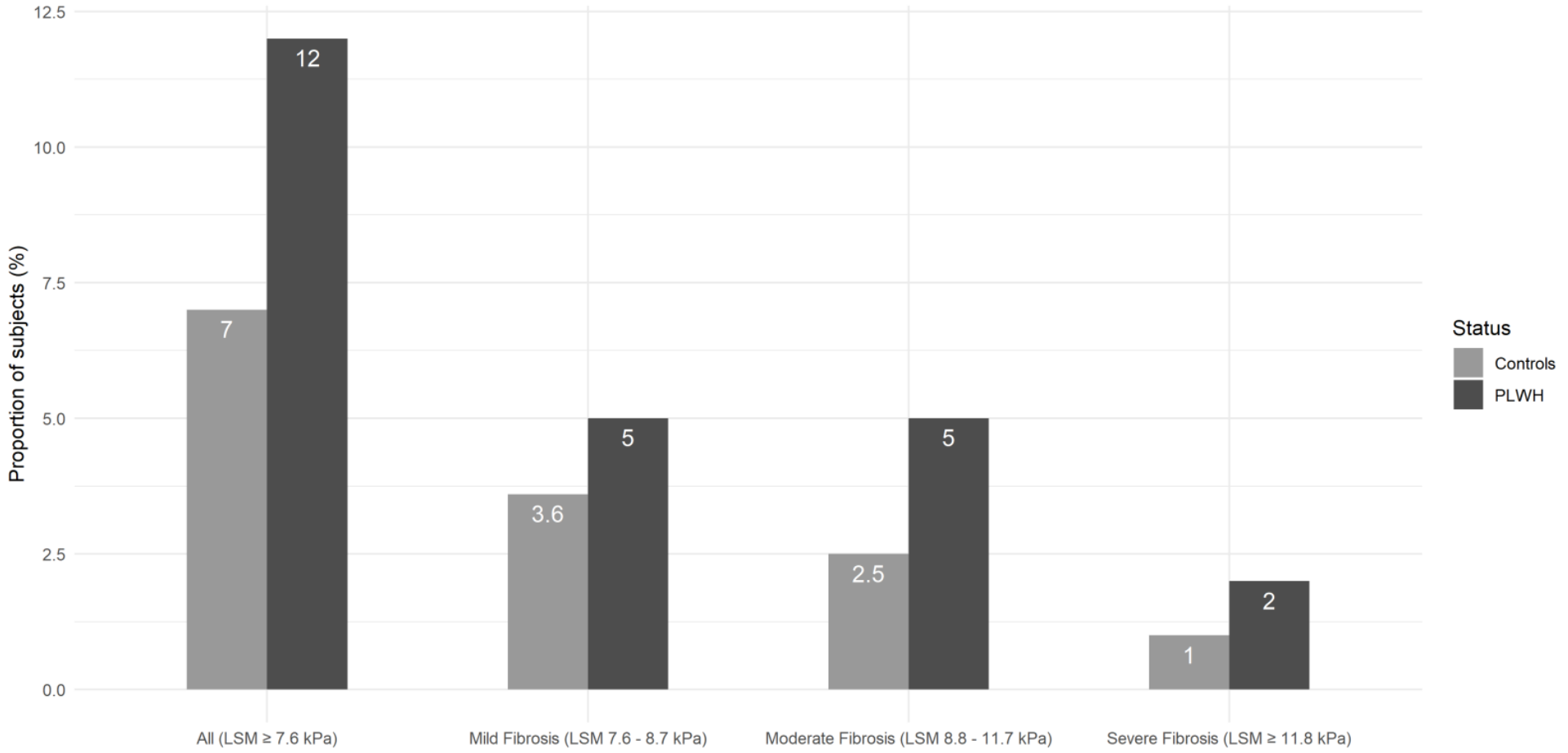
Metabolic Risk Factors
- Abdominal obesity
- Insulin resistance
- Diabetes

Patient-Related Risk Factors
- Age/gender
- Alcohol, drugs
- Diet, lack of physical exercise
- Gut dysbiosis

Aging HIV

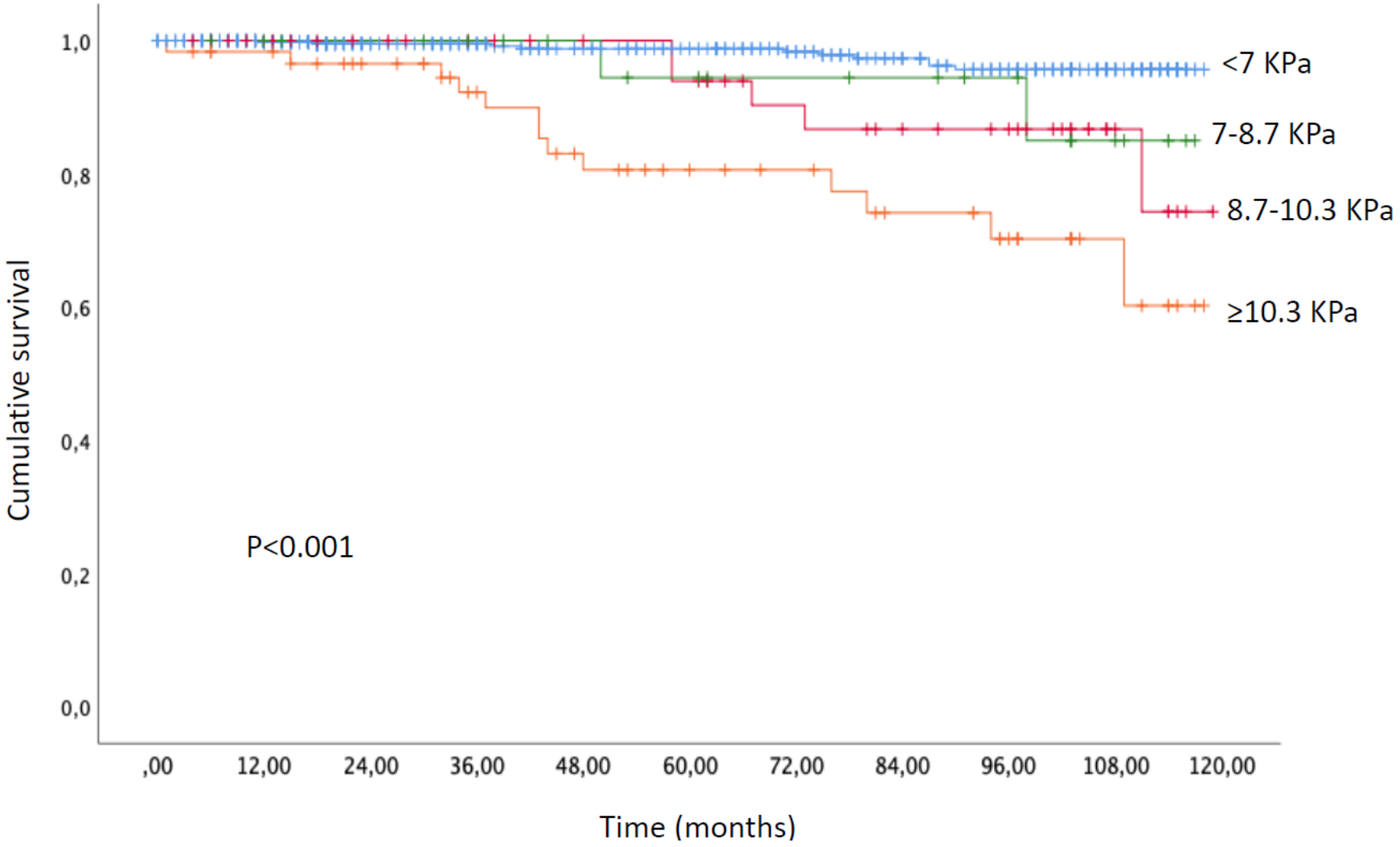
Rockstroh. Curr Opin HIV/AIDS. 2014;9:365. Chamroonkul. Nat Rev Gastroenterol Hepatol. 2019;16:1.

Proportion of subjects with fibrosis in PLWH



Kirkegaard - Klitbo DM et al., JID 2021

Survival according to liver stiffness PLWH without other concomitant causes ofliver disease (n=687)



Macias c et al, . vCROI 2022. Poster 518

Aging With HIV: The Changing Face of Mortality

- ~50% of people living with HIV in the United States are aged 50 yr and older[1]

Deaths caused by liver etiologies increased 10 times in post-ART era[2]

Mortality in PWH by Cause of Death in the First Yr After Diagnosis[3]				
Patients	**Mortality Rate per 10,000 Person-Yr (95% CI)**	**Observed Deaths (n)**	**Expected Deaths (n)**	**Standardized Mortality Ratio (95% CI)**
People diagnosed with HIV	72 965			
All-cause mortality	413 (399-428)	3014	124	24.3 (23.4-25.2)
Non-AIDS deaths	102 (94.6-109)	742	121	6.1 (5.7-6.6)
Non-AIDS infections	21.9 (18.8-25.6)	160	4	40.0 (34.0-46.7)
Non-AIDS cancers	14.9 (12.4-18.0)	109	36	3.0 (2.5-3.7)
CVD and stroke	20.8 (17.8-24.4)	152	28	5.4 (4.6-6.4)
▪ Liver disease[4]	11.0 (8.8-13.7)	80	8	10.0 (7.9-12.4)
Accident	3.4 (2.3-5.1)	25	12	2.1 (1.3-3.1)
Suicide	5.2 (3.8-7.1)	38	8	4.8 (3.4-6.5)
Substance abuse	3.8 (2.6-5.6)	28	7	4.0 (2.7-5.8)
Other	20.6 (17.5-24.1)	150	18	8.3 (7.1-9.8)

1. cdc.gov/hiv/group/age/olderamericans/index.html. 2. Cai. AIDS. 2019;33:1267.
3. Coxford. Lancet Public Health 2017;2:e35. 4. Weber. Arch Intern Med 2006;166:1632.

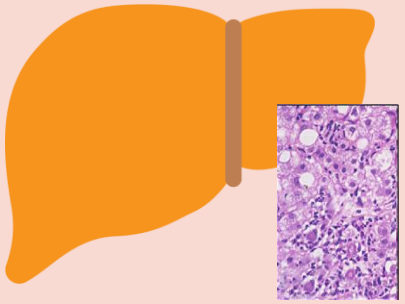
Diagnosis of NAFLD and Fibrosis in PWH

NASH Remains a Histologic Diagnosis

- **Liver biopsy** is essential for NASH diagnosis: cannot distinguish from steatosis using clinical, biochemical or imaging assays

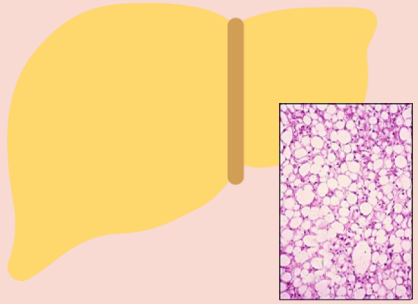
Diagnosis of NASH Involves Measurement of:

Inflammation



Requires biopsy

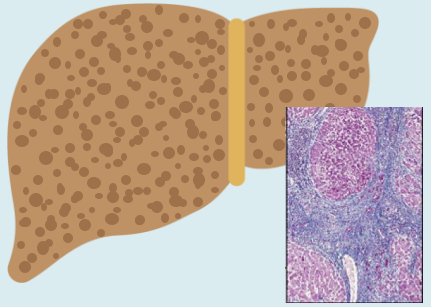
Steatosis



Can use noninvasive tests

Prognosis of NASH Involves Measurement of:

Liver Fibrosis, Cirrhosis



Can use noninvasive tests

EASL-EASD-EASO. J Hepatol. 2016;64:1388.

Available Noninvasive Tests for Hepatic Steatosis and Liver Fibrosis

Serum Biomarkers: Clinical or Laboratory Scores

Simple

- Fibrosis-4[1,2]
- NAFLD fibrosis score[1,2]
- APRI[1]
- BARD score[3]
- Triglyceride glucose index (TyG)[1,2]
- Hepatic Steatosis Index (HSI)[1,2]

Proprietary

- ELF test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[4] (not available in US)
- *FibroSure*[1]
- Hepascore

Imaging

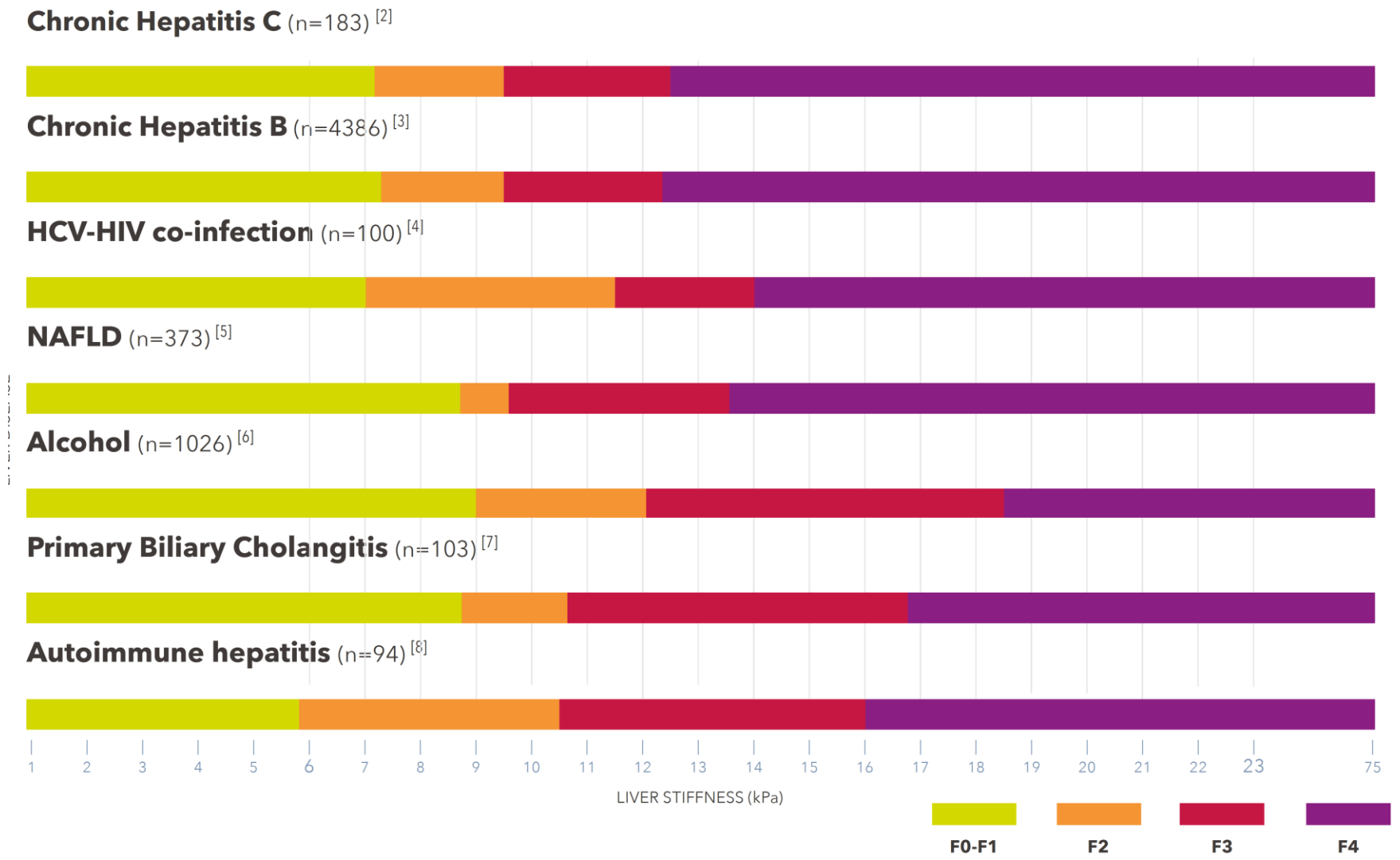
Elastography

- Transient elastography (eg, *FibroScan,* CAP)[1,2]
- 2D shear wave elastography[5]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[6,7]
- MRI-PDFF[8]
- FAST score[9]

Many of these lab values are part of routine assessments in PWH

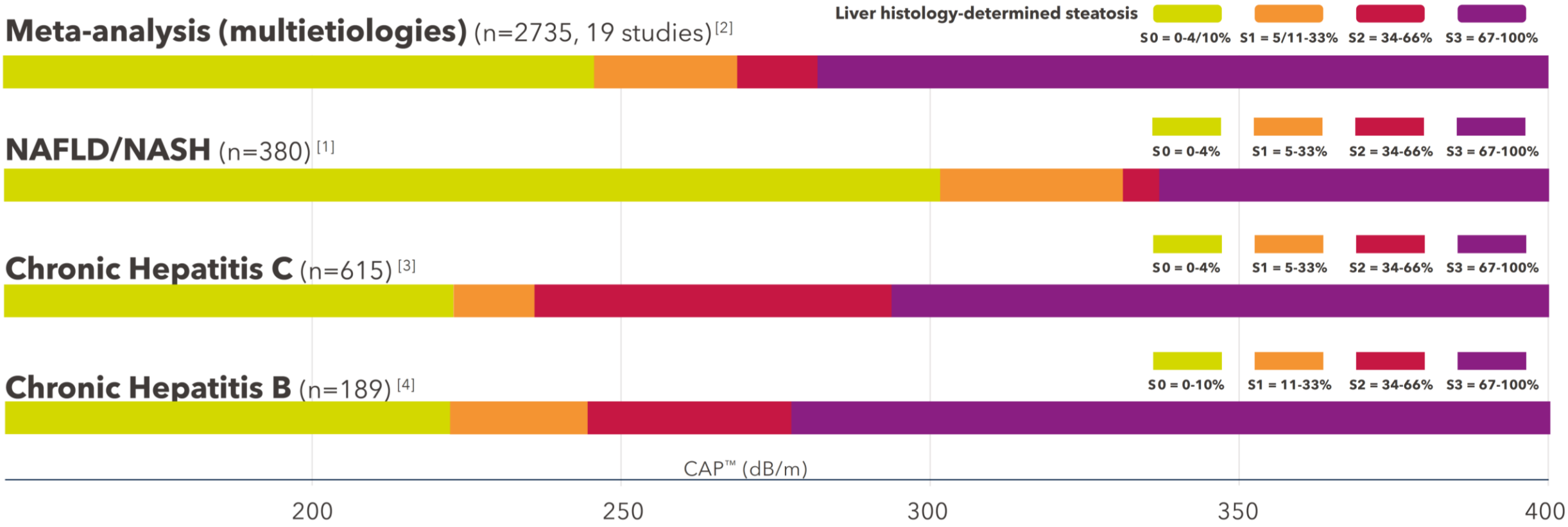
1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Harrison. Gut. 2008;57:1441.
4. Daniels. Hepatology. 2019;69:1075. 5. Sigrist. Theranostics. 2017;7:1303. 6. Jayaswal. AASLD 2018. Abstr. 1042.
6. Jayaswal. Liver Int. 2020;40:3071. 7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2020;5:362.

Quantifying fibrosis with FibroScan®



[1] Recio, E., et al. European Journal of Gastroenterology & Hepatology 2013; 25 (8) : 905-11. [2] Castera, et al., Gastroenterology 2005 Feb;128(2):343-50. [3] Li, et al., Aliment Pharmacol Ther 2016 Feb;43(4):458-69. [4] Sanchez-Conde, et al., J Viral Hepat. 2010 Apr;17(4):280-6. [5] Eddow es, P, et al. Gastroenterology 2019; 156: 6: 1717-1730 [6] Nguyen-Khac E, The lancet. Gastroenterology & hepatology 2018;3:614-625. [7] Corpechot, et al., Hepatology. 2012 Jul;56(1):198-208. [8] Hartl, et al., J hepatol. 2016 Oct;65(4):769-775.

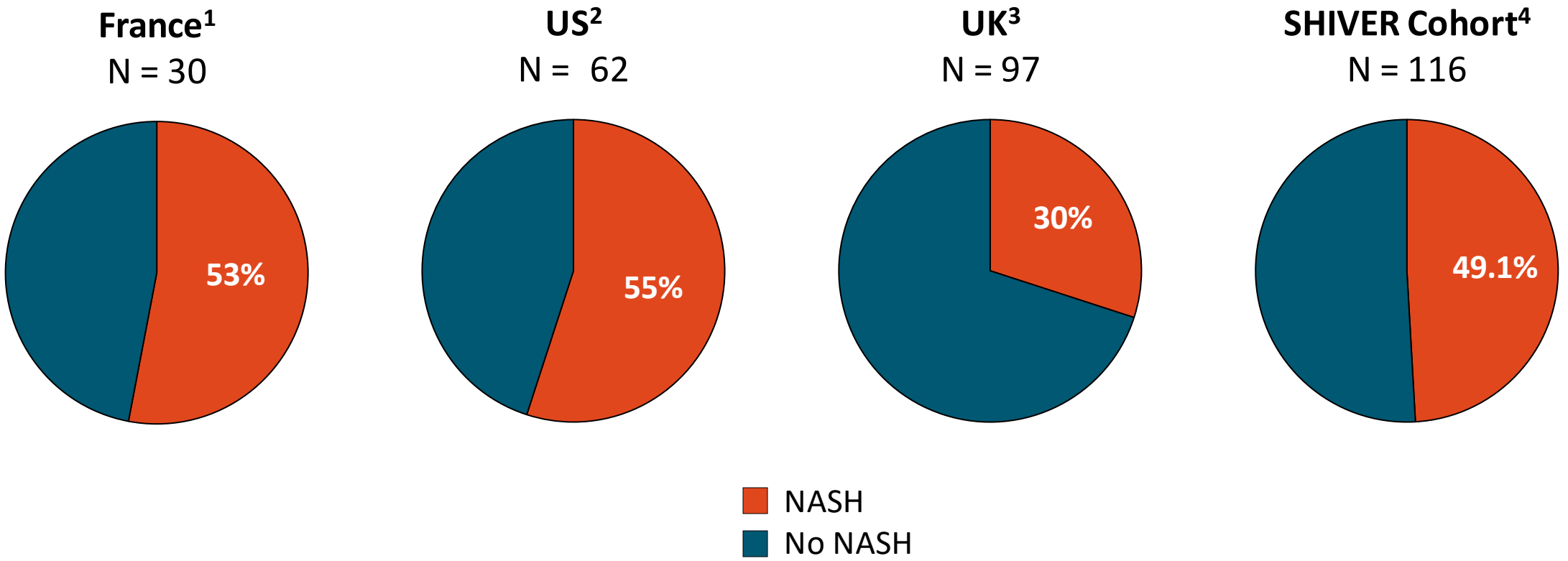
Quantifying steatosis with FibroScan®



[1] Eddowes, P, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease.. Gastroenterology 2019; 156: 6: 1717-1730 [PMID: 30689971 DOI: S0016-5085(19)30105-2; 10.1053/j.gastro.2019.01.042] [2] Karlas, T., et al. Individual Patient Data Meta-Analysis of Controlled Attenuation Parameter (CAP™) Technology for Assessing Steatosis. Journal of Hepatology 2016 ; In Press.[3] Sasso, et al., Novel controlled attenuation parameter for noninvasive assessment of steatosis using Fibroscan : validation in chronic hepatitis C. J Viral Hepat 2012 Apr;19(4):244-53. doi: 10.1111/j.1365-2893.2011.01534.x. Epub 2011 Oct 13. [4] Chen, et al., Controlled attenuation parameter for the detection of hepatic steatosis in patients with chronic hepatitis B. Infect dis. (Lond) 2016 Sep;48(9):670-5. doi: 10.3109/23744235.2016.1165860. Epub 2016 May 31. * Publications published in peer-reviewed journals. You can find all the publications on liver stiffness and CAP™ on the Echosens clinical library: http://www.echosensclinicallibrary.com/ [5] Paul J, et al. Measurement of Controlled Attenuation Parameter: a surrogate marker of hepatic steatosis in patients with non alcoholic fatty liver disease on lifestyle modification - a prospective follow-up study. Arq Gastroenterol None; 55: 1: 7-13 [PMID: 29561981 DOI: S0004-28032018000100007] [6] Park HE, et al. Clinical significance of hepatic steatosis according to coronary plaque morphology: assessment using controlled attenuation parameter.. J. Gastroenterol. 2019; 54: 3: 271-280 [PMID: 30284617 DOI: 10.1007/s00535-018-1516-5]. [6] Shimizu, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease.. Diabetes Obes Metab 2019; 21: 2: 285-292 [PMID: 30178600] These guides are based on a selection of clinical studies from the existing literature reporting use

Prevalence of NASH in PWH and Elevated ALT

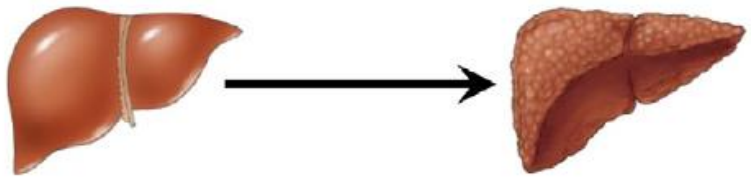
- **NASH** identified by liver biopsy in PWH who had abnormal LFTs



1. Ingiliz. Hepatology. 2009;49:436. 2. Morse. Clin Infect Dis. 2015;60:1569.
3. Prat. JAIDS. 2019;80:474. 4. Maurice. Clin Infect Dis. 2021;73:e2184.

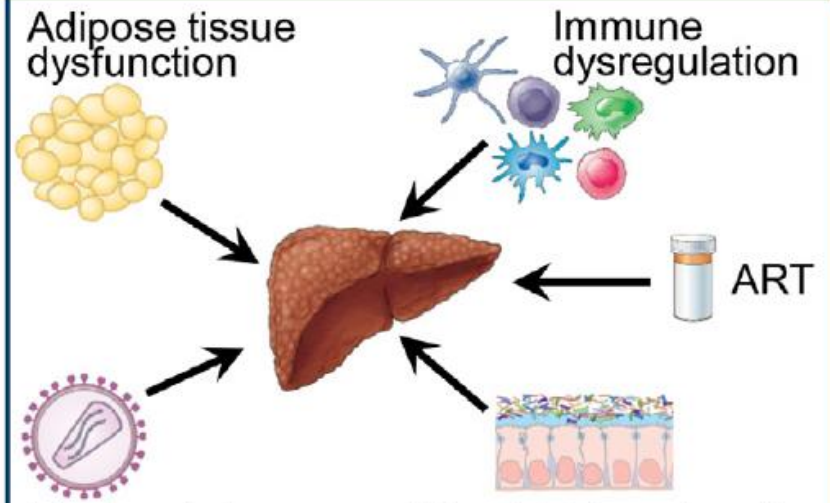
Research Priorities in HIV-Associated NAFLD

Epidemiology, histology, and natural history



- Prevalence of steatosis and fibrosis
- Predictors of fibrosis progression
- Relationship with other metabolic diseases

Pathogenesis



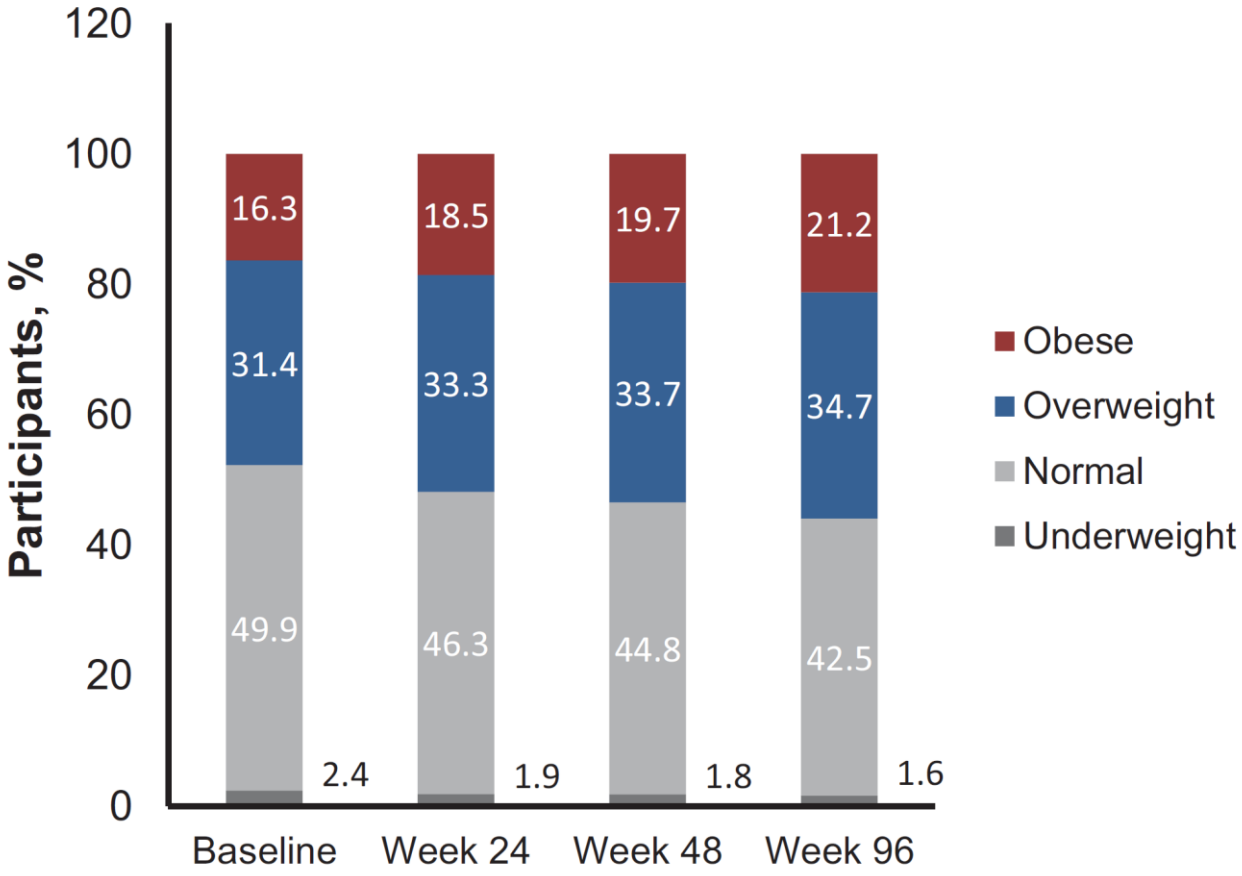
Non-invasive assessment, treatment, and prevention

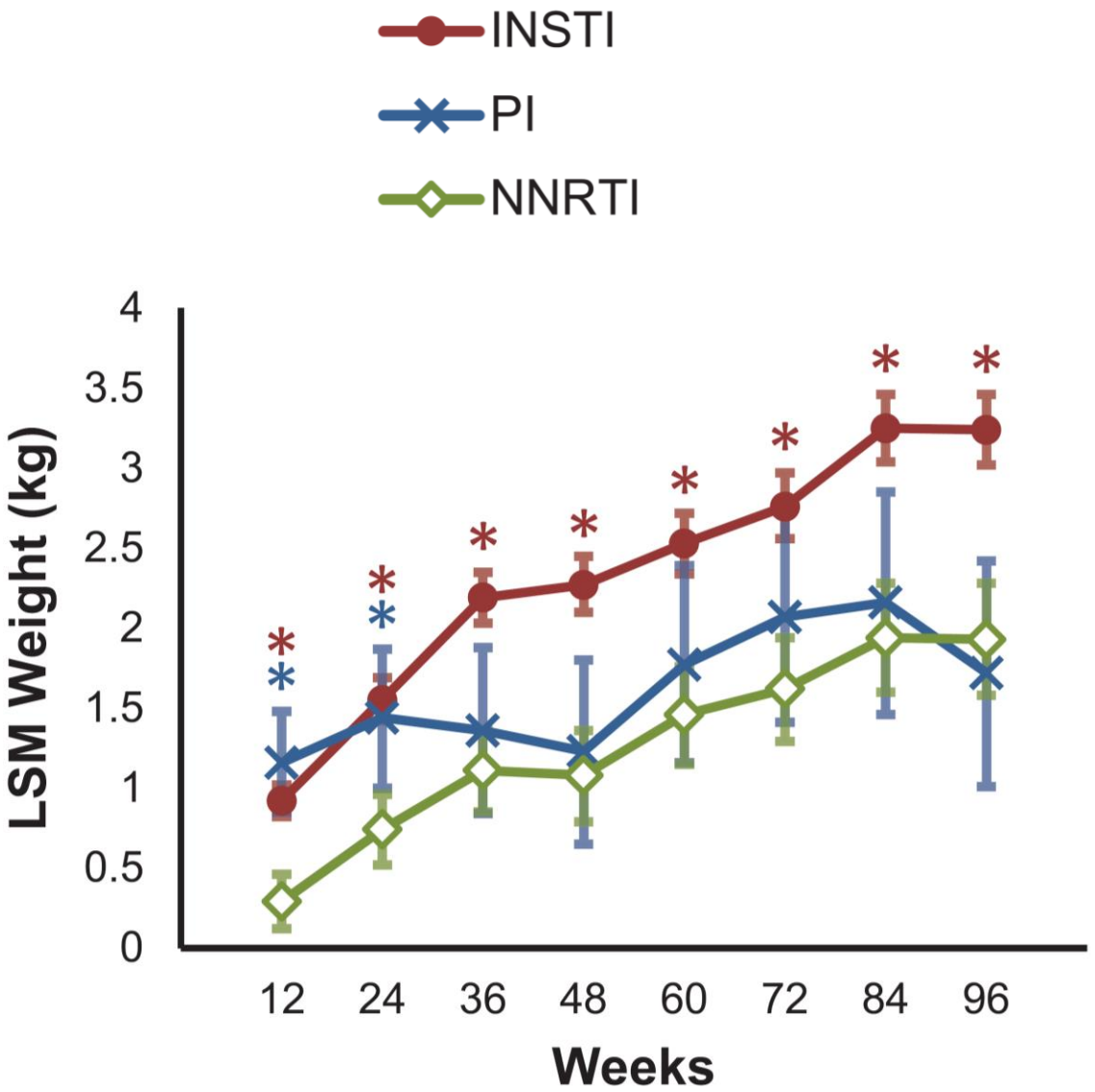
- Identification and validation of non-invasive biomarkers

- Value of current and novel therapies

The impact of ART on NAFLD

Weight trends in PWH initiating antiretroviral therapy





Sax. Clin Infect Dis. 2020;71:1379

Weight trends in PWH initiating antiretroviral therapy

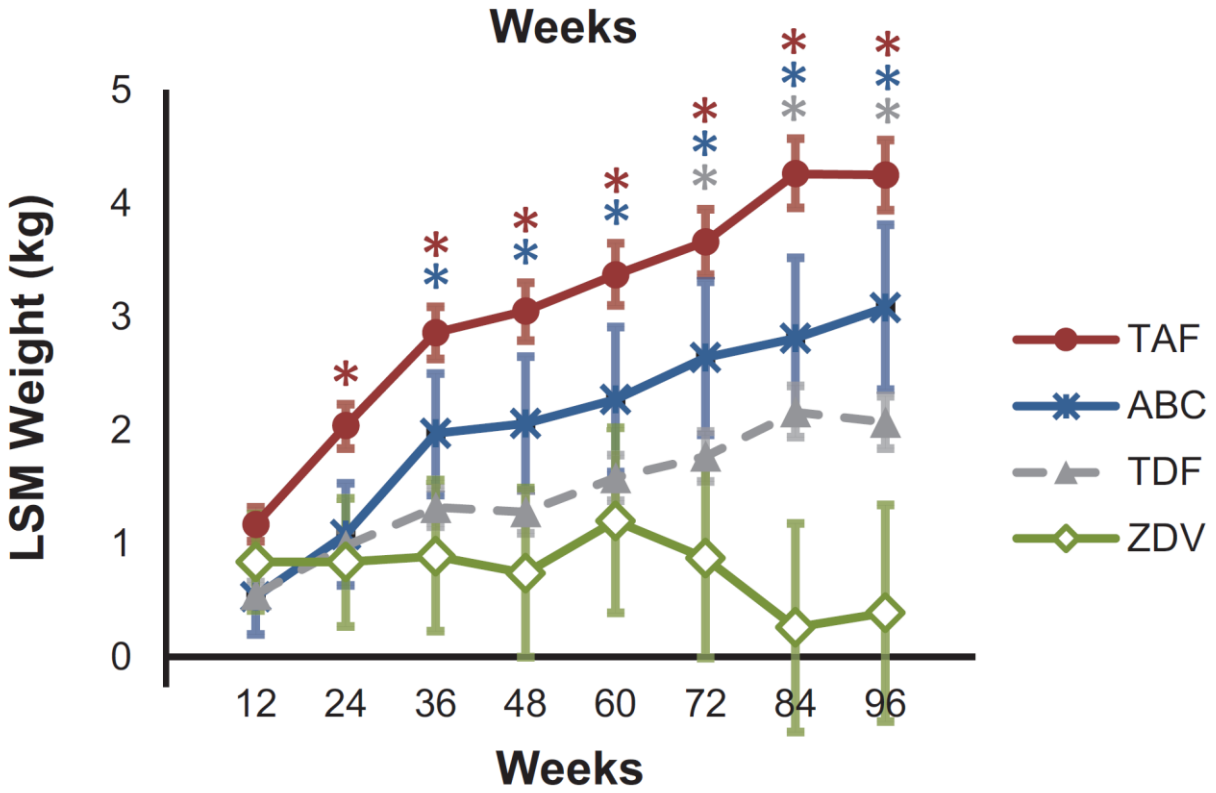


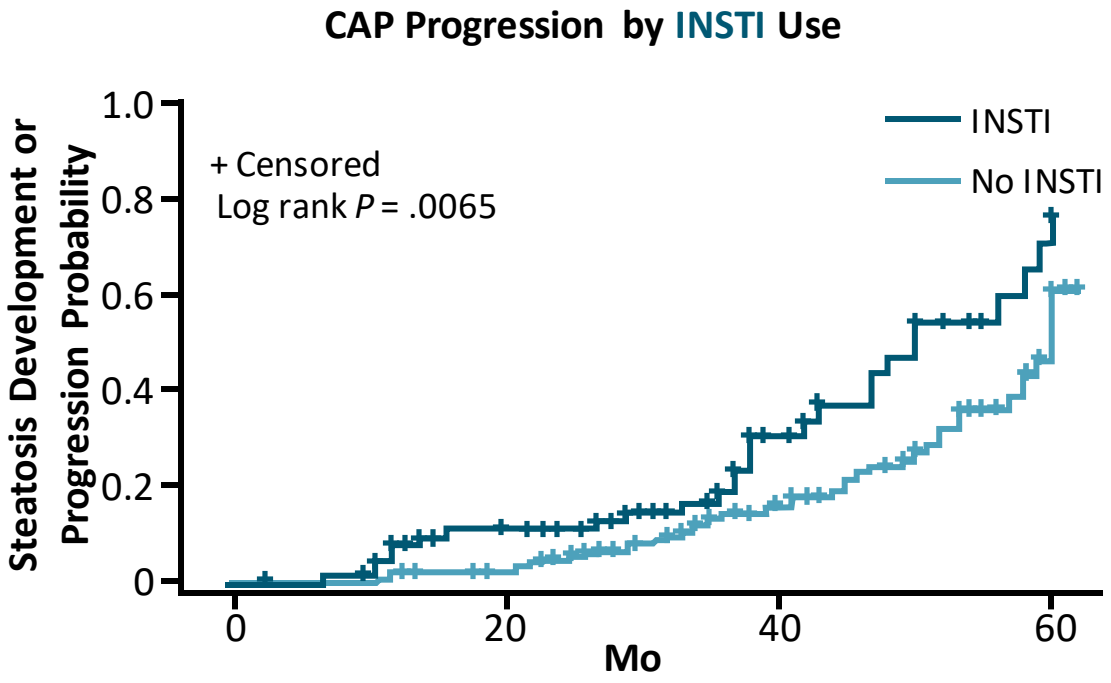
Table 5. Risk Factors for Significant (≥10%) Weight Gain in Individuals Initiating Antiretroviral Therapy

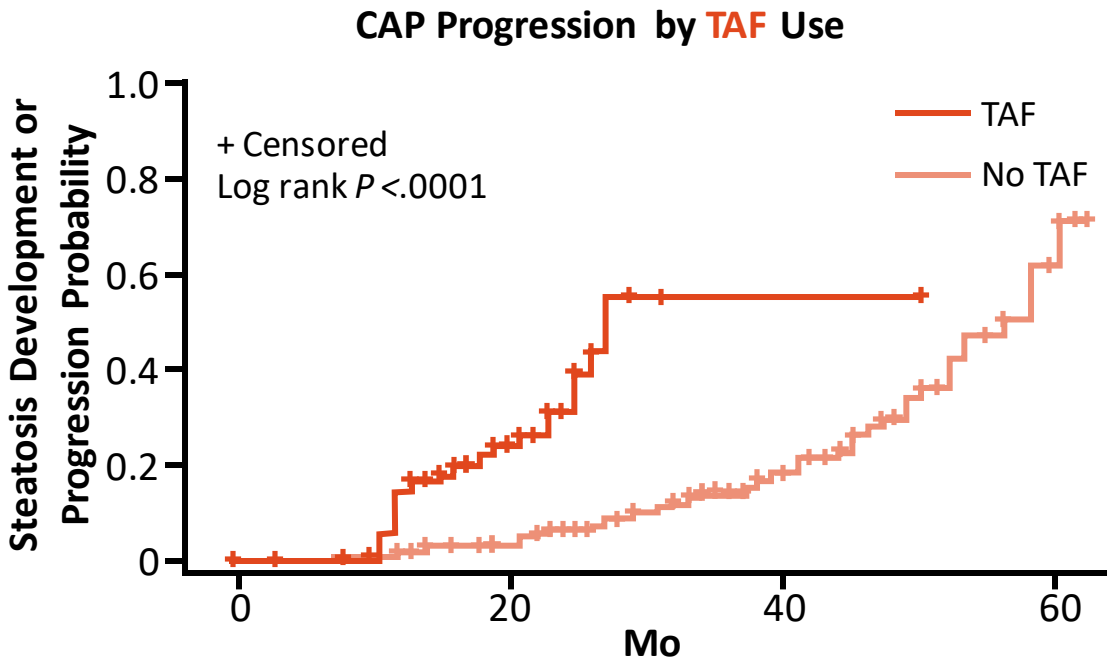
Third ART agent			
BIC/DTG vs EFV	1.82	(1.24–2.66)	.002
EVG/c vs EFV	1.36	(1.04–1.78)	.026
RPV vs EFV	1.51	(1.03–2.20)	.035
ATV/r vs EFV	0.92	(.59–1.45)	.73
NRTI			
TAF vs ZDV	1.75	(1.04–2.95)	.034
TDF vs ZDV	1.19	(.76–1.87)	.44
ABC vs ZDV	0.93	(.47–1.8)	.82
TAF vs ABC	1.9	(1.25–2.88)	.003
TDF vs ABC	1.29	(.79–2.11)	.31
TAF vs TDF	1.47	(1.14–1.90)	.003

Sax. Clin Infect Dis. 2020;71:1379.

Specific ART as Risk Factor for Steatosis Progression

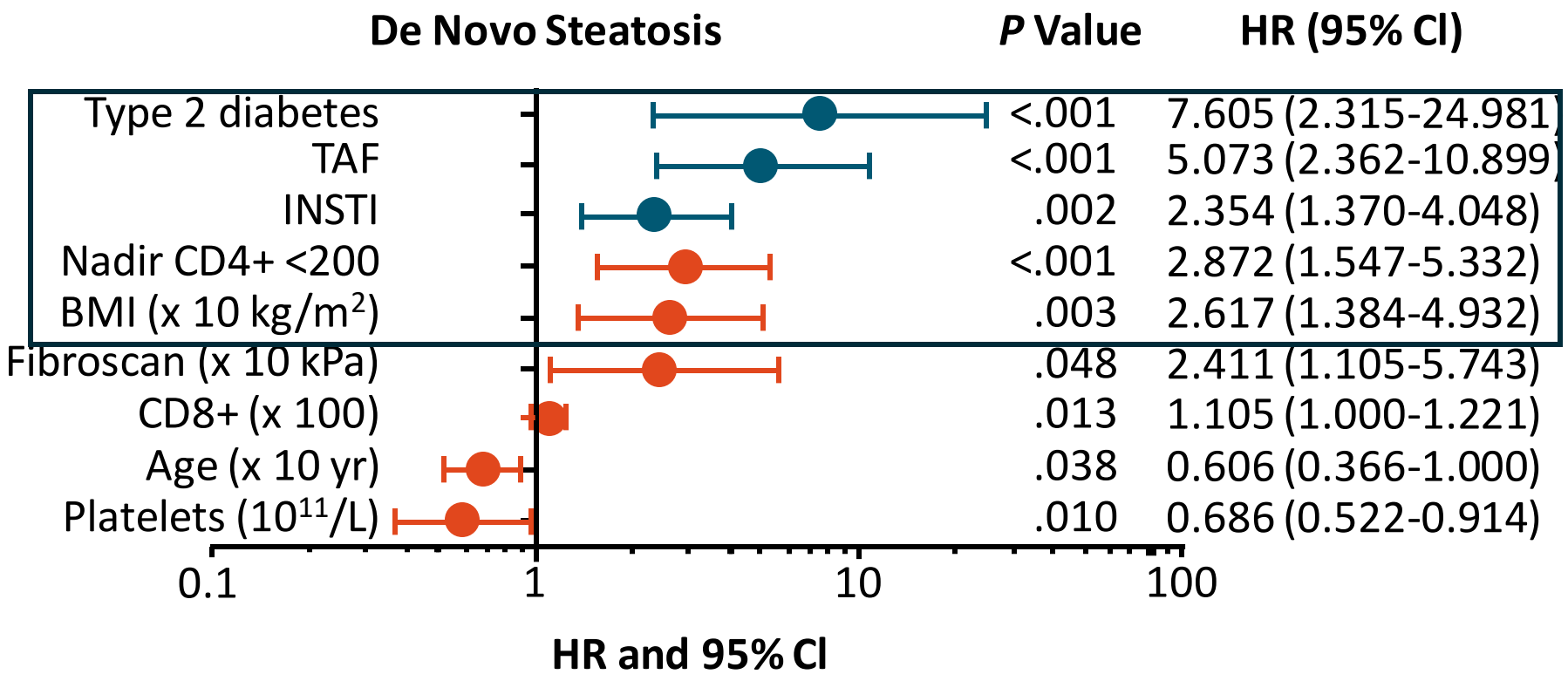
- Single-center, prospective, longitudinal, observational study of patients with HIV monoinfection (N = 301) by serial Fibroscan with CAP; mean follow-up 41.8 ± 14.8 mo
- Individuals who received INSTI- and TAF-based cART demonstrated a significantly faster steatosis development or progression





Bischoff. eClinicalMed. 2021;40:101116.

Risk Factor Determination for De Novo Steatosis

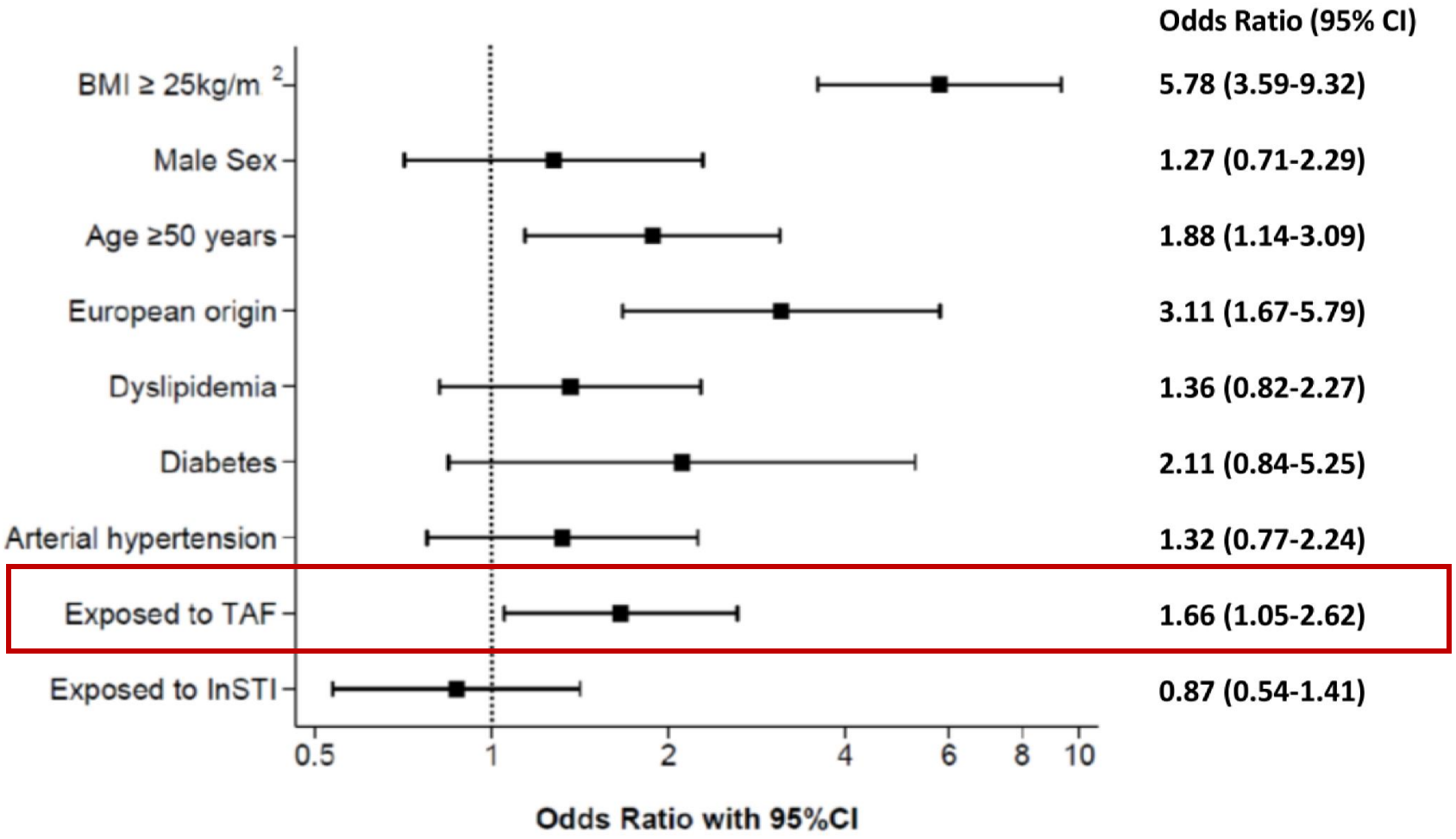


Bischoff. eClinicalMed. 2021;40:101116.

Factors associated with liver steatosis in PLWH

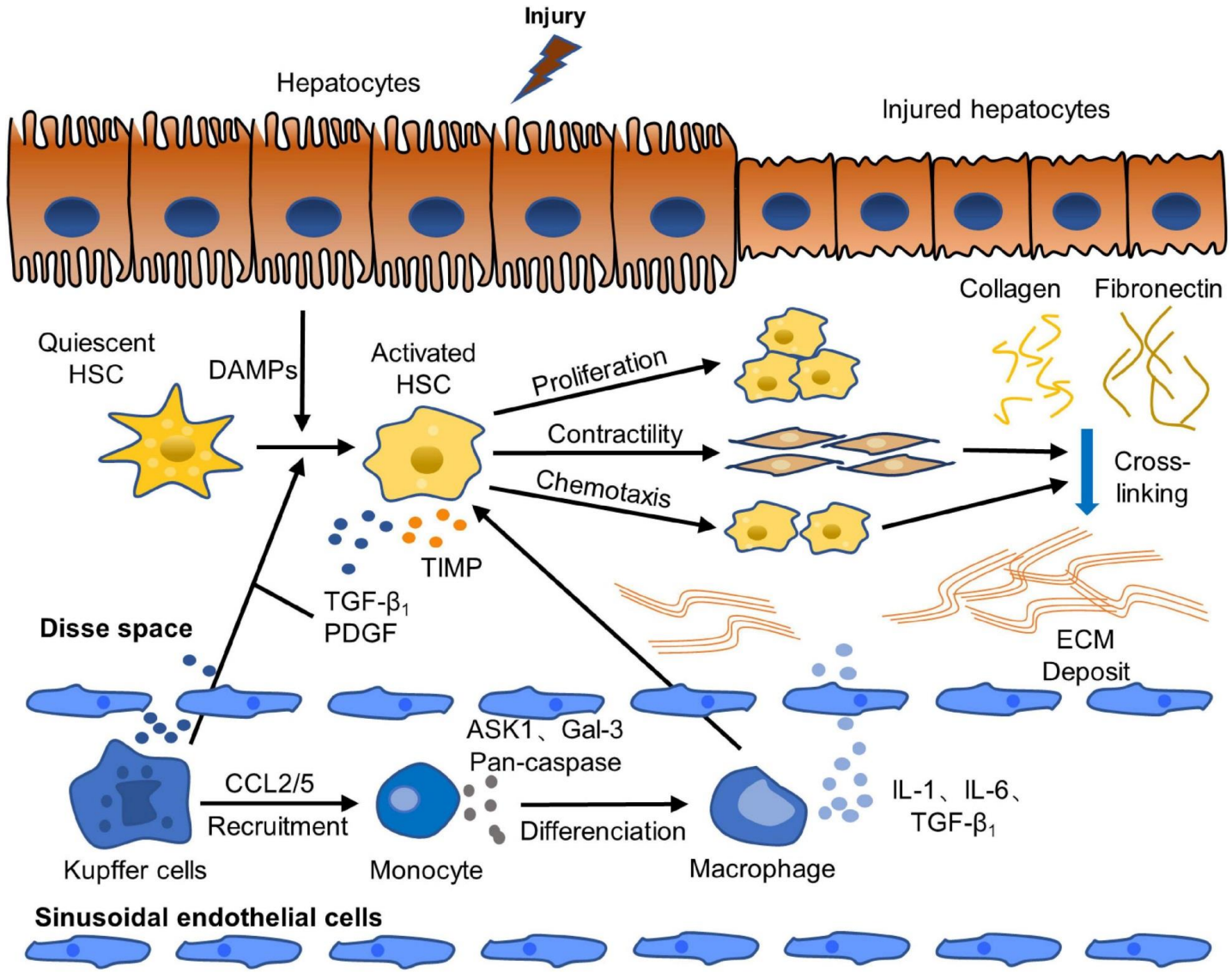
SWISS HIV COHORT STUDY

Figure 1. Multivariate analysis of factors associated with liver steatosis



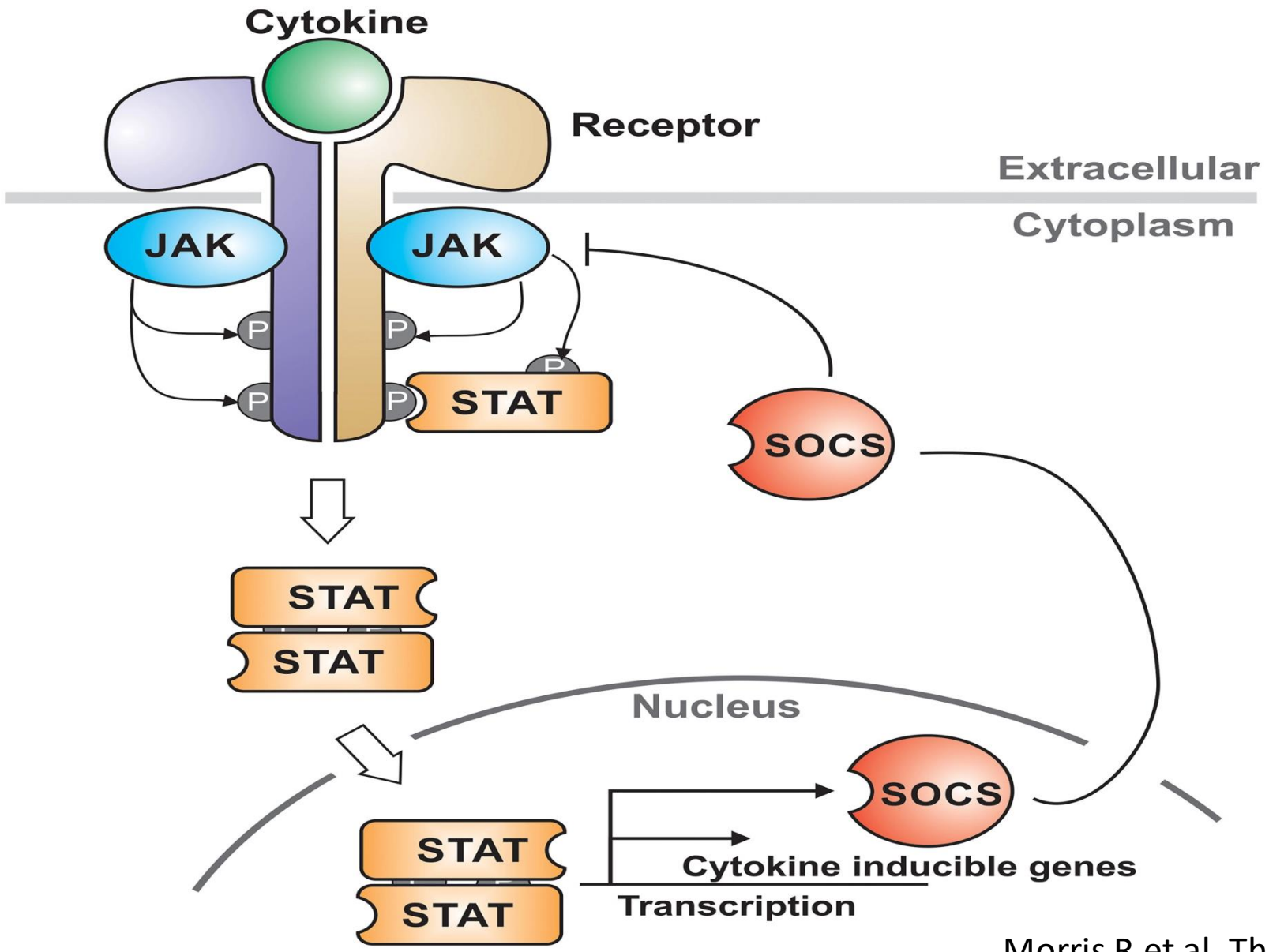
Riebensahn c et al, . vCROI 2022. Poster 1955

Pathogenesis of liver fibrosis. Activation of HSCs is a crucial step of the occurrence and progression of liver fibrosis



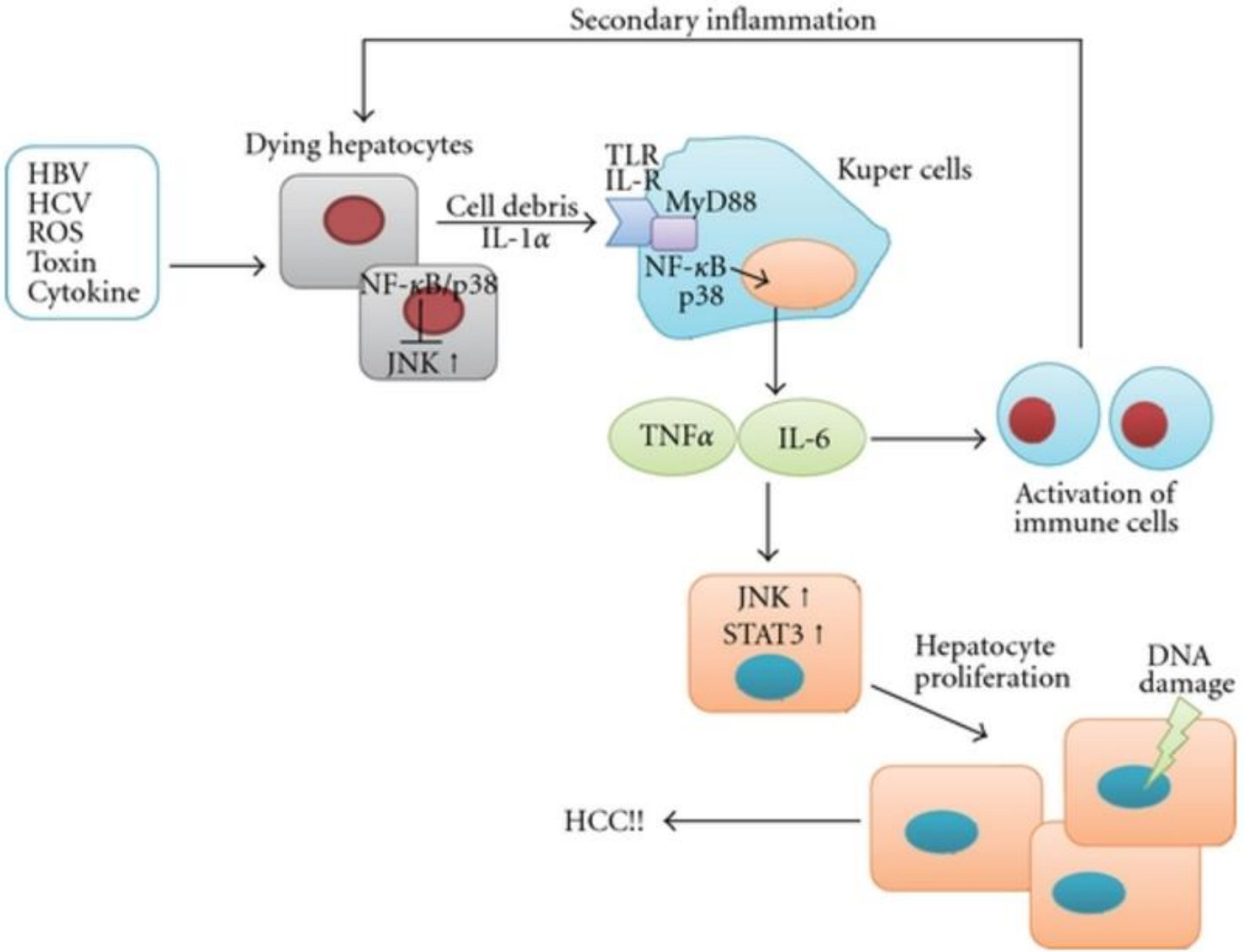
Tan Zui et al, Front. Cell Dev. Biol., 21 September 2021

The JAK/STAT pathway



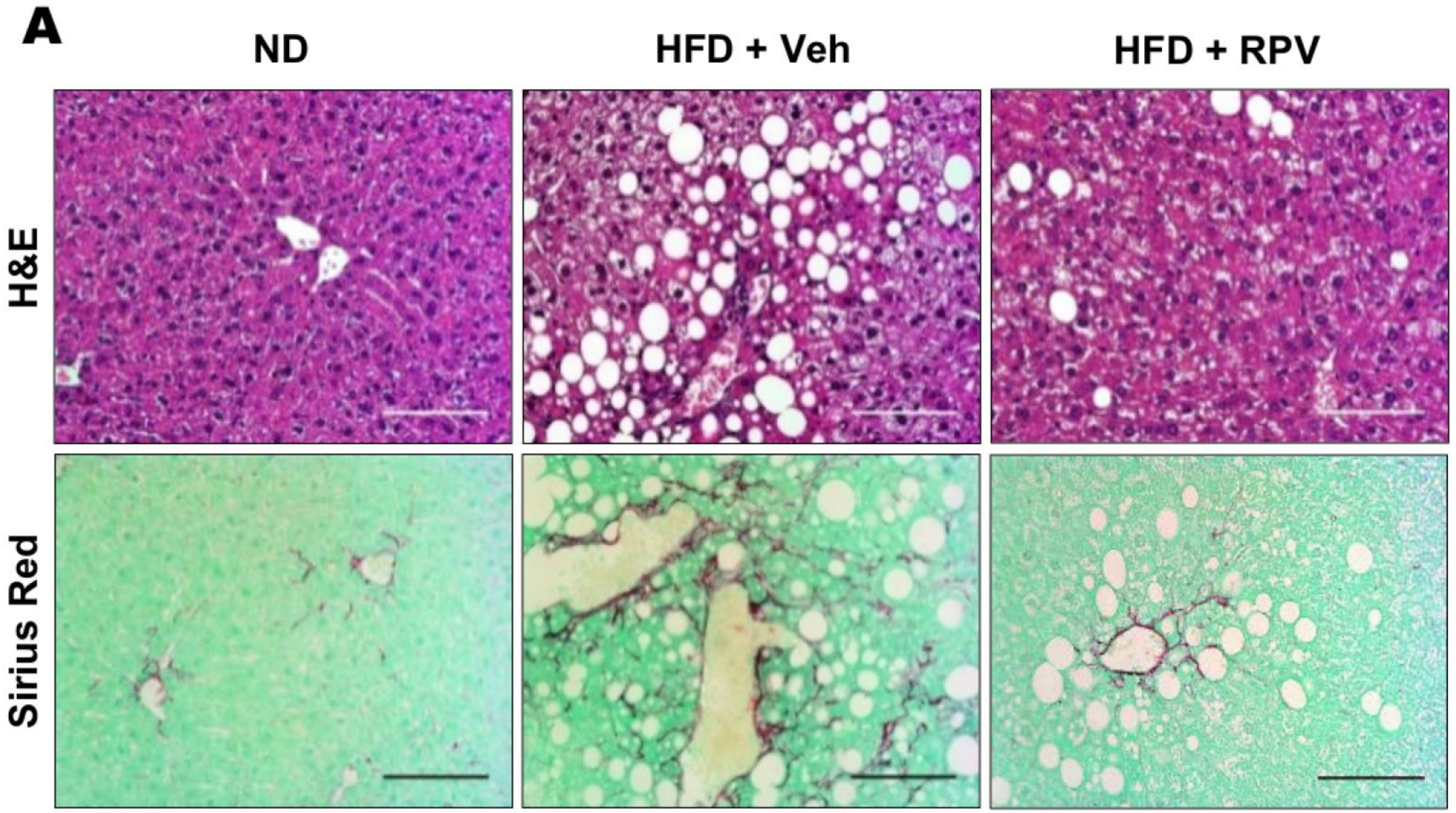
Morris R et al, The protein society , septembre 2019.

The JAK/STAT pathway



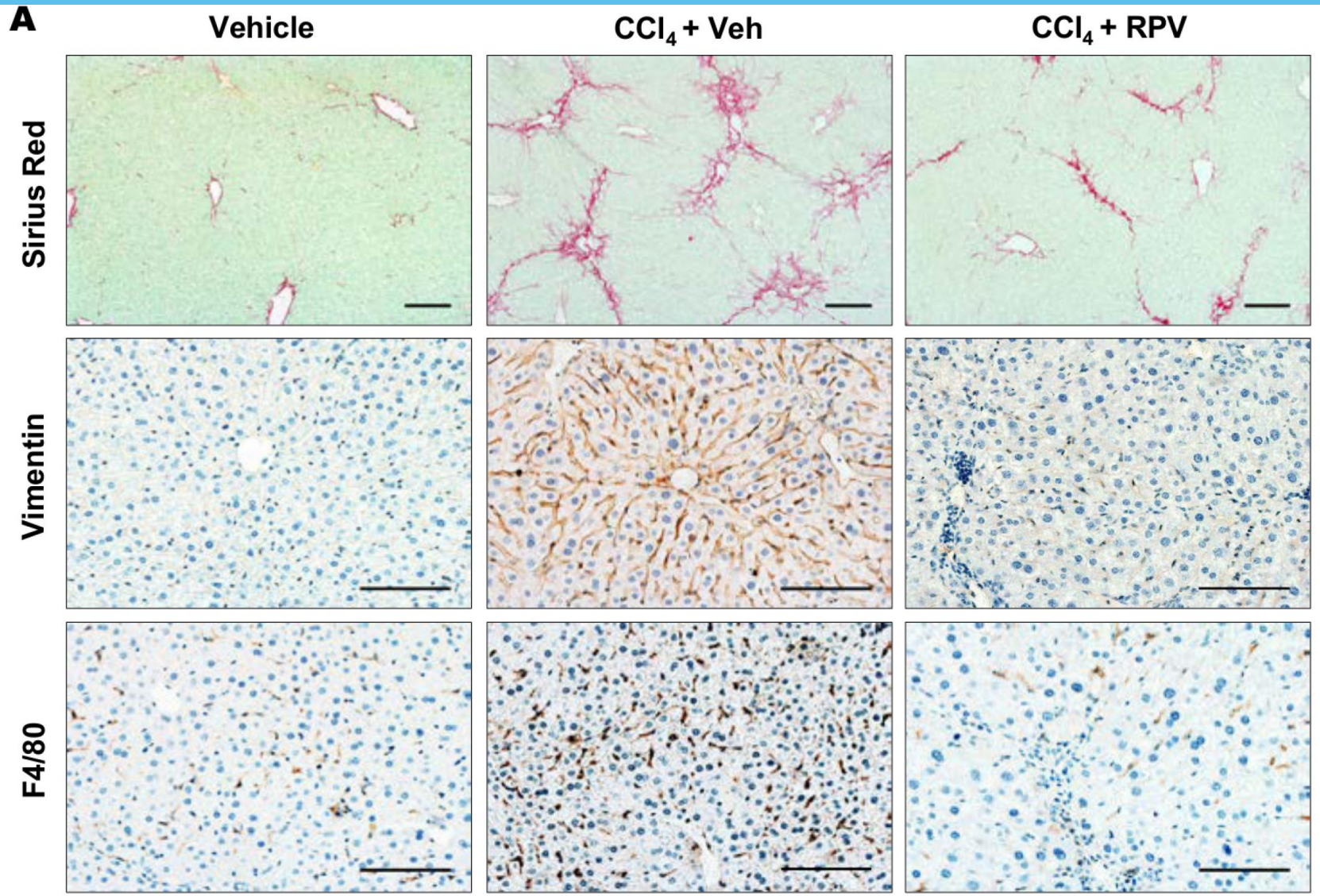
Nakagawa H et al Pathology Research International 2012(2):172894

RPV decreases lipid accumulation, collagen deposition and liver inflammation in a chronic model of non-alcoholic fatty liver disease.

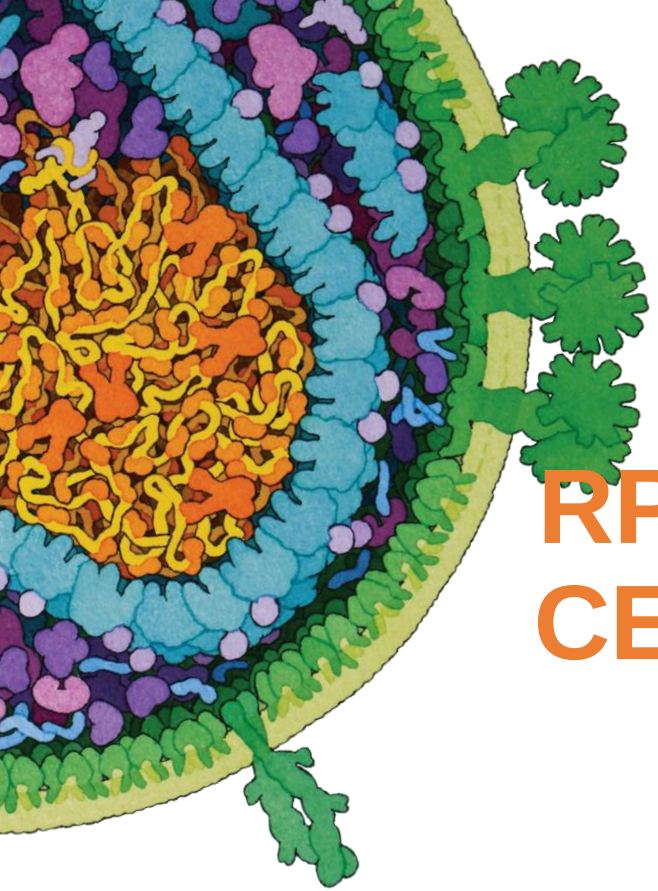


Marti-Rodrigo et al, Gut 2019

Rilpivirine (RPV) decreases liver inflammation and fibrosis progression in a chronic model of carbon tetrachloride (CCl4)-induced liver injury.



Marti-Rodrigo et al, Gut 2019



SCIENCE SPOTLIGHT™

RPV ACTIVATES STAT1 IN STELLATE CELLS TO REGULATE LIVER INJURY IN PLWHIV AND NAFLD

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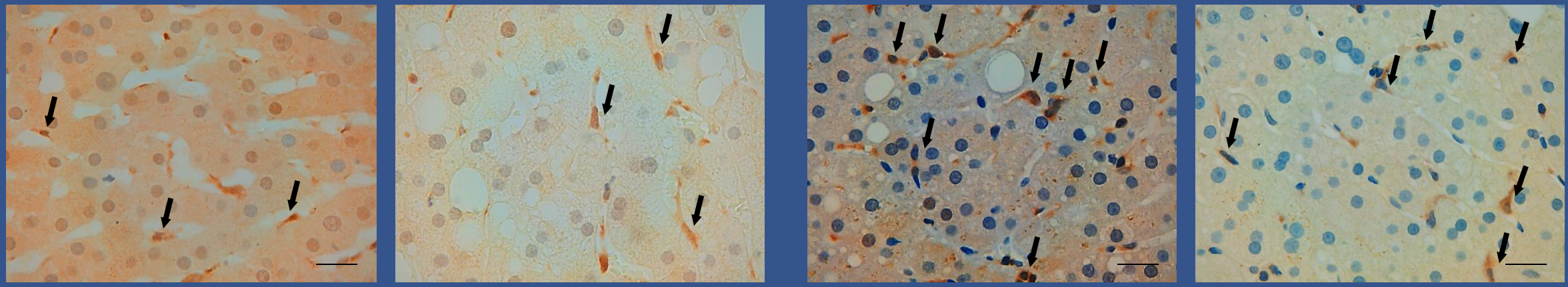
RESULTS

- Studied subjects were 100% male, median age 49 (44-54) years, median CD4 count 802 (608-940) cells/L, and 60% of them had metabolic syndrome.
- All subjects were receiving ART and had undetectable HIV viral load. 45% were receiving RPV-based therapy. There were no significant differences between those who received RPV and those who did not.
- Liver biopsies showed: 43% steatosis >30%, 60% steatohepatitis and 43% fibrosis F≥1.
- Detection of nuclear STAT1 expression in non-parenchymal cells revealed an enhanced activation of this transcription factor in hepatic sections of patients with identified liver injury receiving RPV-based therapy

RPV-FREE REGIMENS ***RPV-BASED REGIMENS***



Black arrows: positive HSC

Impact of the first line of ART in hepatic steatosis.

FIGURE 3: CHANGES IN % SUBJECTS **WTIHOUT** HEPATIC STEATOSIS

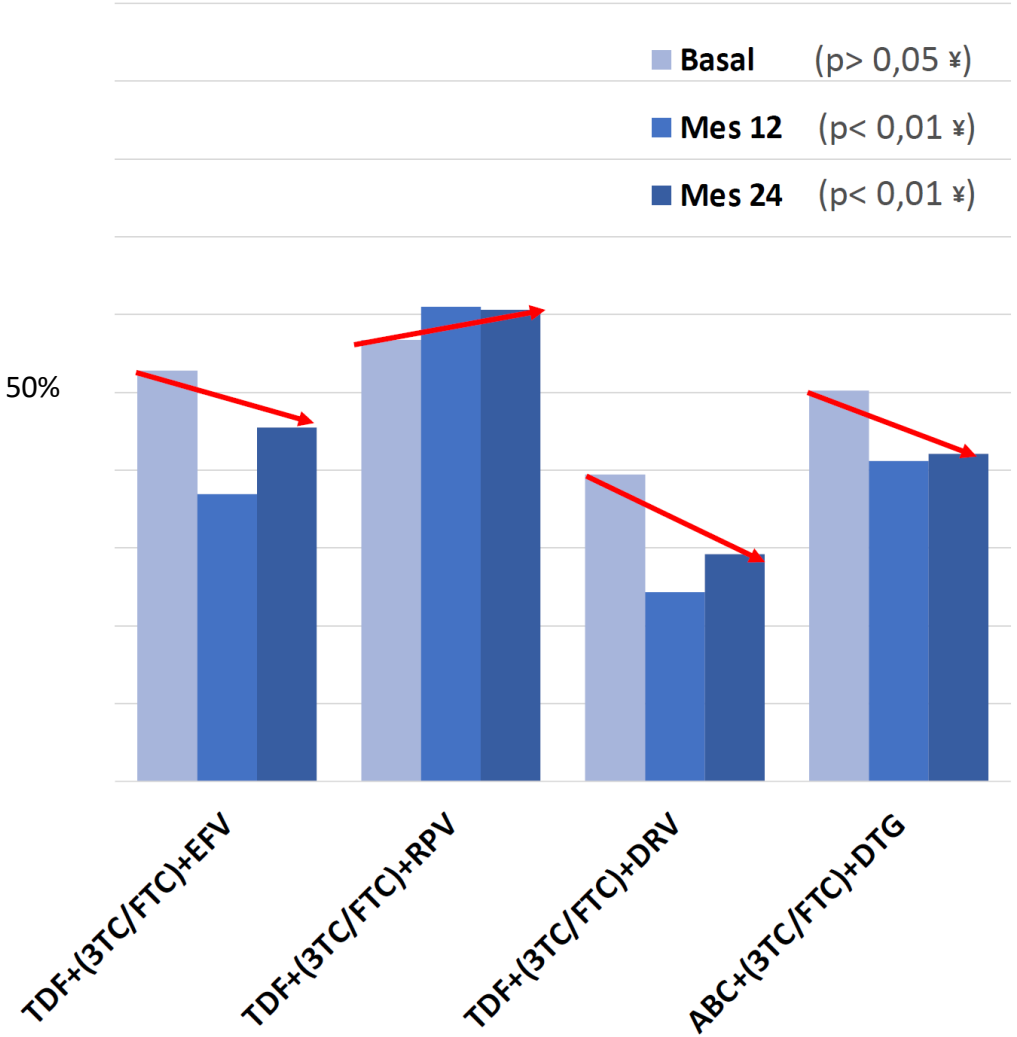


TABLE 3: ASSOCIATED FACTORS WITH HEPATIC STEATOSIS*

	HS at 12 months after ART iniciation				HS at 24 months after ART iniciation			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (IC 95%)	P	OR (IC 95%)	P	OR (IC 95%)	P	OR (IC 95%)	P
Age, (years)	1.1 (1-1.1)	<0.01	1 (1-1)	<0.01	1 (1-1.1)	<0.01	1 (1-1)	0.05
Women	0.4 (0.3-0.7)	<0.01	0.5 (0.2-1)	0.4	0.5 (0.3-0.9)	0.01	0.5 (0.2-1)	0.06
ART starting ≥ 2015	1 (0.8-1.3)	0.92	ns		1.4 (1.1-1.8)	0.01	ns	
C3 CDC Stage	1.6 (0.8-3.3)	0.18	ns		1.7 (0.9-3.1)	0.9	ns	
CD4 <200	1.6 (1-2.3)	0.03	ns		1.9 (1.3-2.7)	<0.01	ns	
Cardiovascular events at baseline	1.6 (0.9-3)	0.14	ns		1.3 (0.7-2.2)	0.39	ns	
DM2	1.5 (0.4-6.2)	0.55	ns		1.4 (0.5-4.3)	0.56	ns	
Baseline TyG index	9.7 (6.4-14.7)	<0.01	9 (5.8-13.9)	<0.01	10 (6.6-15.2)	<0.01	8.9 (5.8-13.7)	<0.01
EFV+TDF+(3TC/FTC)	1.5 (1.1-2)	0.01	1.5 (1-2.3)	0.08	1.1 (0.8-1.4)	0.73		
RPV+TDF+(3TC/FTC)	0.4 (0.3-0.5)	<0.01	0.5 (0.3-0.8)	<0.01	0.5 (0.3-0.7)	<0.01	0.6 (0.4-0.9)	0.01
DRV+TDF+(3TC/FTC)	2.6 (1.5-4.4)	<0.01	2.8 (1.2-6.4)	0.02	2.2 (1.3-3.8)	<0.01	2.8 (1.3-6)	<0.01
DTG+ABC+(3TC/FTC)	1.1 (0.8-1.5)	0.41			1.3 (1-1.8)	0.04	ns	

* Logistic regression analysis: a univariate analysis was performed for each of the independent variables. Those with a p value < 0.1 and/or with clinical relevance were included in the multivariate regression model.

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Take homes……..

- Lifestyle modification and weight reduction are the cornerstones of treatment for NAFLD.
- Avoid metabolically unfavorable treatments, TAF, INSTI? is possible??
- The effect of new ART (LA CAB + RPV) on NAFLD?
- Due to the lack of specific treatment for NALFD and the systematic exclusion of PLWIH from NAFLD-new molecules clinical trials, we believe our results are relevant to future studies.
- Appropriate studies should be designed to address these preliminary findings.