XVII CURSO EN AVANCES EN INFECCIÓN VIH Y HEPATITIS VIRALES

Diagnóstico, prevención y manejo terapéutico del NAFLD/MAFLD en las personas con infección VIH

Vigo, 12 de mayo de 2023

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SERVIZO GALEGO DE SAÚDE

ÁREA SANITARIA DA CORUÑA E CEE

CONFLICTO DE INTERESES

- En los últimos cinco años he recibido honorarios como ponente y/o recibido ayudas para la investigación de:
  - Abbvie
  - Gilead
  - Janssen
  - MSD
  - Viiv

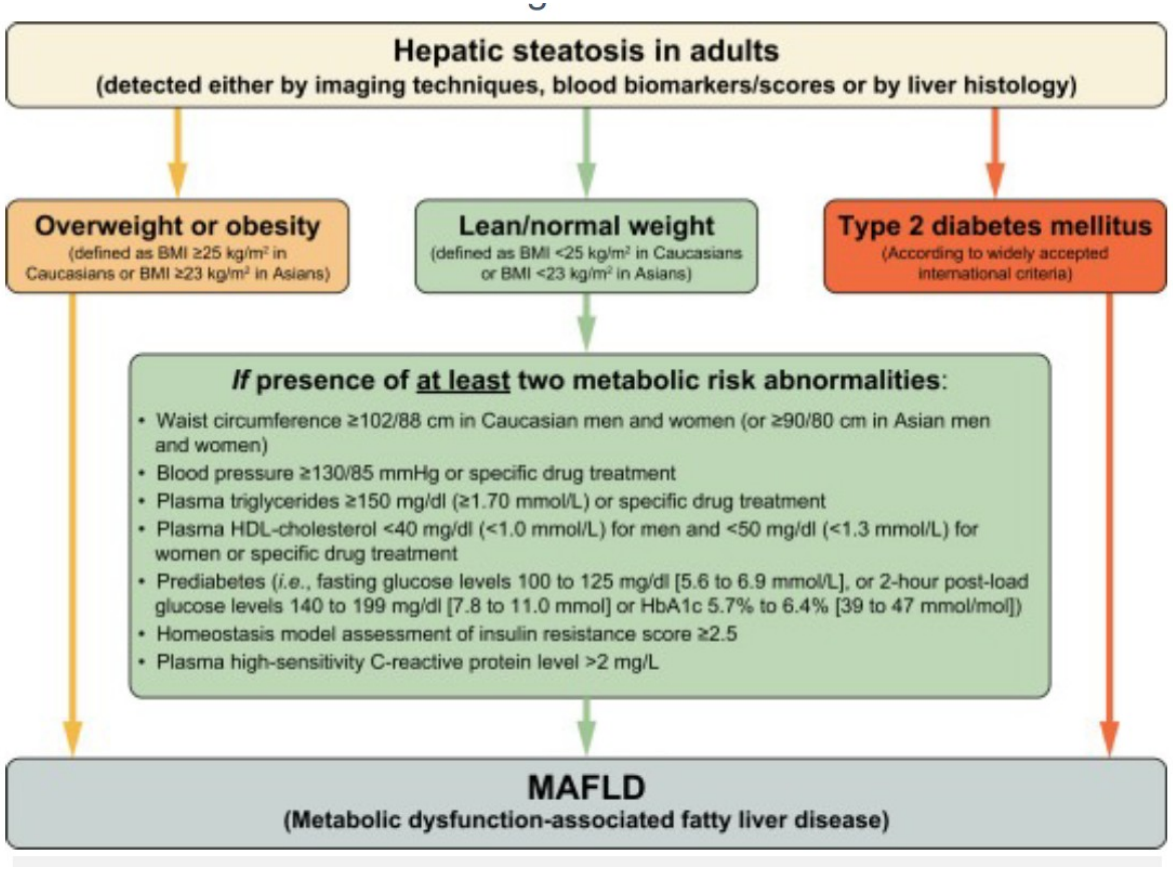
- No tengo ningún conflicto de intereses con esta exposición, recibo honorarios por la misma.

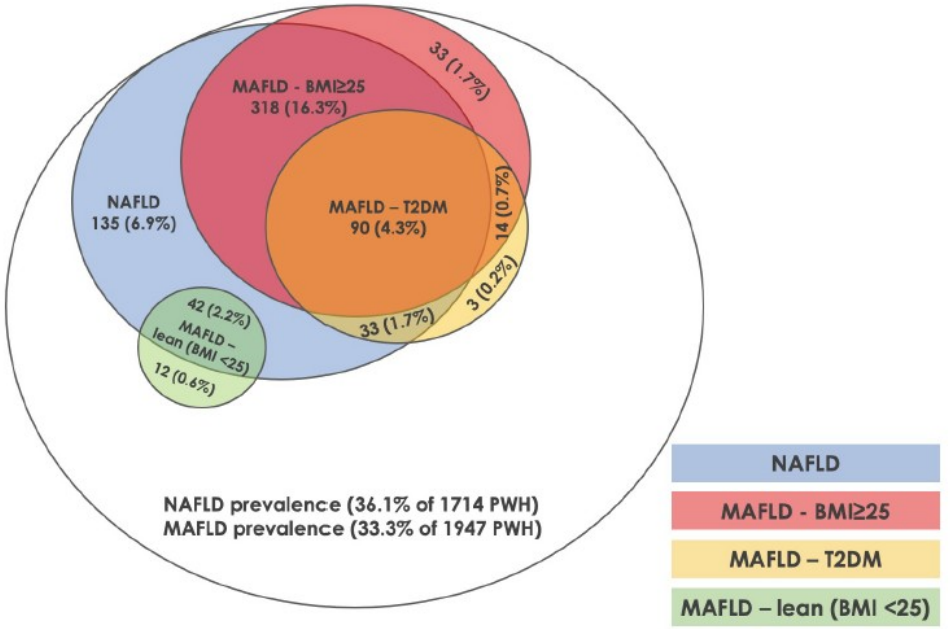
Índice

1. Magnitud del problema
2. Diagnóstico
3. Prevención
4. Manejo terapéutico

¿De qué estamos hablando?

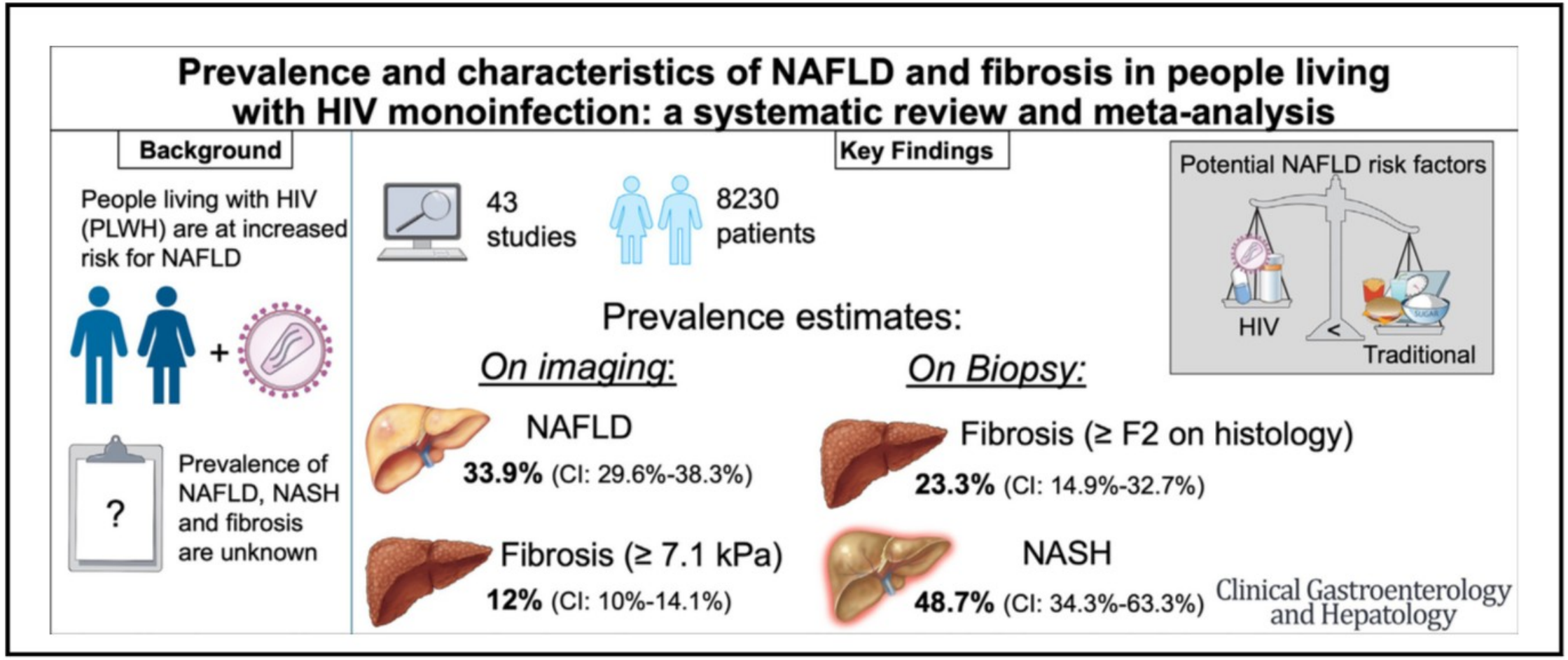
NAFLD/EHGNA | MAFLD | NASH | Syn Met | Syn Met





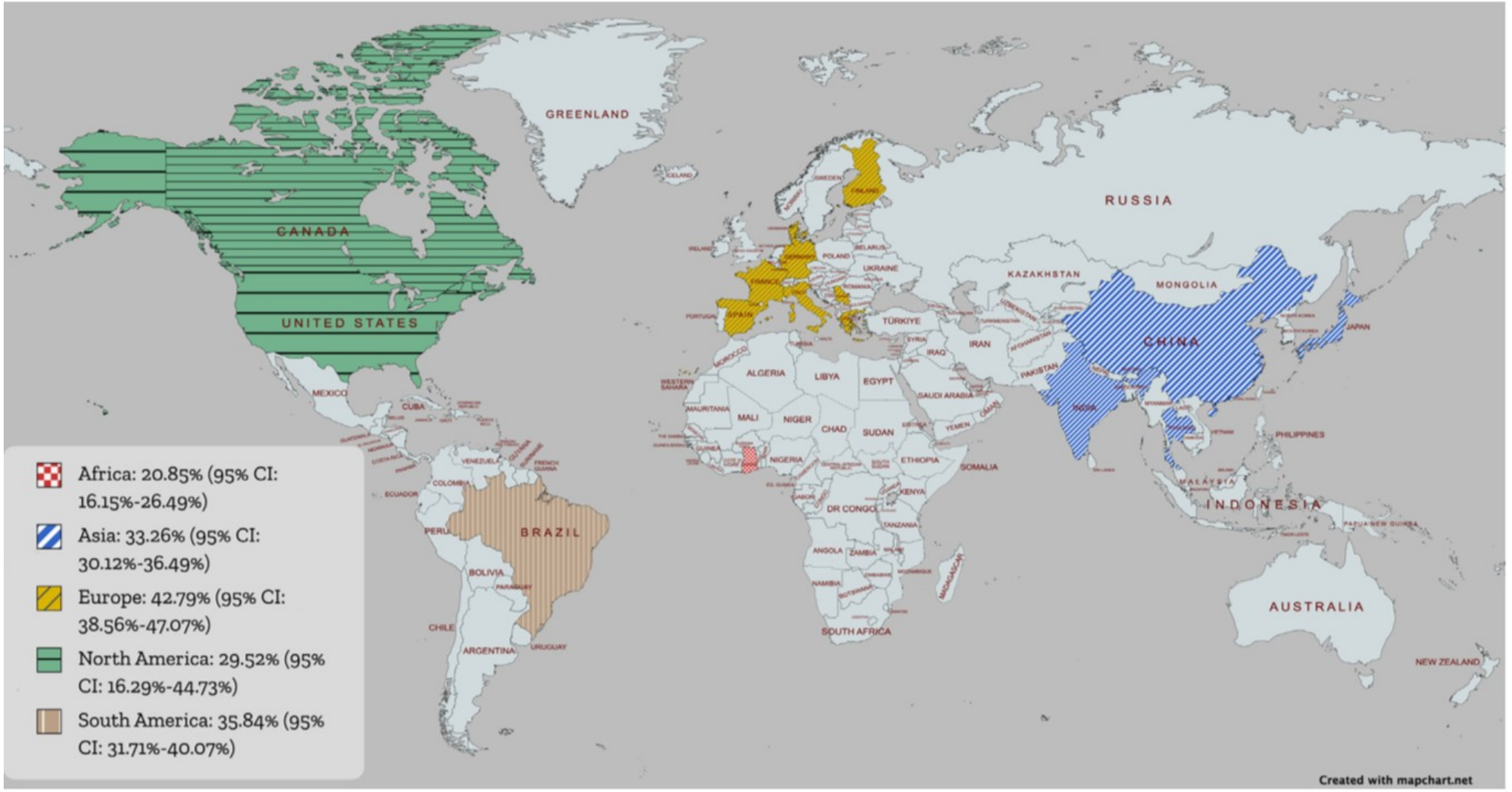
Guaraldi et al, CROI 2022

Magnitud del problema



Kalligeros M et al, 2023

Magnitud del problema



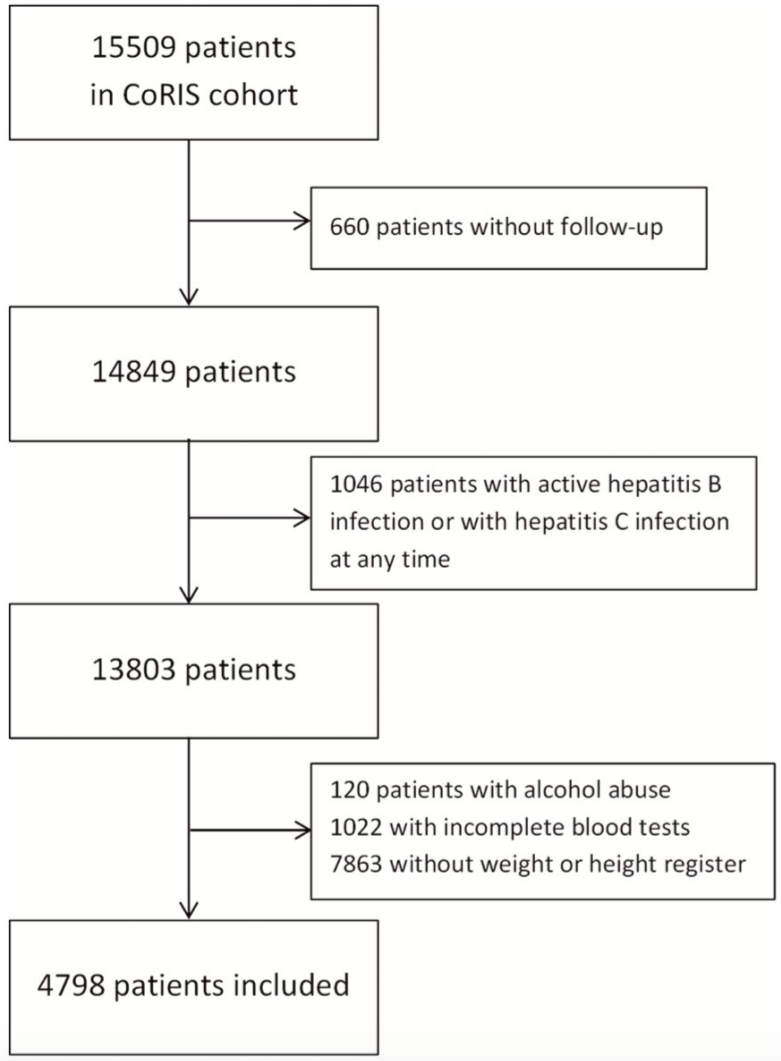
Kalligeros M et al, 2023

Magnitud del problema

Original article

Prevalence of non-alcoholic fatty liver disease in a multicentre cohort of people living with HIV in Spain.

Jordi Navarro [a,b,*], Adrian Curran [a,b,*], Berta Raventós [b,c], Jorge García [a,b], Paula Suanzes [a,b], Vicente Descalzo [a,b], Patricia Álvarez [a,b], Nuria Espinosa [d], Marisa Luisa Montes [e], Inés Suárez-García [f], Concha Amador [g], Roberto Muga [8], Vicenç Falcó [a,b], Joaquín Burgos [a,b], on behalf of the Spanish HIV Research Network (CoRIS)

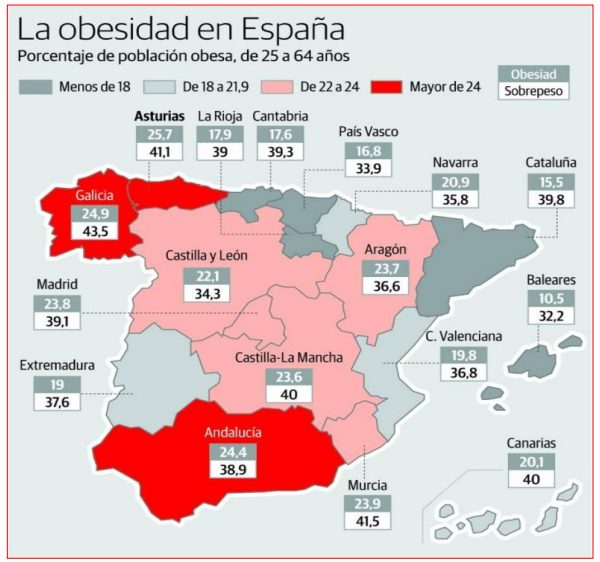


NAFLD (HSI >36) → 30,5%
Fibrosis significativa (NFS >0.675) → 1,1%

European Journal of Internal Medicine 110 (2023) 54–61

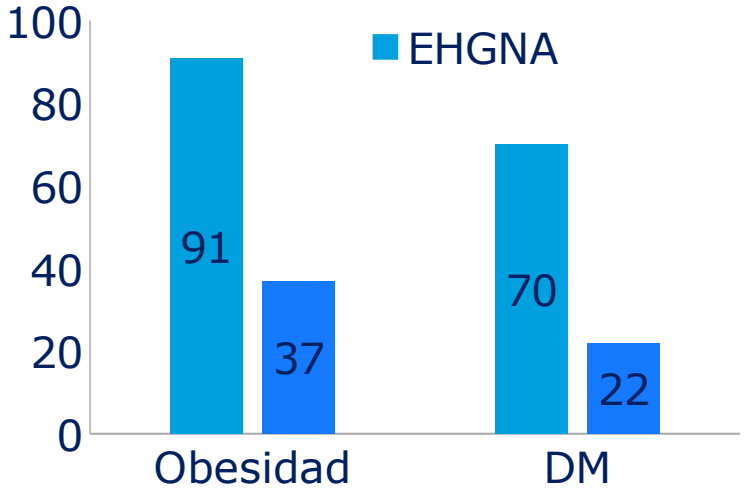
Prevalencia de EHGNA en pacientes con factores de riesgo. Situación Española

Prevalencia aumenta en paralelo al síndrome metabólico y sus componentes (obesidad, dislipemia y DM)

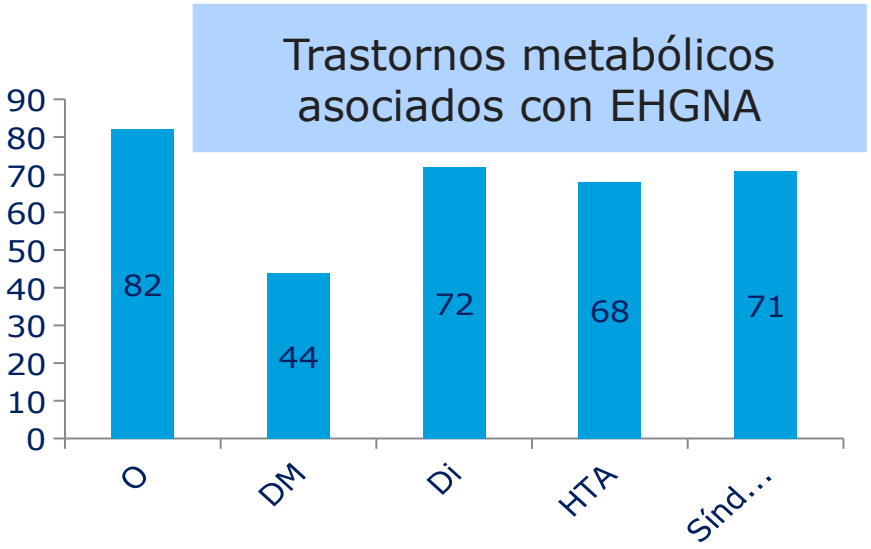


Andalucía y Galicia, Comunidades Autónomas con una mayor prevalencia de Obesidad

En España, obesidad aumento de 2-3 veces en últimas 3 décadas

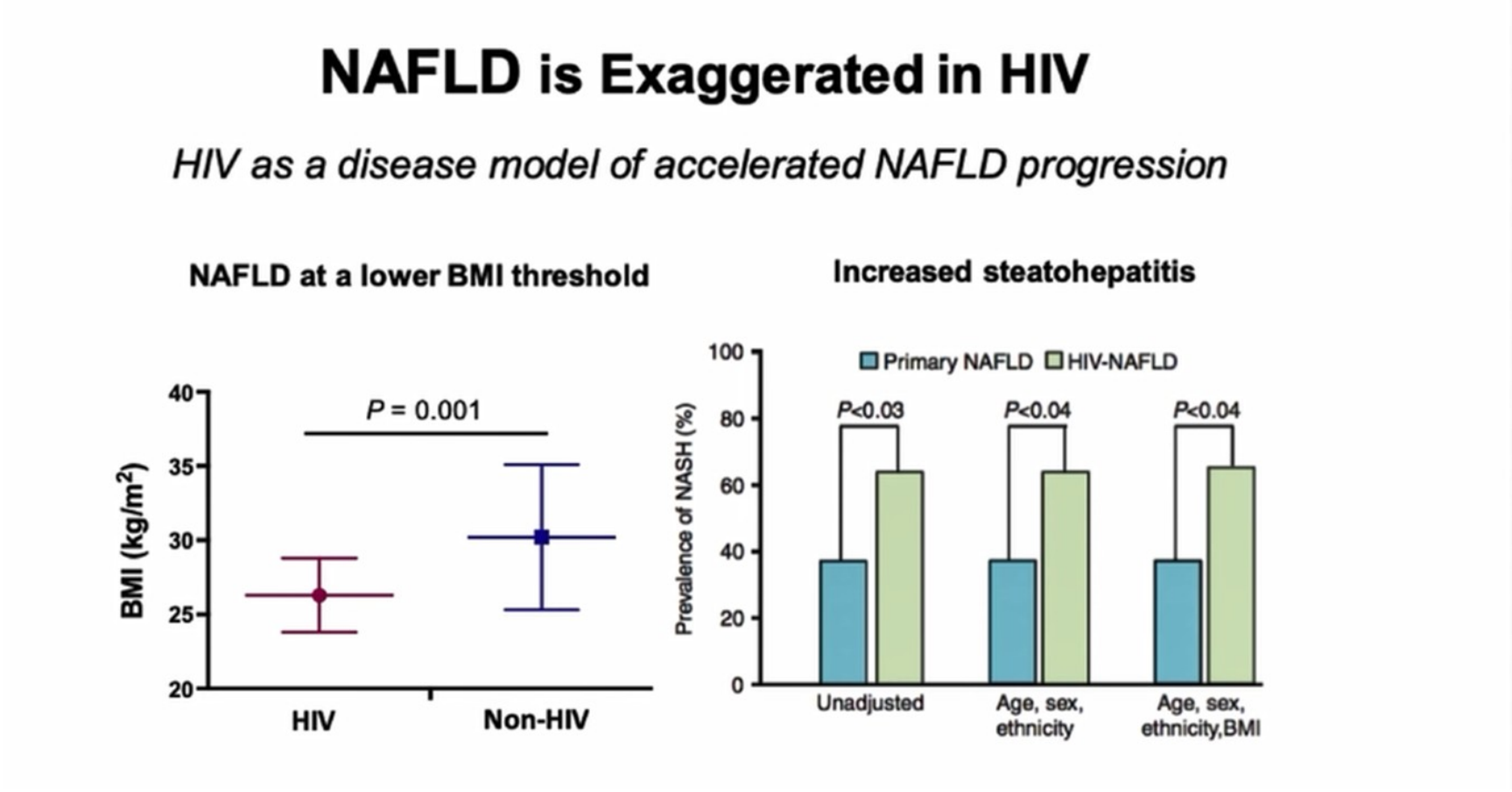


Machado M et al. J Hepatol 2006,45:600-6
Soriguer F et al. Diabetología 2012;55:88-93



Younossi ZM et al. Hepatology 2016;64:73-84

NAFLD en PLWH se presenta con un IMC menor

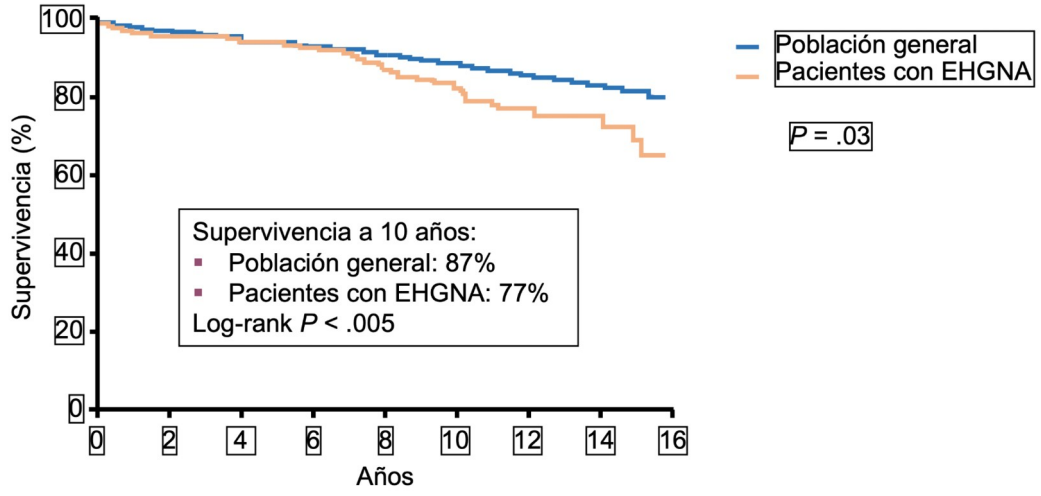


Vodkin, I., Valasek, M.A., Bettencourt, R., Cachay, E. and Loomba, R. (2015), Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case–control study. Aliment Pharmacol Ther, 41: 368-378. https://doi.org/10.1111/apt.13052

Mortalidad EHGA

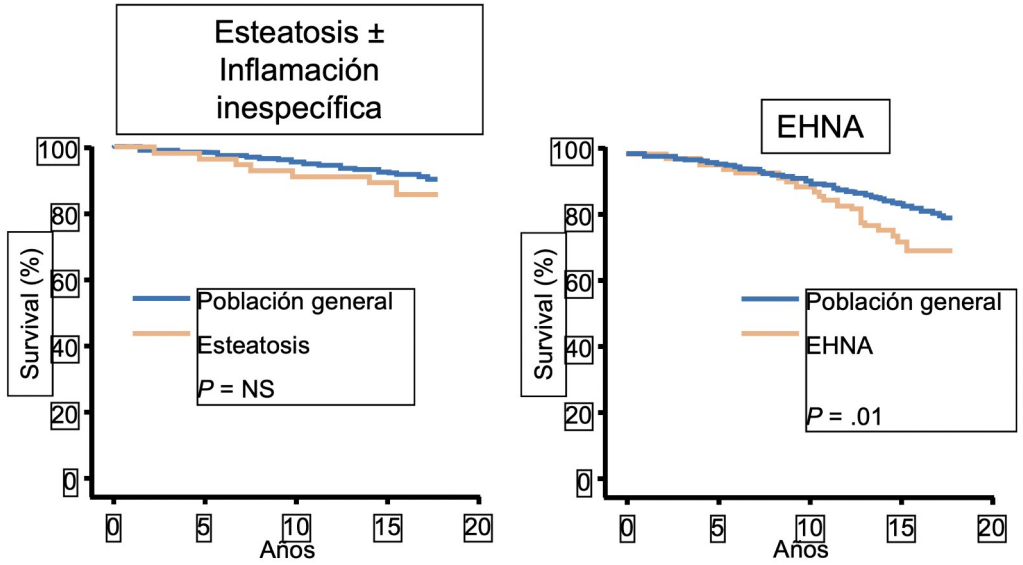
420 pacientes con EHGNA ajustados por edad y sexo

Seguimiento durante 7,6 ± 4 años



129 pacientes suecos con EHGNA ajustados por edad y sexo

Seguimiento durante 13,7 años



Menor supervivencia en pacientes con EHGNA que en población general

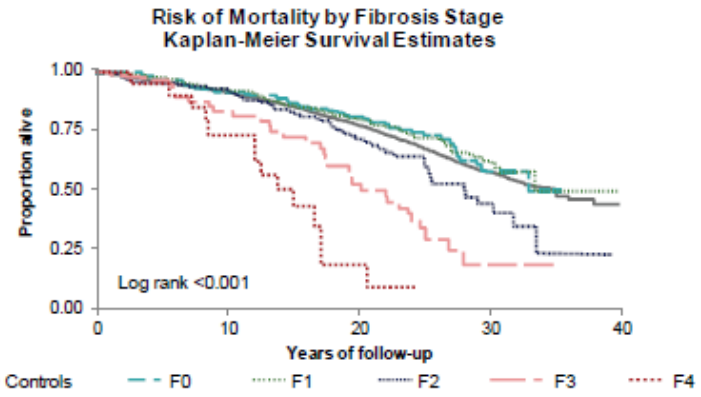
Ekstedt M, et al. Hepatology. 2006;44:865-873.
Adams LA, et al. Gastroenterology. 2005;129:113-121.

Mortalidad EHGA

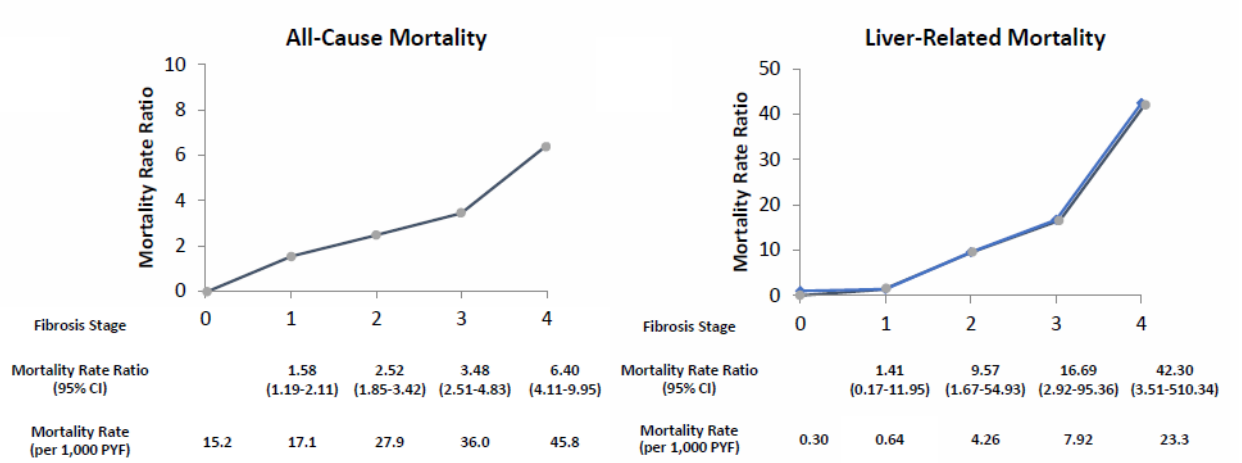
La fibrosis es el único predictor independiente de mortalidad

Fibrosis Stage	Liver-Related Events	Hazard Ratio (95% CI)
0	1.6%	1.0 (reference)
1	2.8%	2.3 (0.6-8.7)
2	7.1%	6.7 (2.0-22.0)
3	13.7%	13.4 (4.2-42.6)
4	23.5%	52.9 (13.3-210)

Retrospective cohort study of 646 biopsy-proven NAFLD patients



Risk of mortality increased per stage of fibrosis, with significant increases for F3 and F4; NASH did not significantly change these estimates

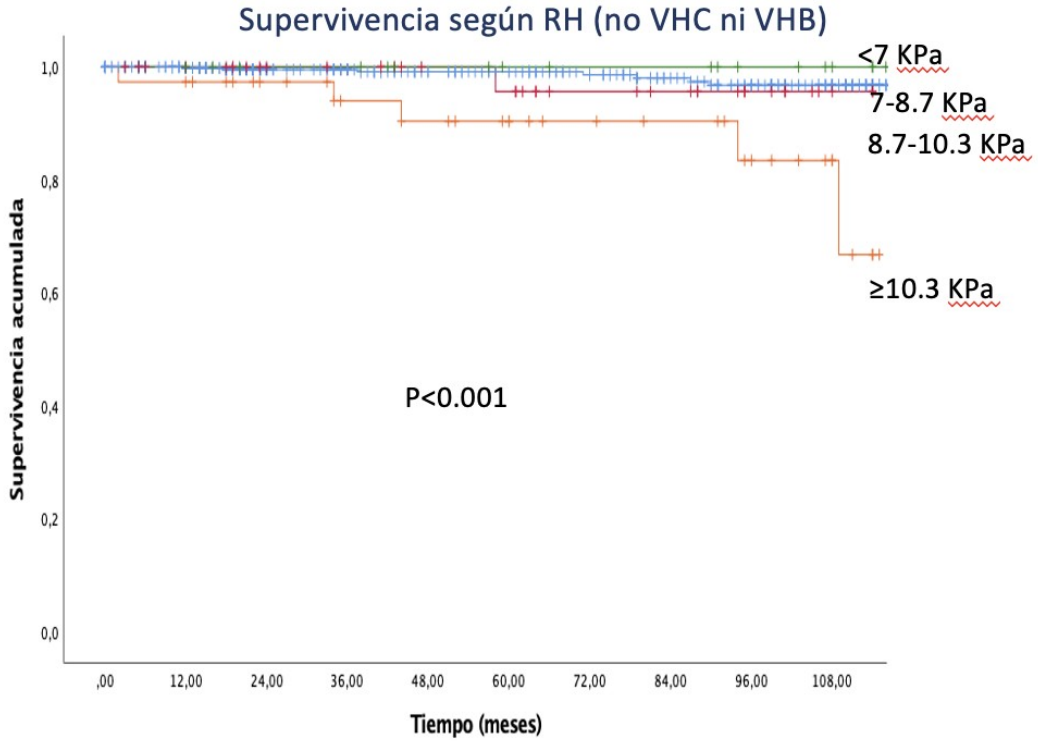


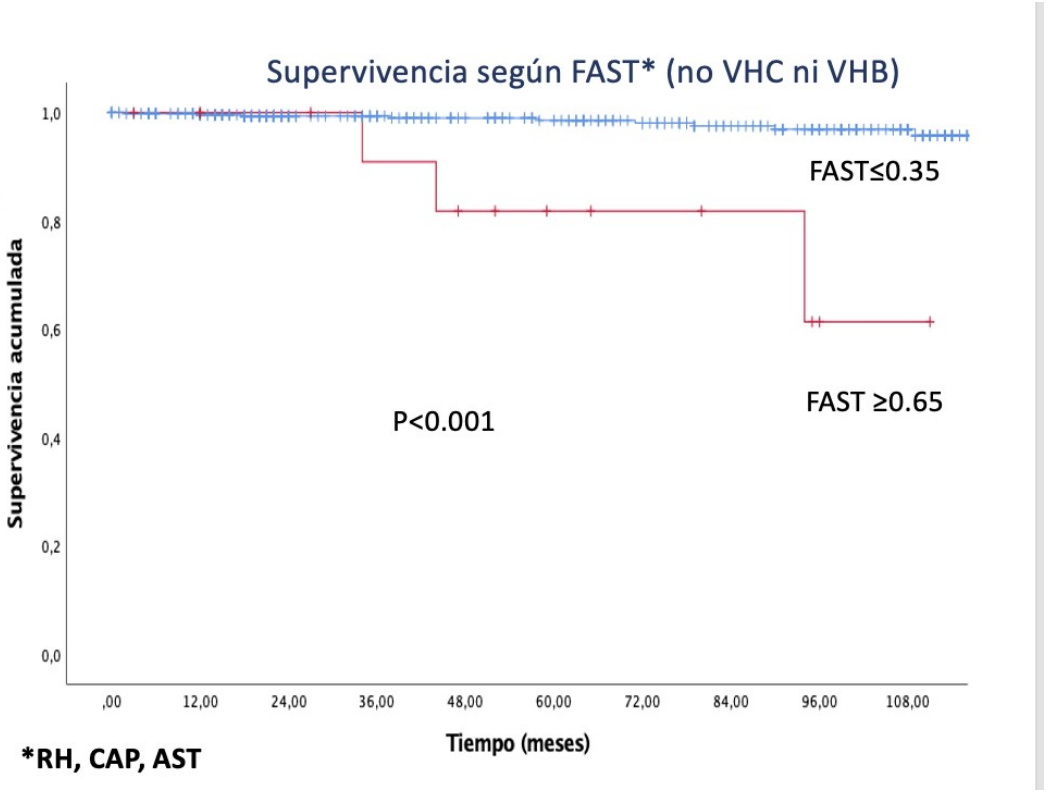
El riesgo de mortalidad hepática aumenta exponencialmente con cada estadio de fibrosis

Angulo P et al. Gastroenterology 2015;149:389-97
Hagström H. J Hepatol 2017;67(6):1265-1273
Dulai P et al. Hepatology 2017; 65(5):1557-1565

Mortalidad EHGA en PVVIH. Rigidez y FAST

- Estudio multicéntrico prospectivo de cohortes. España.
- N=1570 PVV con NAFLD probada por CAP; 614 no VHC ni VHB
- Seguimiento: 63 (22-100) meses





Macías, J et al. Impact of NASH on the survival of people living with HIV.

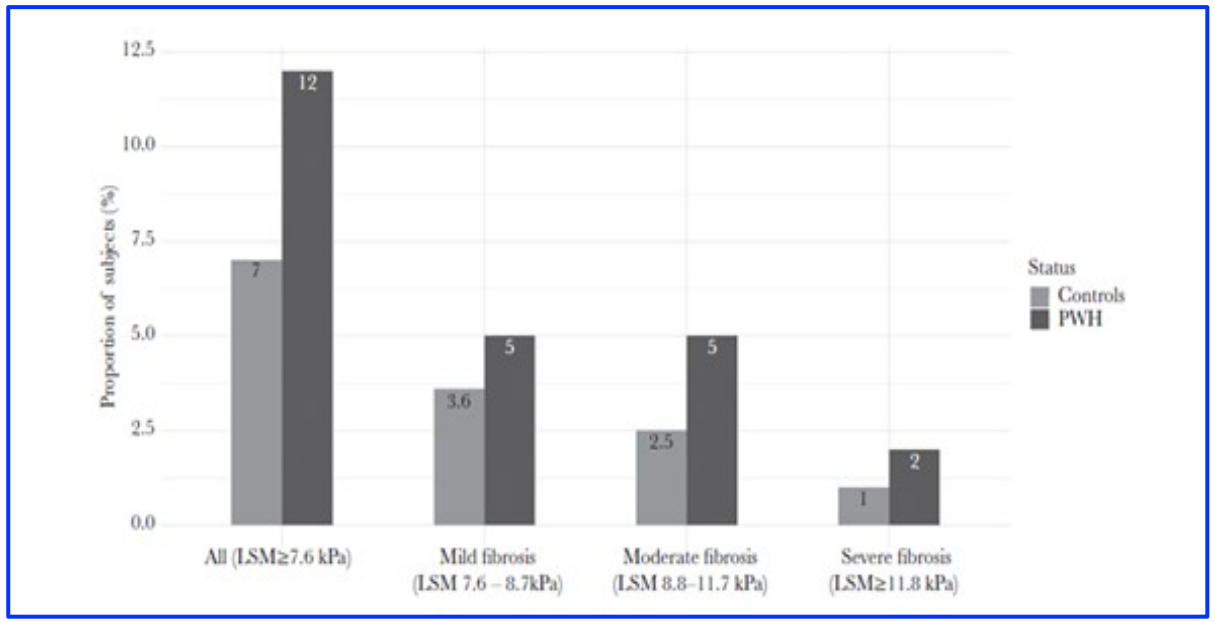
Progresión de la fibrosis en PVVIH

The Journal of Infectious Diseases

MAJOR ARTICLE

Increased Prevalence of Liver Fibrosis in People Living With Human Immunodeficiency Virus Without Viral Hepatitis Compared to Population Controls

Ditte Marie Kirkegaard-Klitbo,[1] Flemming Bendtsen,[2,3] Jens Lundgren,[3,4,©] Robert J. de Knegt,[5] Klaus Fuglsang Kofoed,[6,7] Susanne Dam Nielsen,[3,8] and Thomas Benfield[1,3]; for the Copenhagen Co-Morbidity in HIV Infection (COCOMO) Study Group



Mayor prevalencia y progresión de fibrosis en VIH

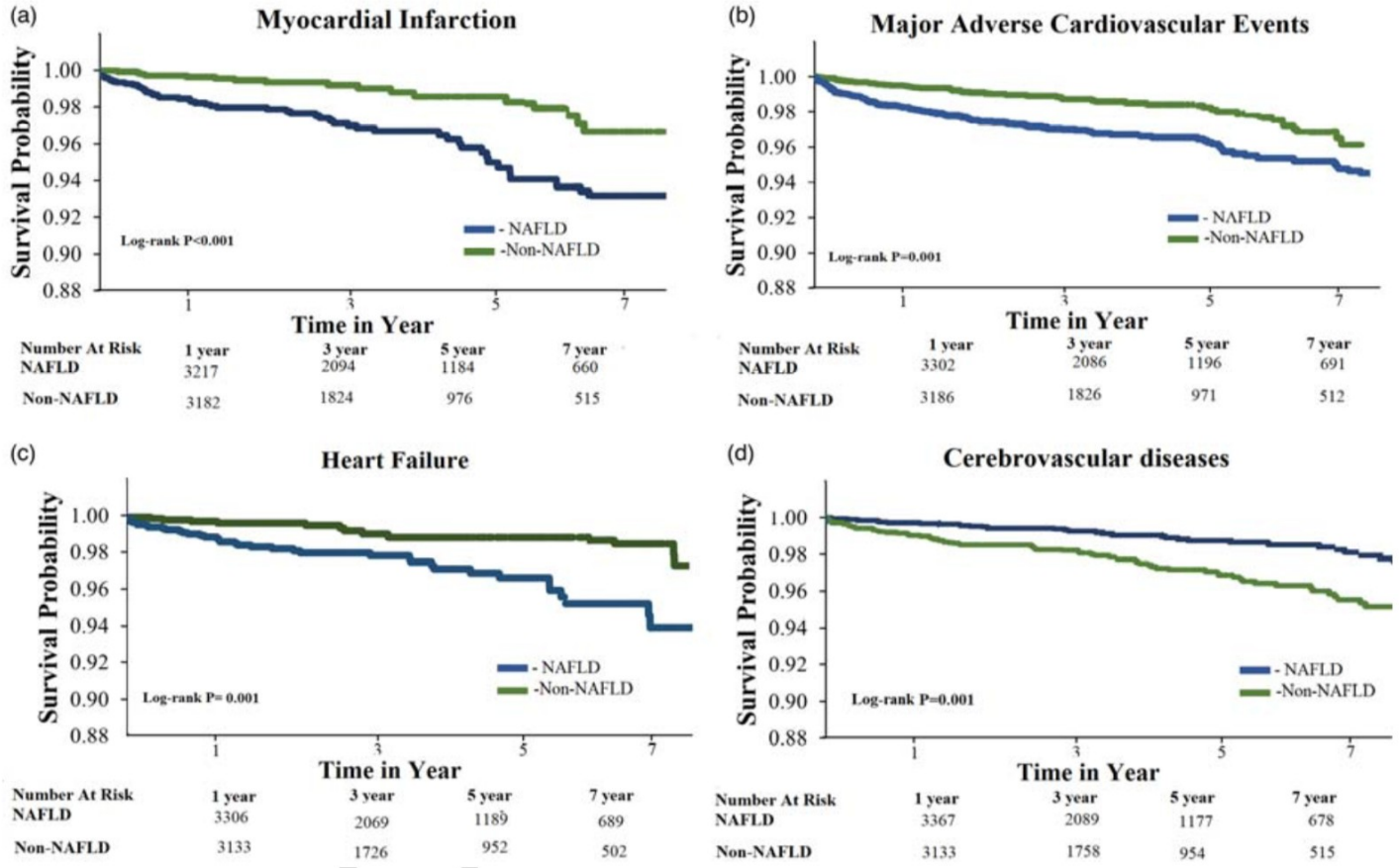
Kirkegaard-Klitbo, Ditte Marie et al. The Journal of infectious diseases 224,3 (2021): 443-452

Mortalidad EHGA

AIDS, Publish Ahead of Print

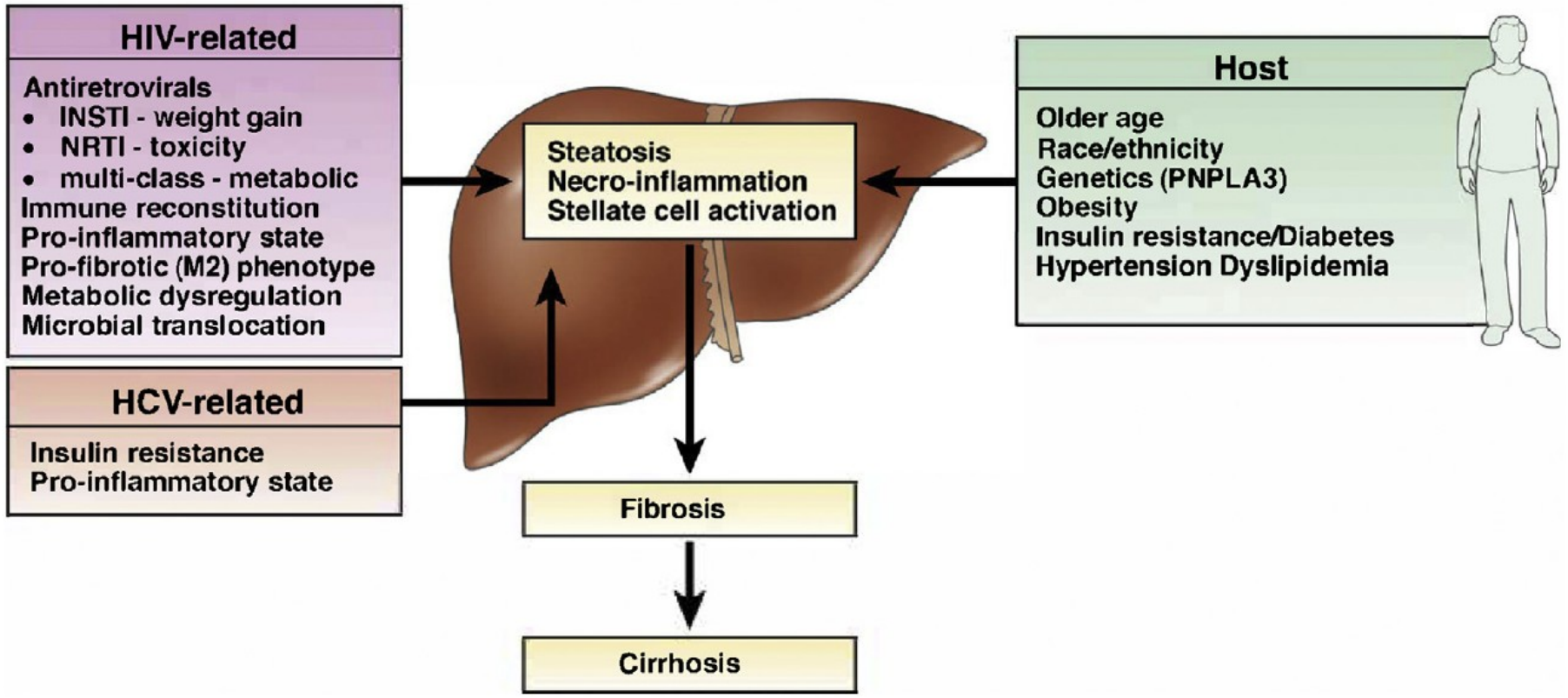
DOI: 10.1097/QAD.0000000000003537

Risk of Adverse Cardiovascular Outcomes Among Persons living with HIV and Nonalcoholic Fatty Liver Disease: A Multicenter Matched Cohort Study



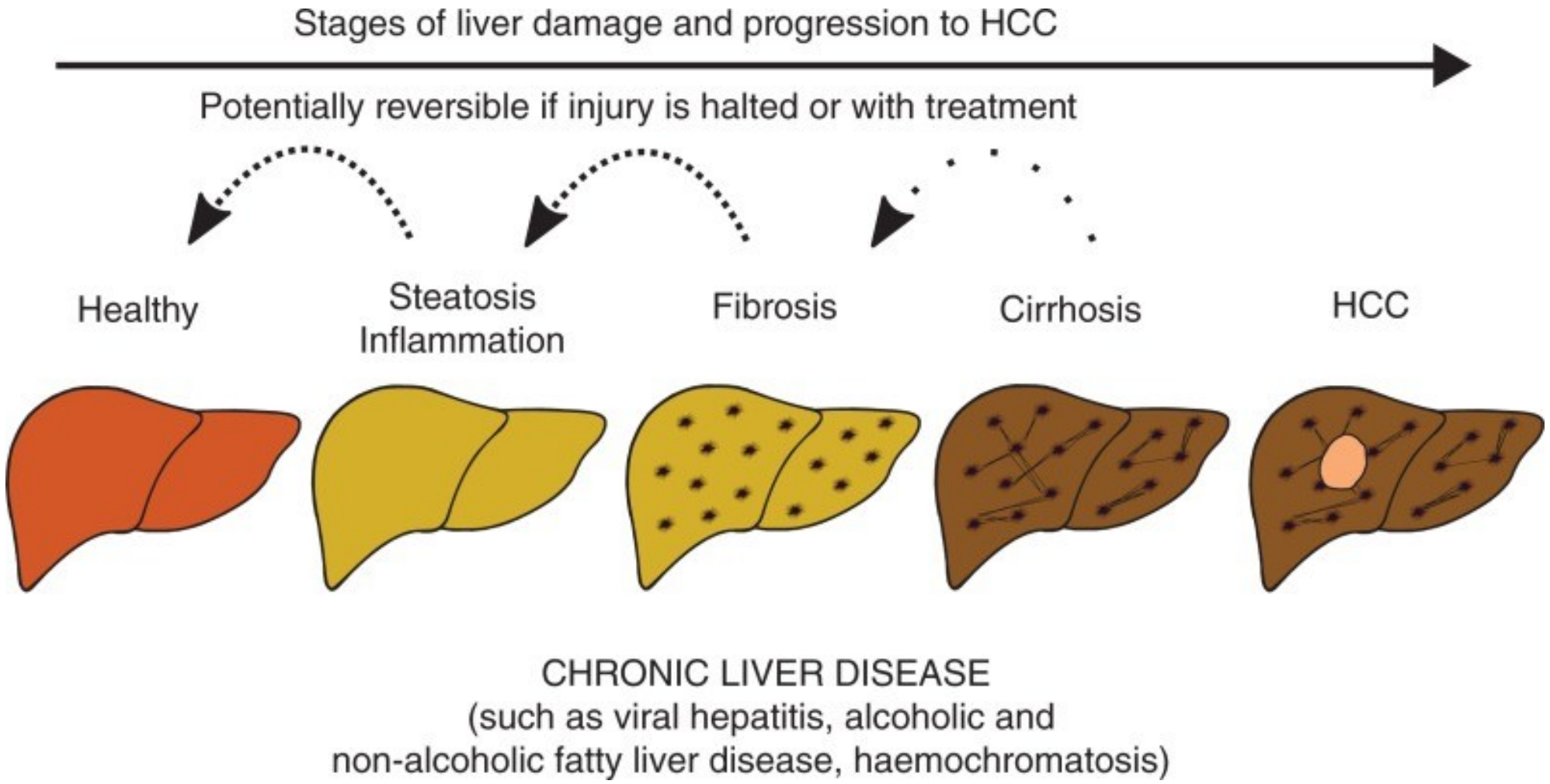
Krishnan A et al

NAFLD en PVVIH



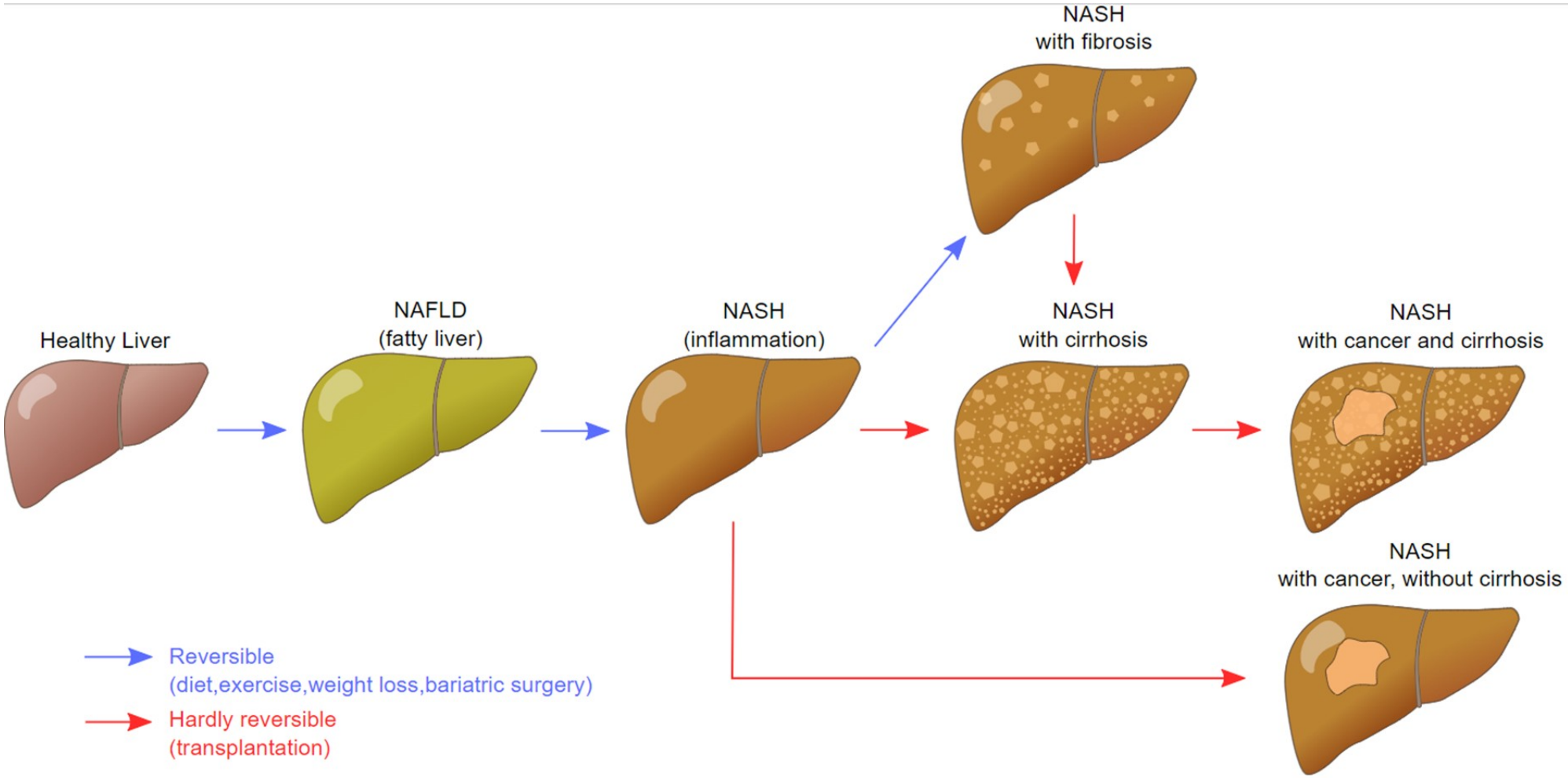
Lake et al, Clinical Gastroenterology and Hepatology 2022;20:256

Diagnóstico

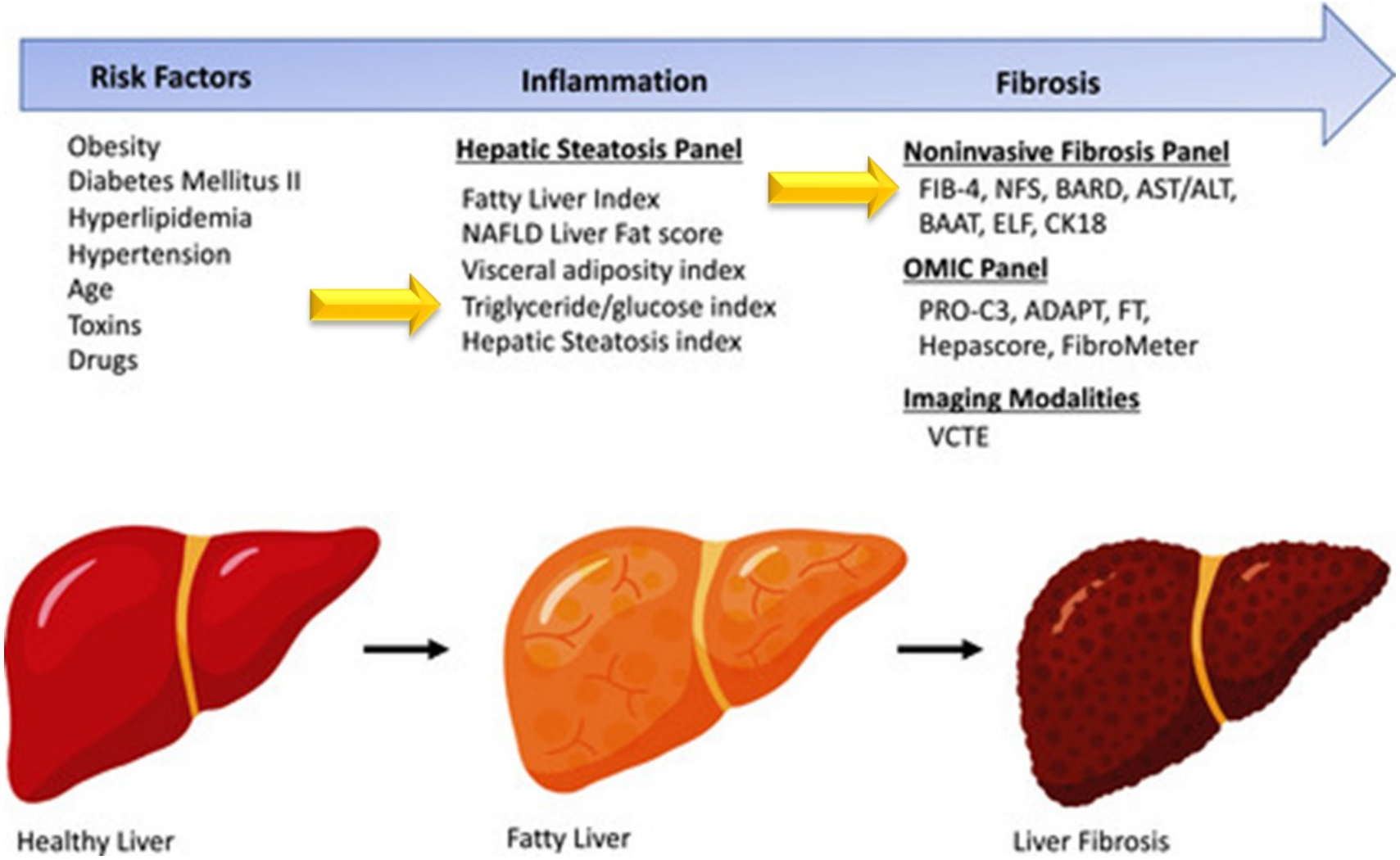


Carlessi R, Köhn-Gaone J, Olynyk JK, et al. Mouse Models of Hepatocellular Carcinoma. In: Tirnitz-Parker JEE, editor. Hepatocellular Carcinoma [Brisbane (AU): Codon Publications; 2019 Oct 24.

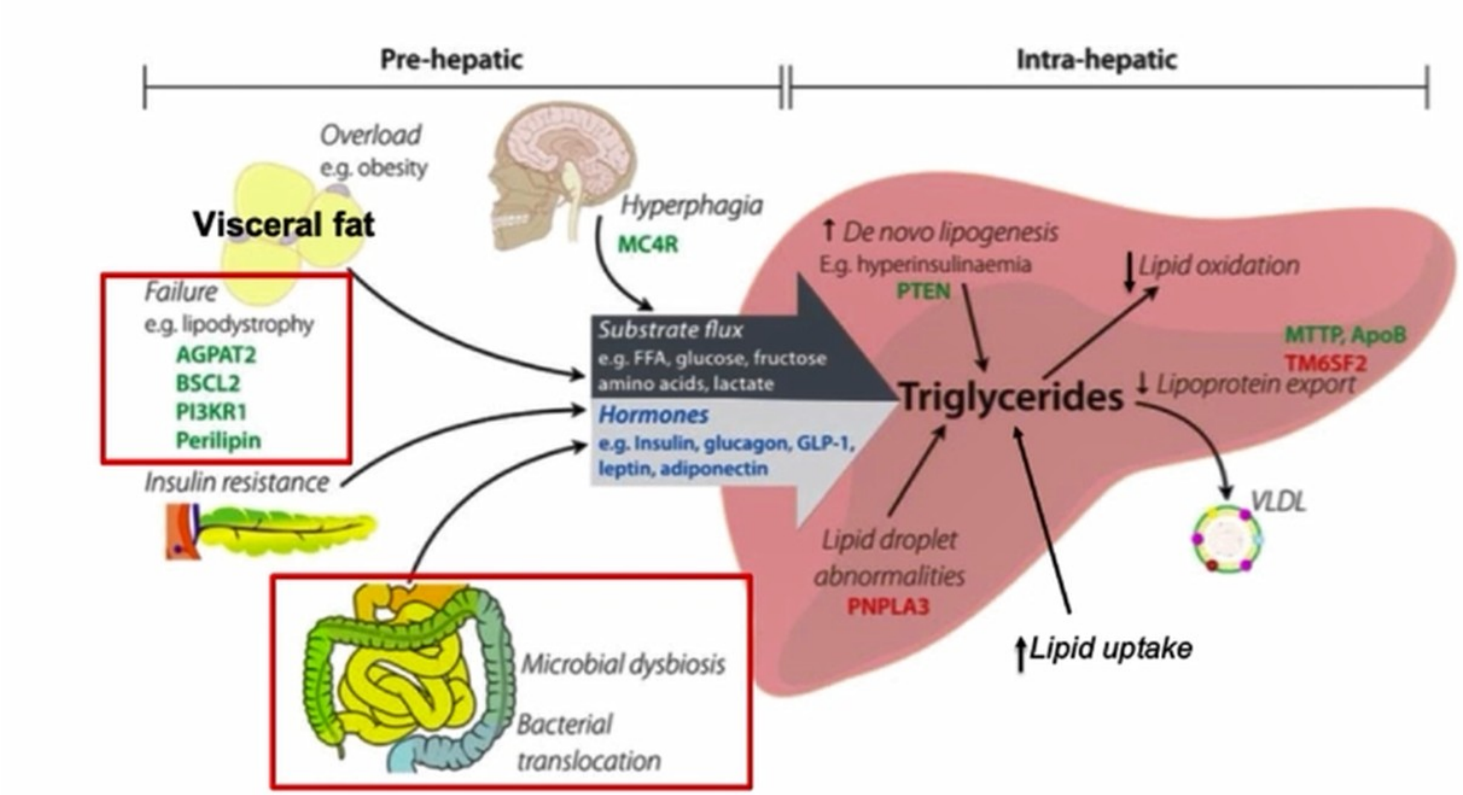
Diagnóstico



Diagnóstico

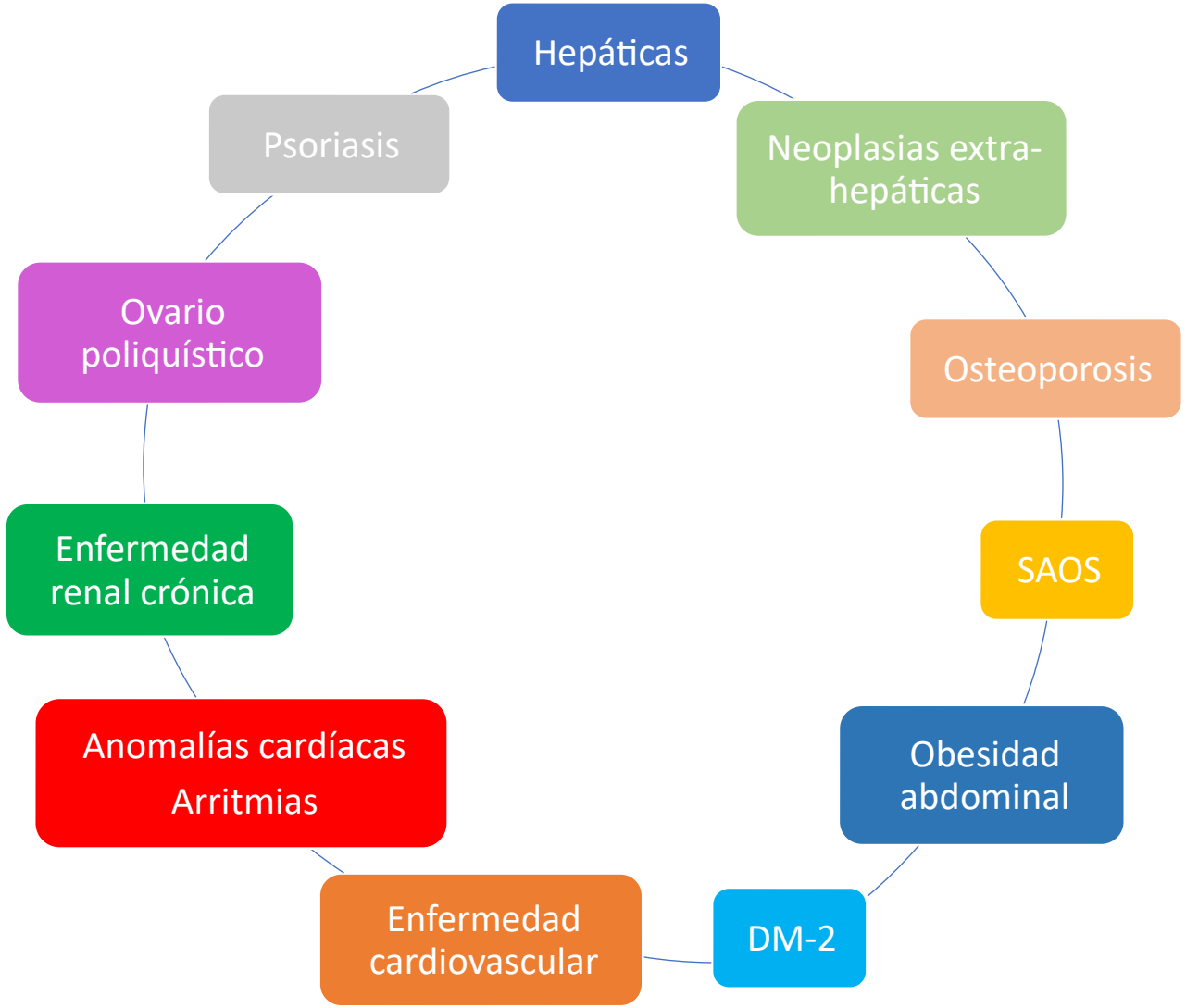


Diagnóstico



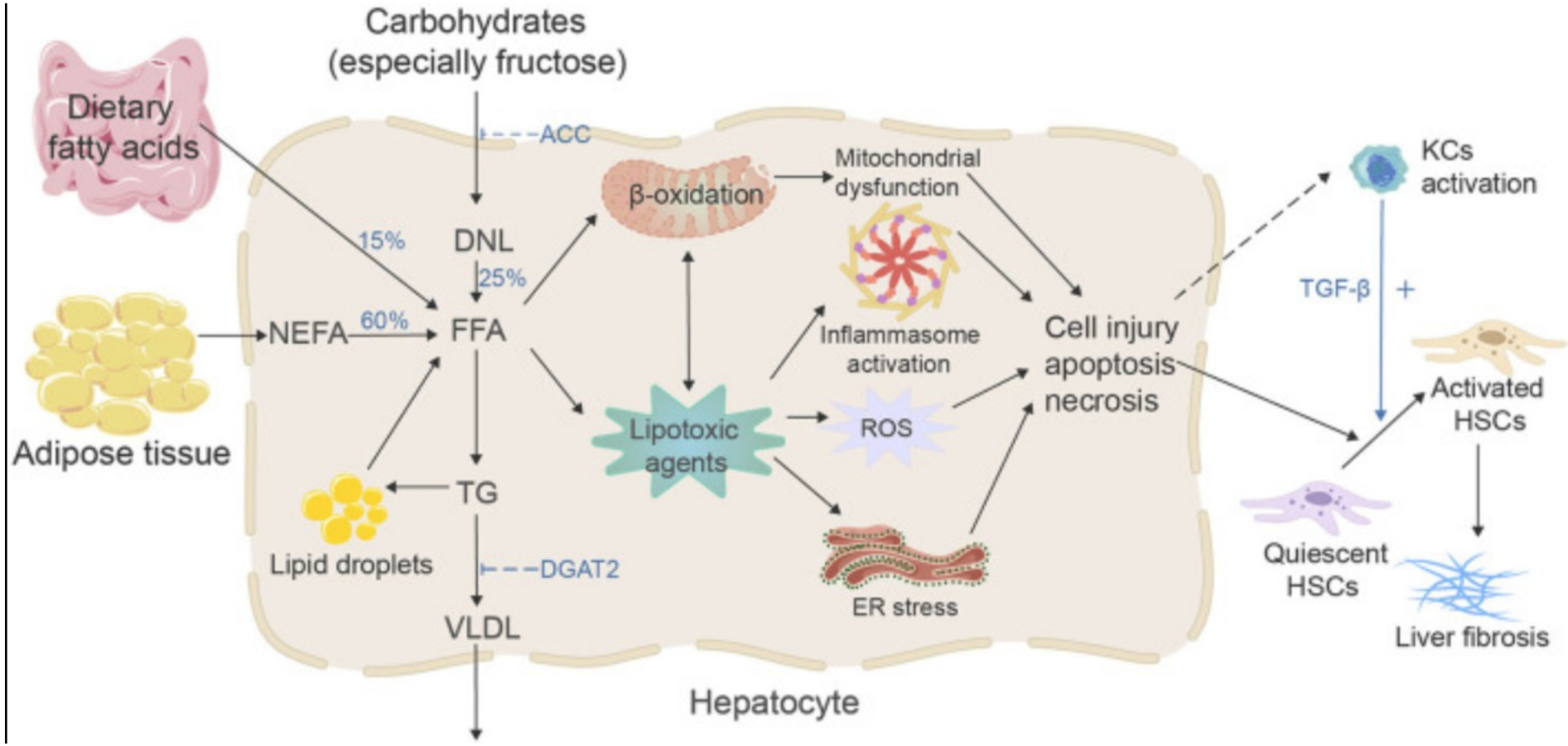
Mann, Jake P et al. “How Useful Are Monogenic Rodent Models for the Study of Human Non-Alcoholic Fatty Liver Disease?.” Frontiers in endocrinology vol. 7 145. 16 Nov. 2016, doi:10.3389/fendo.2016.00145

EHGNA como enfermedad sistémica



Adams LA et al. Gut. 2017;66(6):1138-1153

Prevención y tratamiento



Prevención y tratamiento

Therapeutics	Superiorities	Shortcomings
Lifestyle intervention	Applicable to the whole population Reduces all-cause mortality	Difficult to persist Failed to control the prevalence of MAFLD effectively
Bariatric metabolic surgery	Surgery is becoming less invasive Gets rid of taking medicines every day	Risk of post-operative complications Lack of adequate clinical research Is excluded as the first-line treatment of MAFLD
Liver transplantation	A life-saving method	Expensive Lack of liver resources Immune rejection, MAFLD relapsing
Pharmacological therapies	Convenient Affordable Various mechanisms of disease progression can be targeted	No specific drugs Drug side effects The impact of single-drug therapy is minimal

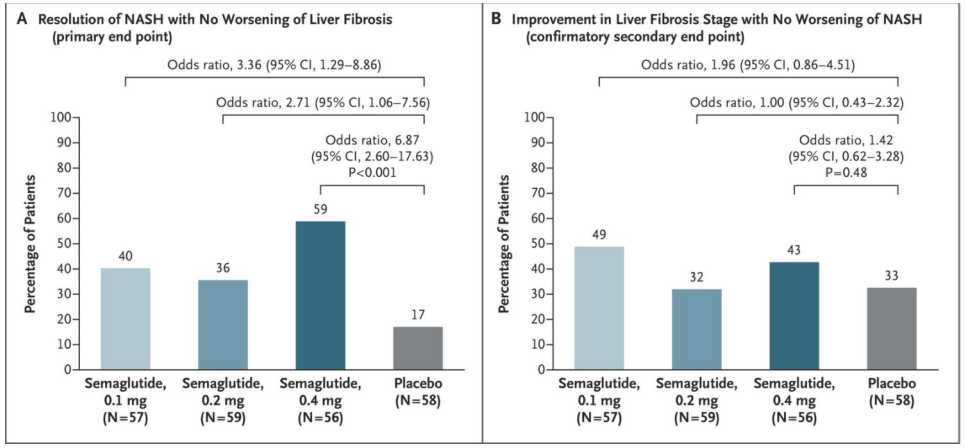
Front. Med. 10:1120621. doi: 10.3389/fmed.2023.1120621

Prevención y tratamiento

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

Philip N. Newsome, M.B., Ch.B., Ph.D., Kristine Buchholtz, M.D., Ph.D., Kenneth Cusi, M.D., Martin Linder, M.Sc., Takeshi Okanoue, M.D., Ph.D., Vlad Ratziu, M.D., Ph.D., Arun J. Sanyal, M.D., Anne-Sophie Sejling, M.D., Ph.D., and Stephen A. Harrison, M.D. for the NN9931-4296 Investigators*

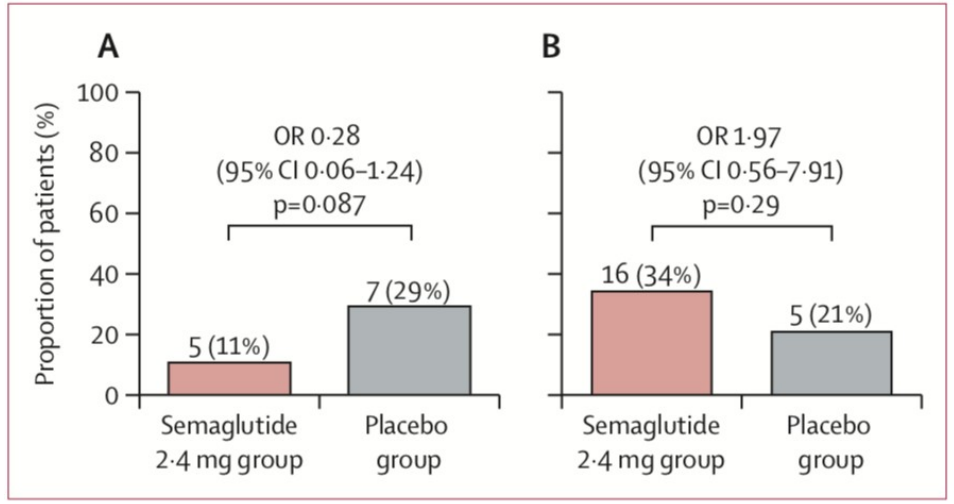


THE LANCET
Gastroenterology & Hepatology

Volume 8, Issue 6, June 2023, Pages 511-522

Articles

Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

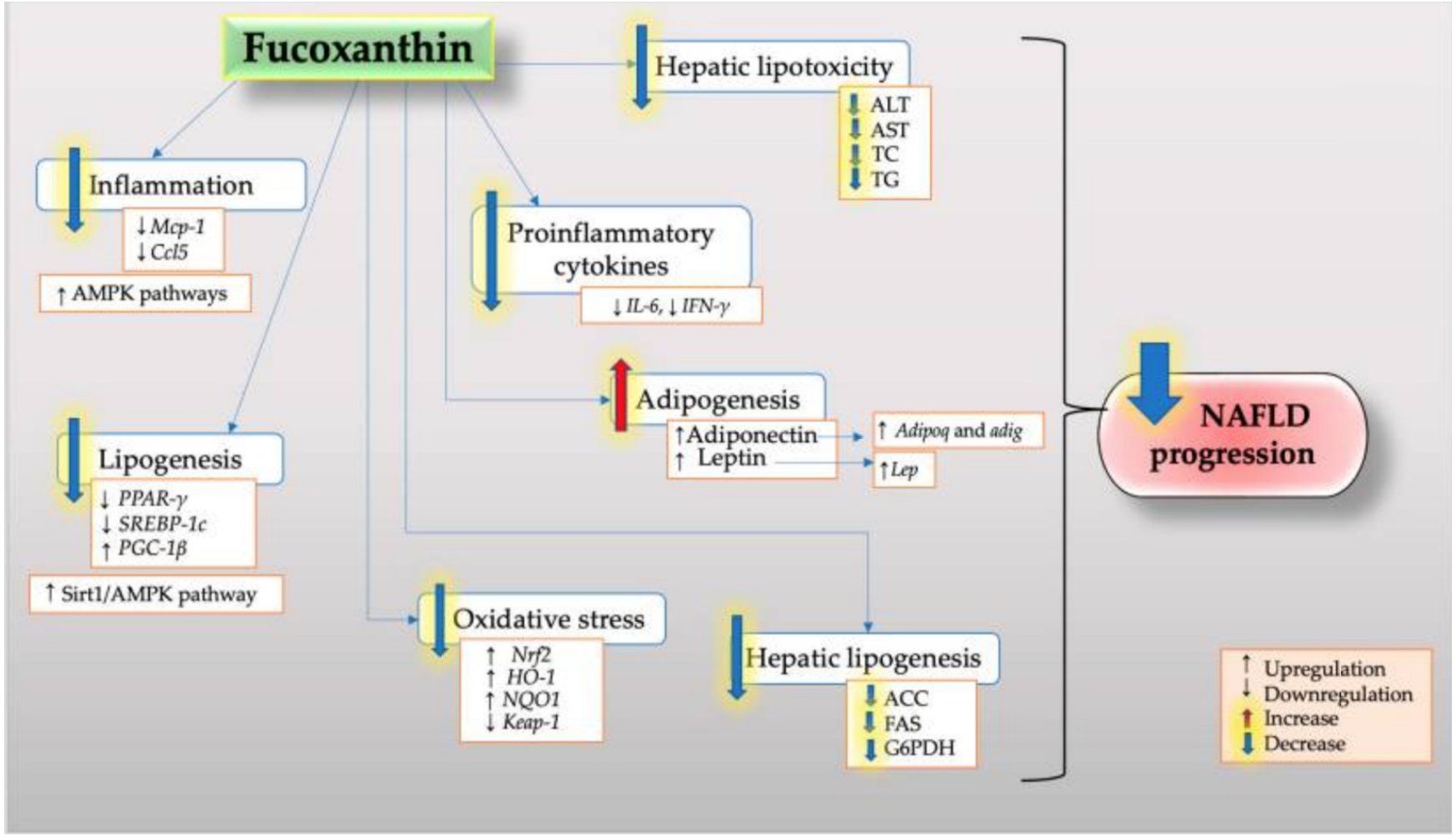


Prevención y tratamiento

Agents	Primary mechanism	Patients	Pros and cons of combined therapy	NCT number (and Phase)
Cilofexor + firsocostat	FXR agonist ACC inhibitor	392 patients with bridging fibrosis or compensated cirrhosis (F3–F4)	Combined therapy has better anti-fibrosis potential but still induces hypertriglyceridemia	NCT03449446 (Phase 2b)
Cilofexor + firsocostat + semaglutide	FXR agonist ACC inhibitor GLP-1 receptor agonist	Patients with NASH	Cilofexor and firsocostat-induced hypertriglyceridemia is alleviated by semaglutide	NCT03987074 (phase 2)
Cilofexor + firsocostat + fenofibrate	FXR agonist ACC inhibitor PPARα agonist	Patients with NASH with elevated TG (≥150 and <500 mg/dL)	Fenofibrate was safe and effectively mitigated increases in TG associated with ACC inhibitor	NCT02781584
PF-05221304 + PF-06865571	ACC inhibitor DGAT2 inhibitor	Adults with NAFLD	ACC inhibitor-mediated serum TG elevation was mitigated	NCT03776175 (phase 2a)
OCA + atorvastatin	FXR agonist HMGR inhibitors	84 participants with NASH	Atorvastatin attenuates OCA-induced LDL-C elevation	NCT02633956 (Phase 2)
Pioglitazone +tofogliflozin	PPARγ agonist SGLT-2 inhibitor	Patients with NAFLD with T2DM and a hepatic fat fraction of ≥10%	Therapeutic potential to prevent the progression of NASH to HCC	/
HXT + vitamin E	Natural compounds Antioxidant	Children with biopsy-proven NAFLD	Ameliorate steatosis and hypertriglyceridemia, reducing the fibrosis stage	NCT02842567

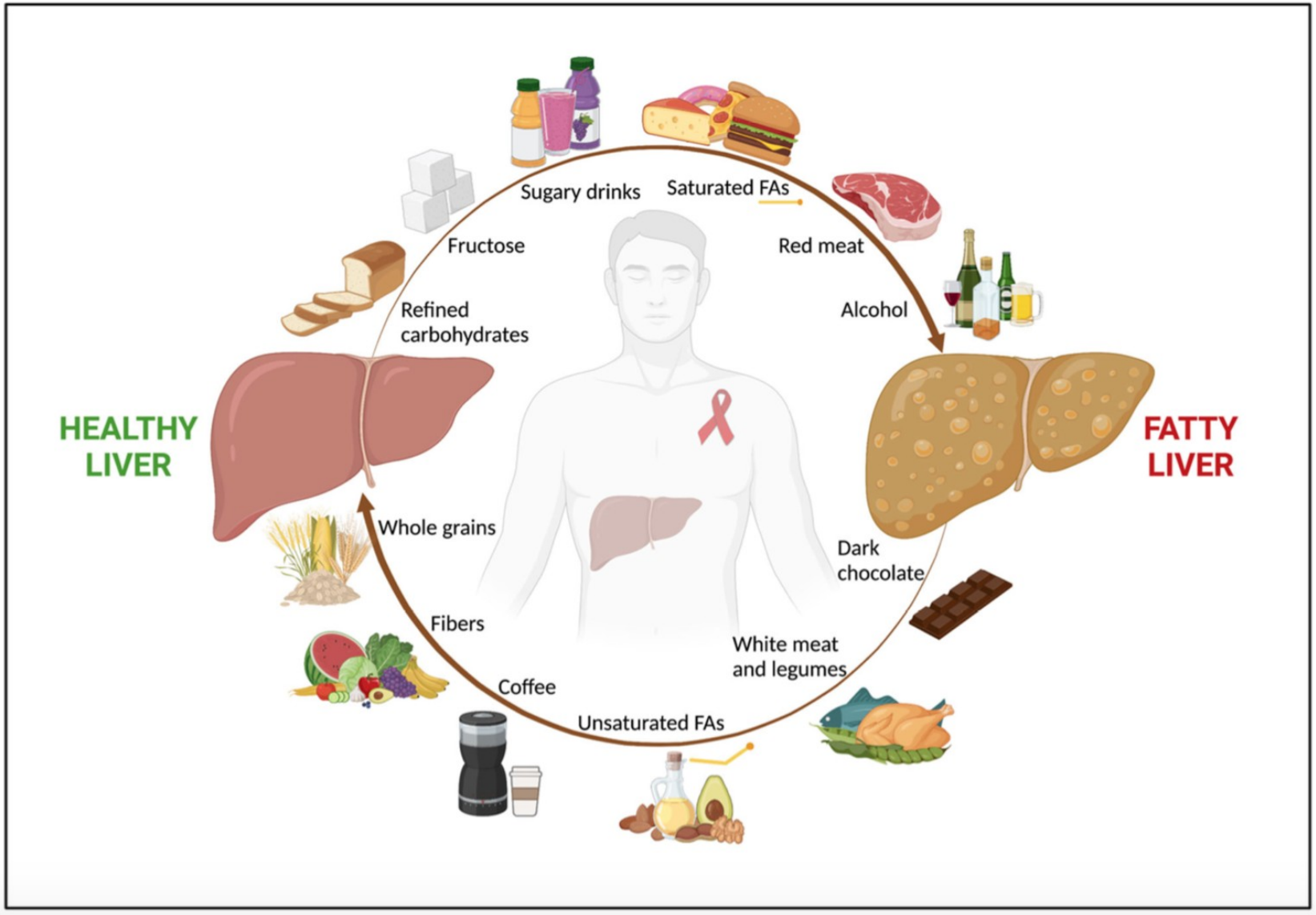
Front. Med. 10:1120621. doi: 10.3389/fmed.2023.1120621

Prevención y tratamiento



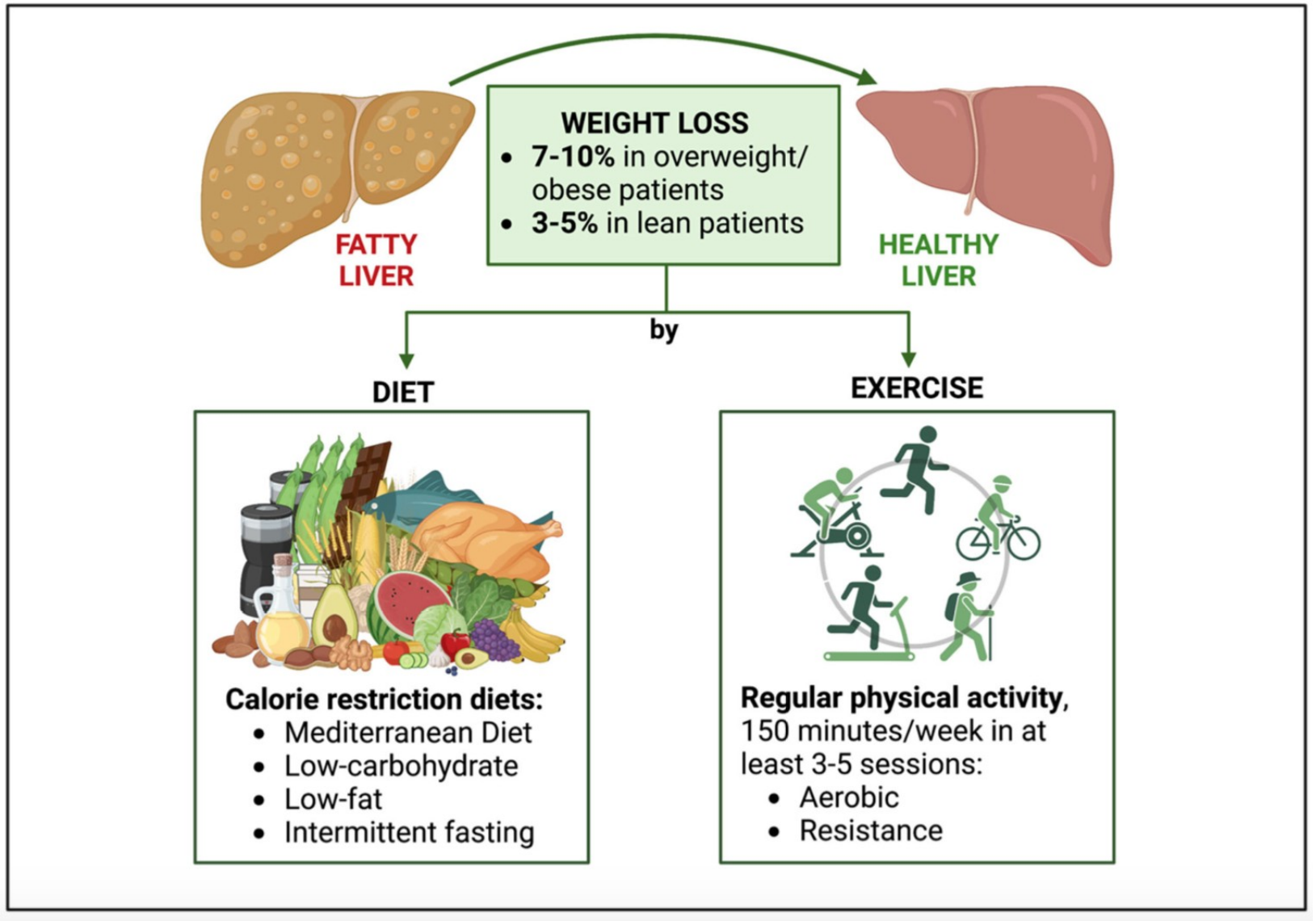
Nutrients. 2023 Apr; 15(8): 1954

Prevención y tratamiento



Nutrients 2023, 15, 1990. https://doi.org/10.3390/ nu15081990

Prevención y tratamiento



Nutrients 2023, 15, 1990. https://doi.org/10.3390/ nu15081990

Prevención y tratamiento

¿Papel del TAR?

J Antimicrob Chemother
doi:10.1093/jac/dkab157

Journal of Antimicrobial Chemotherapy

Liver stiffness change with HCV cure in HIV-infected patients on non-nucleoside analogues

A. Gonzalez-Serna[1], A. Corma-Gomez[1], F. Tellez[2], S. García-Martin[3], A. Rivero-Juarez[4], M. Frias[4], F. J. Vera-Méndez[5], I. De los Santos[6], D. Merino[7], L. Morano[8], A. Imaz[9], C. Galera[10], M. Serrano[11], J. Macias[1] and J. A. Pineda[1*]

CHANGES IN LIVER STEATOSIS AFTER SWITCHING FROM EFAVIRENZ TO RILPIVIRINE AMONG HIV-INFECTED PATIENTS: THE RIFLE STUDY

Sayago, C; Macías, J; Conde M; Merchante, N; Gómez-Mateos, J; Pineda, JA.

Unit of Infectious Diseases and Microbiology. Hospital Universitario de Valme. Seville. Spain

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

- Maria Luisa Montes[1] , Carmen Busca[1] , Angela B. Moragrega[2] , Nadezda Apostolova[2] , Antonio Olveira[1] ,
- Luz Martin Carbonero[1] , Eulalia Valencia[1] , Victoria Moreno[1], Jose I. Bernardino[1] , Ignacio Perez-Valero[1] , Juan
- González-García[1] , Juan V. Espluges[2] , Jose R. Arribas[1] , Ana Blas-García[2].

1 Hospital La Paz Institute for Health Research, Madrid, Spain,

2 Facultad de Medicina, Universidad de Valencia, VALENCIA, Spain]

Nothing to declare

Hepatology

ORIGINAL ARTICLE

Rilpivirine attenuates liver fibrosis through selective STAT1-mediated apoptosis in hepatic stellate cells

Alberto Martí-Rodrigo,[1] Fernando Alegre,[1,2] Ángela B Moragrega,[1] Francisco García-García,[3] Pablo Martí-Rodrigo,[1] Anabel Fernández-Iglesias,[4] Jordi Gracia-Sancho,[4,5] Nadezda Apostolova,[1] Juan V Esplugues,[1,2] Ana Blas-García[1]

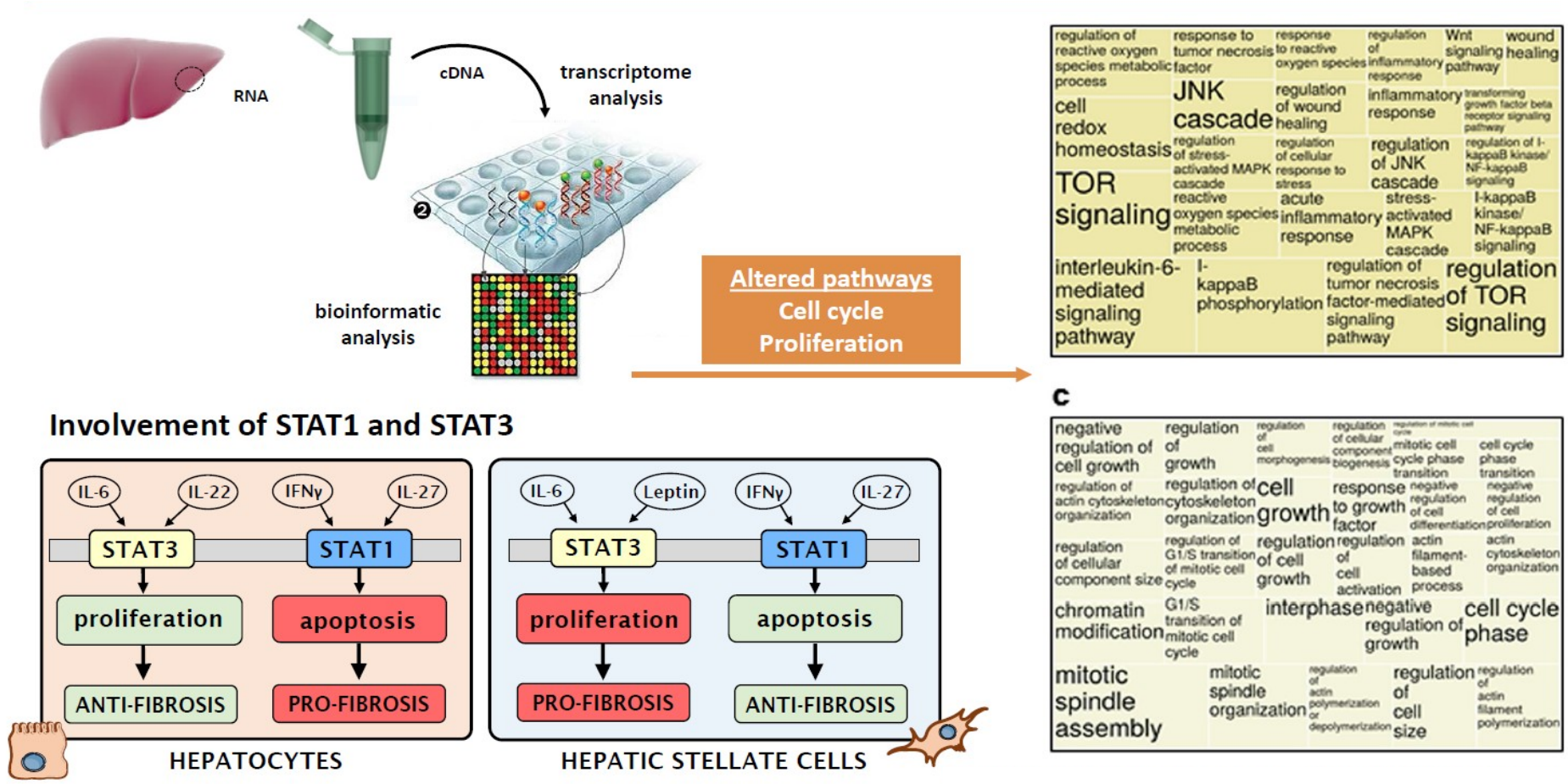
Determinants of liver steatosis in people living with HIV on antiretroviral therapy

Riebensahm C[1,2], Berzigotti[3,4], Surial B[1], Günthard H[5,6], Tarr, P.E.[7], Furrer H[1], Rauch A[1], Wandeler, G[1,8], Swiss HIV Cohort Study

CROI 2022 (poster)

¿Papel del TAR?

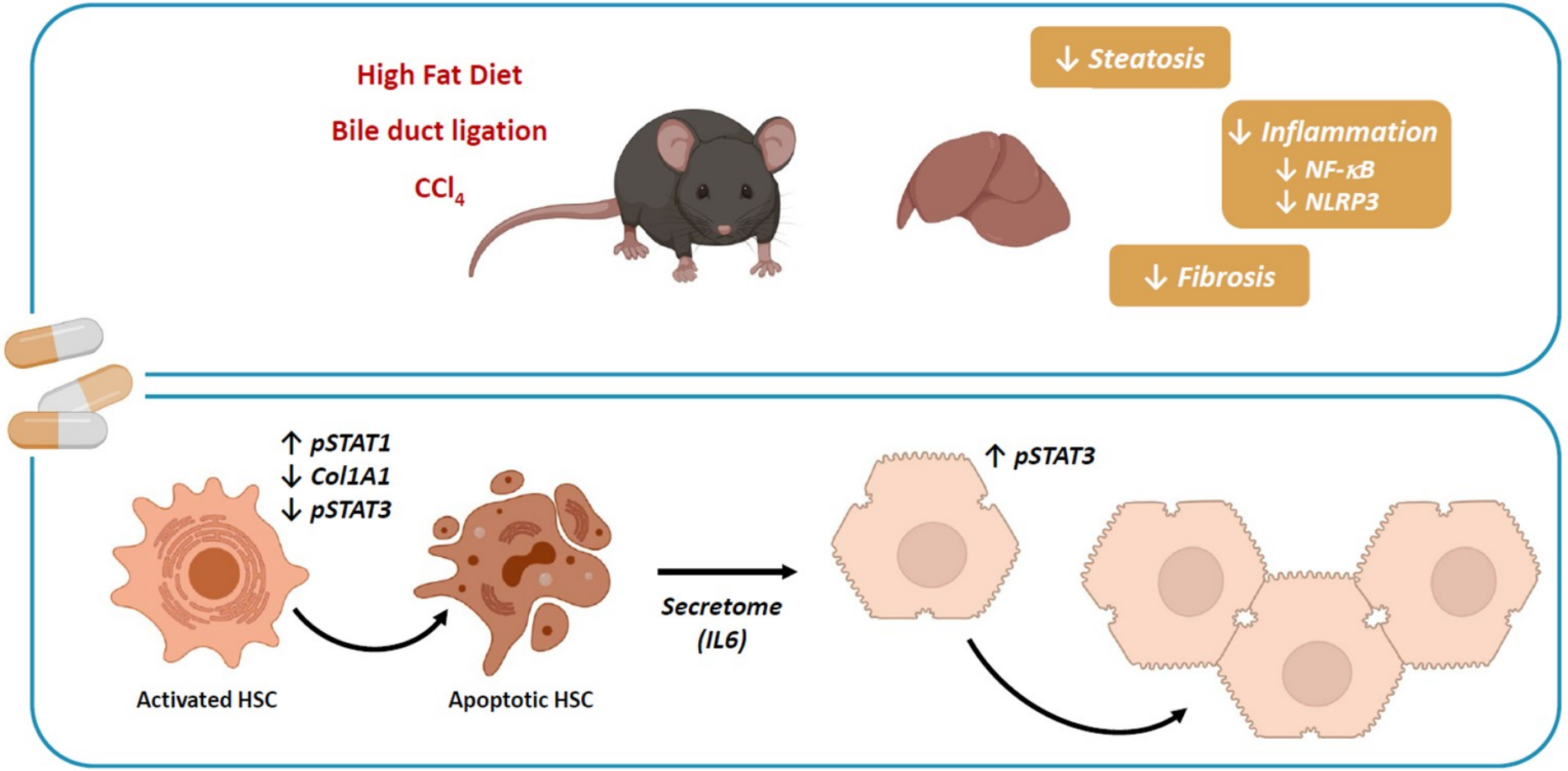
Rilpivirine attenuates liver fibrosis through selective STAT1-mediated apoptosis in hepatic stellate cells



Martí-Rodrigo, A et al. Gut 2020;69:920-932. DOI:10.1136/gutjnl-2019-318372

¿Papel del TAR?

Rilpivirine attenuates liver fibrosis through selective STAT1-mediated apoptosis in hepatic stellate cells



Martí-Rodrigo, A et al. Gut 2020;69:920-932. DOI:10.1136/gutjnl-2019-318372

¿Papel del TAR?

Analysis of STAT-1 levels considering RPV-exposition

			LnSTAT-1 Mean (CI 95%)	LnSTAT-1 Mean difference (CI 95%)	p
Steatosis > 30%	No	RPV non-exposed	9.2 (8.2; 10.2)	1.12 (-0.50; 2.74)	0.17
		RPV exposed	10.3 (9.3; 11.3)		
	Yes	RPV non-exposed	8.9 (7.9; 9.9)	2.06 (0.25; 3.87)	**0.03**
		RPV exposed	10.9 (9.7; 12.2)		
Steatohepatitis	No	RPV non-exposed	9.7 (8.5; 10.8)	0.5 (-0.8; 1.7)	0.447
		RPV exposed	10.2 (9.1; 11.3)		
	Yes	RPV non-exposed	8.8 (8.0; 9.7)	2.07 (0.46; 3.67)	**0.01**
		RPV exposed	10.9 (9.8; 12.0)		
Fibrosis ≥ F1	No	RPV non-exposed	9.0 (8.2; 9.9)	1.66 (0.21; 3.11)	**0.03**
		RPV exposed	10.7 (9.7; 11.7)		
	Yes	RPV non-exposed	8.9 (7.8; 9.9)	1.77 (0.02; 3.53)	**0.048**
		RPV exposed	10.6 (9.5; 11.7)		

* Marginal mean (95% CI) adjusted for exposure time to RPV (months) and BMI

Montes ML, Arenzana CB, Moragrega AB, et al. RPV ACTIVATES STAT1 in stellate cells to regulate liver injury in PLWHIV and NAFLD. CROI 2021. March 6-10, 2021

En resumen

- La EHGNA es un problema creciente en población general y más en PVVIH, debido fundamentalmente al estilo de vida.
- La EHGNA es una enfermedad sistémica, muy relacionada con el perfil lipídico y el metabolismo de los HC.
- La fibrosis hepática es el principal predictor de mortalidad.
- Las intervenciones más eficaces son la dieta y el ejercicio.
- El TAR puede jugar un papel en el desarrollo o prevención de EHGNA bien de manera directa, bien alterando los factores RCV.

AGIDEI
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XVII CURSO EN AVANCES EN INFECCIÓN VIH Y HEPATITIS VIRALES

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