

Fatty Liver Disease and HIV: What the HIV Clinician Needs to Know



The webinar will begin at
1:00 PM (ET); 12:00 PM (CT); 11:00 AM (MT); 10:00 AM (PT)

Completing the Webinar Check-in Form ensures that your evaluation form will be activated in your IAS–USA account under “My Activities.” **You must be preregistered and confirmed in the IAS–USA system by 4:00 PM PT on Monday, May 25, 2020, to be eligible to claim credits or a certificate.**

Evaluations, and information on how to claim CME, pharmacy, nursing, or pharmacotherapy credits, and certificate of participation, will be **emailed by 5 PM PT tomorrow.**

Not Receiving Our Emails?

Check the FAQ section on the IAS-USA website for more information

Cases on the Web Board

The Cases on the Web (COW) Board is a select group of experts in the management of HIV and other viral infections. Dedicated to teaching practitioners who are actively involved in medical care for people with HIV or other viral infections, the COW Board ensures that the program remains a relevant and useful educational tool for the IAS-USA audience.

<https://www.iasusa.org/activities/cases-on-the-web/about-cows/cow-webinars-editorial-board/>

Board Chair

Michael S. Saag, MD
Professor of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Board Co-chair

Marshall J. Glesby, MD, PhD
Professor of Medicine and Healthcare Policy
and Research
Weill Cornell Medicine
New York, New York

Board Members

Judith A. Aberg, MD, FIDSA, FACP
George Baehr Professor of Medicine
ICAHN School of Medicine at Mount Sinai
New York, New York

Roger J. Bedimo, MD, MS
Director of Infectious Disease Fellowship
Training
University of Texas Southwestern Medical
Center
Dallas, Texas

Kara W. Chew, MD, MS
Assistant Clinical Professor of Medicine
University of California Los Angeles David
Geffen School of Medicine
Los Angeles, California

Steven C. Johnson, MD
Professor of Medicine
University of Colorado School of Medicine
Aurora, Colorado

Harry W. Lampiris, MD
Professor of Clinical Medicine
University of California San Francisco
San Francisco, California

Paul E. Sax, MD
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

David L. Wyles, MD
Chief of the Division of Infectious Diseases
Denver Health Medical Center
Denver, Colorado

*Register
Now!*

<https://www.iasusa.org/activities/webinars/upcoming-webinars/>

HIV Infection and the Kidney in 2020

Christina M. Wyatt, MD
Tuesday, June 23, 2020

HIV 101: Fundamentals of HIV Infection and Applications of Antiretroviral Therapy

Michael S. Saag, MD
Rajesh T. Gandhi, MD
Tuesday, June 30, 2020

Weigh Gain: A Growing Issue in Antiretroviral Therapy

John R. Koethe, MD
Tuesday, July 21, 2020

Physical Function and Frailty in HIV: What Does It Mean, How Do We Measure It, Why Should We Care, and What Can We Do?

Kristine M. Erlandson, MD MS
Tuesday, July 28, 2020

Management and Prevention of HIV Infection Among Transgender Adults

Asa E. Radix, MD
Tuesday, August 18, 2020

Liver Transplant Among People With HIV

Christine M. Durand, MD
Tuesday, August 25, 2020

PEP to PrEP Transitions: Evidence and Innovations

Douglas S. Krakower, MD
Tuesday, October 13, 2020

4-PART Webinar Series on Pain and Addiction:

PART 1—Chronic Pain in People With HIV: An Evidence-Based, Practical

Jessica Merlin, MD, PhD, MBA
Tuesday, September 1, 2020

PART 2—Medical Cannabis in People With HIV: What's the Evidence?

Jessica Merlin, MD, PhD, MBA
Tuesday, October 6, 2020

PART 3—Opioid Use and HIV/Hepatitis C Made Easy: A Practical Implementation of the Evidence

R. Douglas Bruce, MD, MA, MSc
Tuesday, November 3, 2020

PART 4—More Than One Problem: Mental Illness as a Contributing Factor of Pain and Substance Use in People With HIV

R. Douglas Bruce, MD, MA, MSc
Tuesday, December 1, 2020

COVID-19: What We Know Today That We Didn't Know Yesterday and Other Scientific Conversations

An IAS-USA roundtable series that will go over updates regarding COVID-19

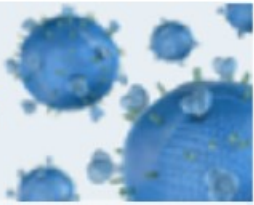


Paul A. Volberding, MD
George Rutherford, MD
Early June
TBD



Jeanne M. Mrazzozzo, MD
Judith S. Currier, MD
Wednesday, June 17
4:00 PM – 5:00 PM PT

More details will be release on <https://www.iasusa.org/>



IAS-USA **VIRTUAL Update on HIV:
A Focus on Antiretroviral Therapy, New ART Drugs and
Strategies, and the Intersection of COVID-19 and HIV**



West Coast

Monday, June 29
10:00 AM - 3:15 PM PT

To register, visit <https://www.iasusa.org/>



IAS-USA **VIRTUAL Update on HIV:
A Focus on Antiretroviral Therapy, New ART Drugs and
Strategies, and the Intersection of COVID-19 and HIV**



West Coast

Monday, June 29
10:00 AM - 3:15 PM PT



East Coast

Tuesday, July 14
10:00 AM - 2:50 PM PT

To register, visit <https://www.iasusa.org/>



IAS-USA **VIRTUAL Update on HIV:
A Focus on Antiretroviral Therapy, New ART Drugs and
Strategies, and the Intersection of COVID-19 and HIV**



West Coast

Monday, June 29
10:00 AM - 3:15 PM PT



East Coast

Tuesday, July 14
10:00 AM - 2:50 PM PT



Midwest

Thursday, July 30
10:00 AM - 2:45 PM PT

To register, visit <https://www.iasusa.org/>

Fatty Liver Disease and HIV: What the HIV Clinician Needs to Know



Jennifer C. Price, MD, PhD
Associate Professor of Medicine
University of California San Francisco
San Francisco, CA

Dr Price has received grant support from Gilead Sciences, Inc and Merck, and served on advisory boards for Theratechnologies. Her spouse has held stock options for Bristol-Myers Squibb, Johnson and Johnson, Merck, and Abbvie. (Updated 05/26/20)

Planner/Reviewer Financial Disclosures:

Planner/Reviewer 1 has no relevant financial affiliations to disclose. (Updated 05/26/20)

Planner/Reviewer 2 has no relevant financial affiliations to disclose. (Updated 05/26/20)

CME Information

The International Antiviral Society–USA (IAS–USA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.



The IAS–USA designates this live activity for a maximum of **1.25 AMA PRA Category 1 Credits™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing and Pharmacy Credits

Nursing Credits

Educational Review Systems is an approved approver of continuing nursing education by the Alabama State Nursing Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. Provider # 5-115. This program is approved for **1.25** hours of continuing nursing education.

Educational Review Systems is also approved for nursing continuing education by the state of California, the state of Florida and the District of Columbia.

This program is approved for **1.25** hours of pharmacotherapy credit

Pharmacy Credits



Educational Review Systems is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. Participants of the session who complete the evaluation and provide accurate NABP e-Profile information will have their credit for **1.25** contact hours (**0.125** CEU) submitted to CPE Monitor as early as 14 days after the event and no later than 60 days after the event. Please know that if accurate e-Profile information is not provided within 60 days of the event, credit cannot be claimed after that time. The participant is accountable for verifying the accurate posting of CE credit to their CPE Monitor account within 60 days.

UAN # 0761-9999-20-066-L02-P

Grant Support for this Webinar

This activity is part of the IAS–USA national educational effort that is funded, in part, by contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers. Generous support for this activity has been received from the following contributors:

PLATINUM SUPPORTERS

Gilead Sciences, Inc.

Merck & Co, Inc.

ViiV Healthcare

SILVER SUPPORTERS

Janssen Therapeutics

We appreciate the funders supporting this activity and those observing this activity today. Per ACCME guidelines funder observers may not participate in discussions or ask questions during the webinar. Thank you.

Navigating the Webinar

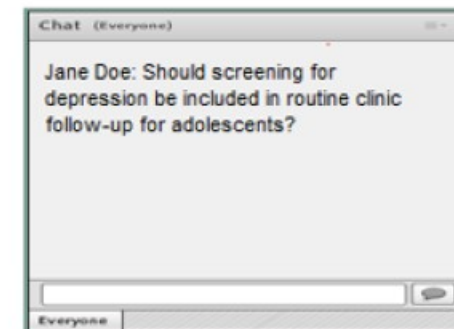
- Poll questions
 - A *separate* window will show the poll questions.
 - Choose your response from the POLL, *not* in the CHAT box.
 - Responses will be displayed after the poll closes.



Option	Progress	Percentage	Count
<input type="radio"/> Medical student	0%	0%	0/100
<input type="radio"/> Registered nurse	0%	0%	0/100
<input type="radio"/> Therapist/counselor	0%	0%	0/100
<input type="radio"/> Public health professional	0%	0%	0/100
<input checked="" type="radio"/> Physician assistant	100%	100%	100/100
<input type="radio"/> Pharmacist	0%	0%	0/100
<input type="radio"/> Health administrator/manager	0%	0%	0/100
<input type="radio"/> Educator	0%	0%	0/100
<input type="radio"/> Other	0%	0%	0/100
<input checked="" type="radio"/> No Vote	0%	0%	0/100



- To ask questions, type into the chat box; questions will be answered at the end of the webinar.



Poll 1

From which geographic region are you viewing this webinar?

1. Western United States
2. Midwest United States
3. Southwest United States
4. Southeast United States
5. Northeast United States
6. Canada
7. Mexico
8. Central/South America
9. Europe
10. Asia/Australia
11. Africa
12. Other

Fatty Liver Disease and HIV: What the HIV Clinician Needs to Know



Jennifer C. Price, MD, PhD
Associate Professor of Medicine
University of California San Francisco
San Francisco, CA

Dr Price has received grant support from Gilead Sciences, Inc and Merck, and served on advisory boards for Theratechnologies. Her spouse has held stock options for Bristol-Myers Squibb, Johnson and Johnson, Merck, and Abbvie. (Updated 05/26/20)

Planner/Reviewer Financial Disclosures:

Planner/Reviewer 1 has no relevant financial affiliations to disclose. (Updated 05/26/20)

Planner/Reviewer 2 has no relevant financial affiliations to disclose. (Updated 05/26/20)

Learning Objectives

Upon completion of this webinar, learners will be able to:

- **Recognize the clinical and histologic spectrum of nonalcoholic fatty liver disease (NAFLD)**
- **Identify which persons living with HIV are most likely to have NAFLD**
- **Describe the work-up for patients with suspected NAFLD**
- **Identify the non-pharmacologic management of NAFLD**

Nonalcoholic Fatty Liver Disease (NAFLD)

- Fatty liver (hepatic steatosis) without excessive alcohol or other cause of liver disease
 - >14 drinks/wk in women, >21 drinks/wk in men

Nonalcoholic Fatty Liver Disease (NAFLD)

- Fatty liver (hepatic steatosis) without excessive alcohol or other cause of liver disease
 - >14 drinks/wk in women, >21 drinks/wk in men
- Lack secondary causes of hepatic steatosis

Nonalcoholic Fatty Liver Disease (NAFLD)

- Fatty liver (hepatic steatosis) without excessive alcohol or other cause of liver disease
 - >14 drinks/wk in women, >21 drinks/wk in men
- Lack secondary causes of hepatic steatosis

Medications

- Tamoxifen
- Corticosteroids
- Methotrexate
- Amiodarone
- Valproate

Other Conditions

- Wilson's disease
- Hepatitis C Virus (genotype 3)
- TPN
- Abetalipoproteinemia
- Inborn errors of metabolism

Nonalcoholic Fatty Liver Disease (NAFLD)

- Fatty liver (hepatic steatosis) without excessive alcohol or other cause of liver disease

 - >14 drinks/wk in women, >21 drinks/wk in men

- Lack secondary causes of hepatic steatosis

Medications

- Tamoxifen
- Corticosteroids
- Methotrexate
- Amiodarone
- Valproate

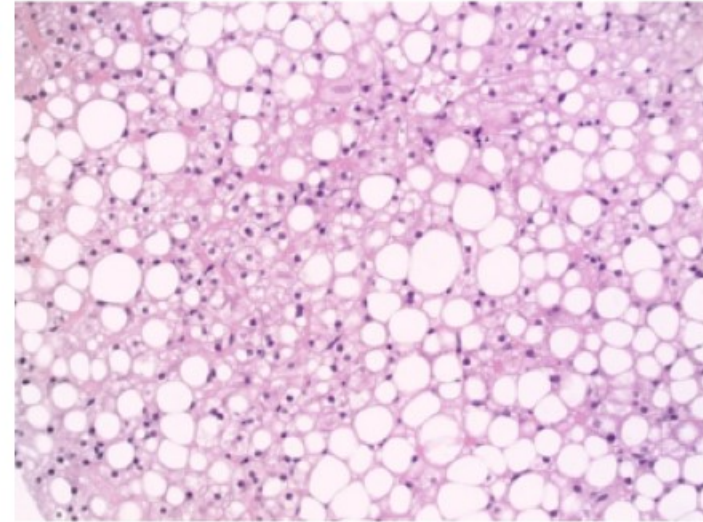
Other Conditions

- Wilson's disease
- Hepatitis C Virus (genotype 3)
- TPN
- Abetalipoproteinemia
- Inborn errors of metabolism

- Primary-NAFLD versus HIV-associated NAFLD

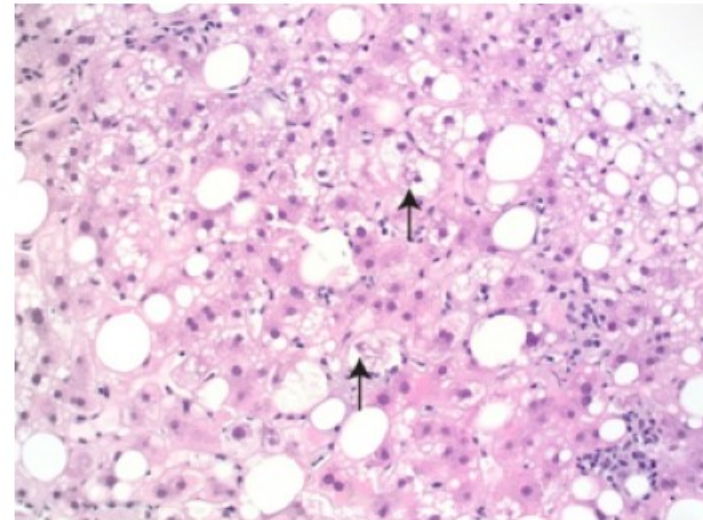
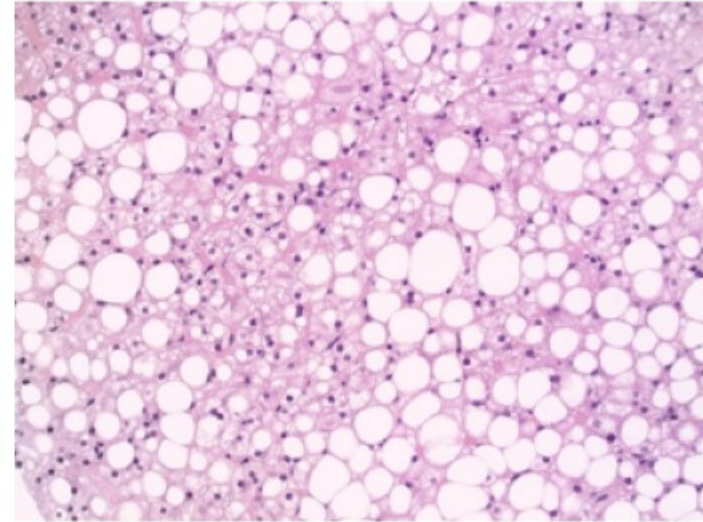
NAFLD: Definitions

- Nonalcoholic fatty liver (NAFL) aka simple steatosis
 - Steatosis without hepatocellular injury



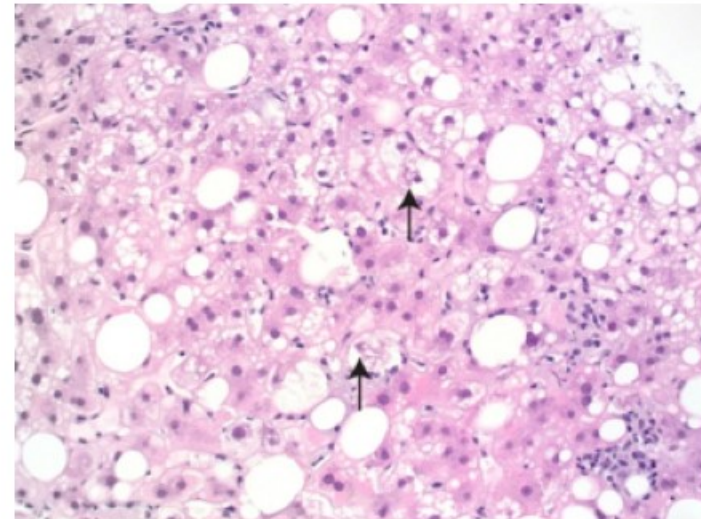
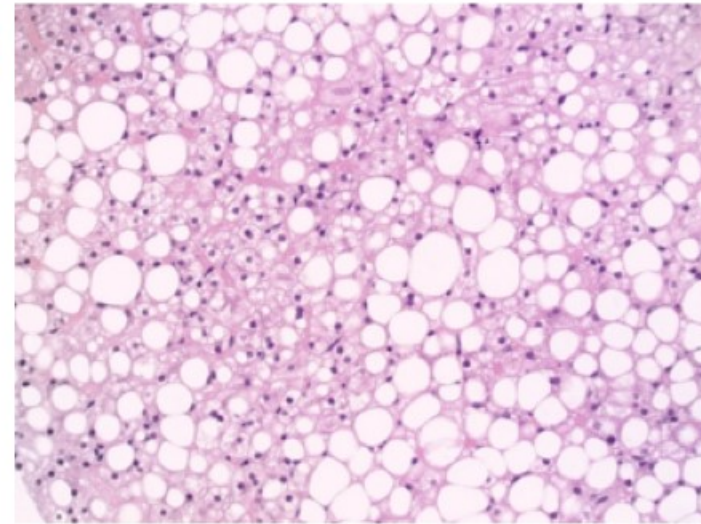
NAFLD: Definitions

- Nonalcoholic fatty liver (NAFL) aka simple steatosis
 - Steatosis without hepatocellular injury
- Nonalcoholic steatohepatitis (NASH)
 - Steatosis + inflammation with hepatocyte injury with/without fibrosis



NAFLD: Definitions

- Nonalcoholic fatty liver (NAFL) aka simple steatosis
 - Steatosis without hepatocellular injury
- Nonalcoholic steatohepatitis (NASH)
 - Steatosis + inflammation with hepatocyte injury with/without fibrosis
- Advanced fibrosis
 - Bridging fibrosis or cirrhosis ($\geq F3$)



NAFLD Risk Factors

- **Obesity/central adiposity**
- **Type 2 diabetes**
- **Dyslipidemia**
- **Metabolic syndrome**
- Race and ethnicity
- Hereditary/genetic (for example *PNPLA3*)
- Sex
- Age

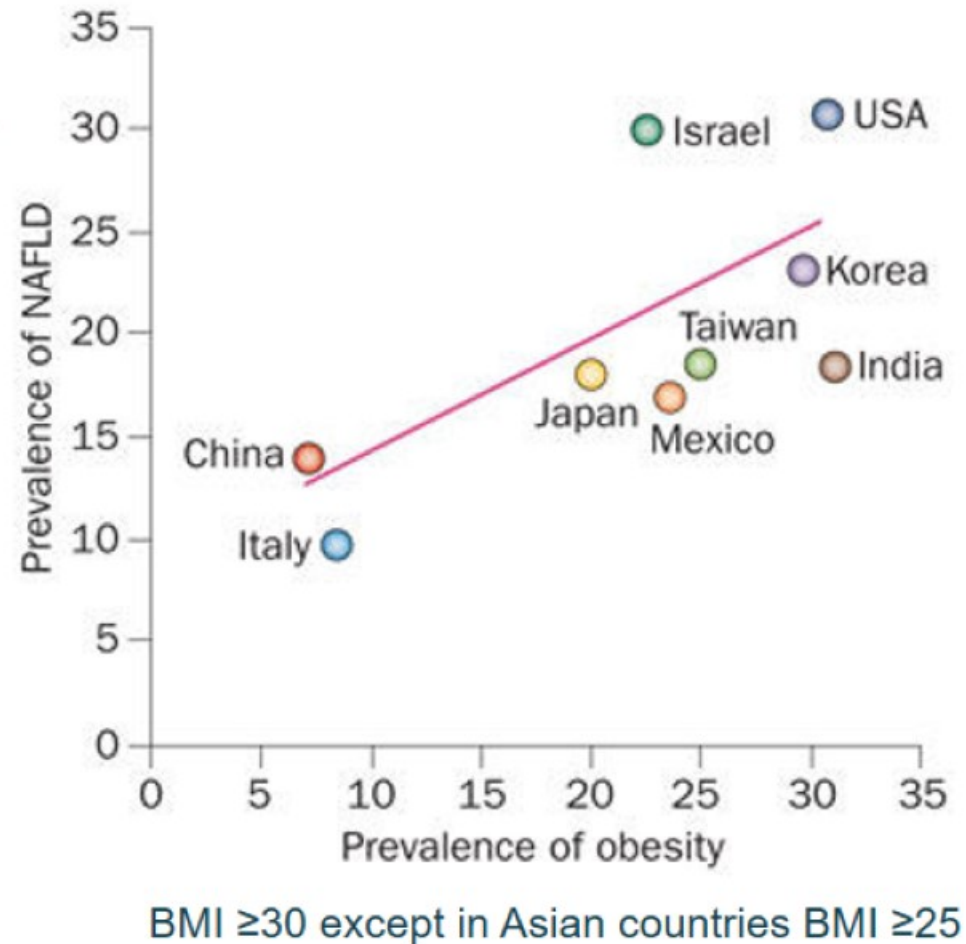
Audience Response Question #1

What is the estimated prevalence of NAFLD in the general US population?

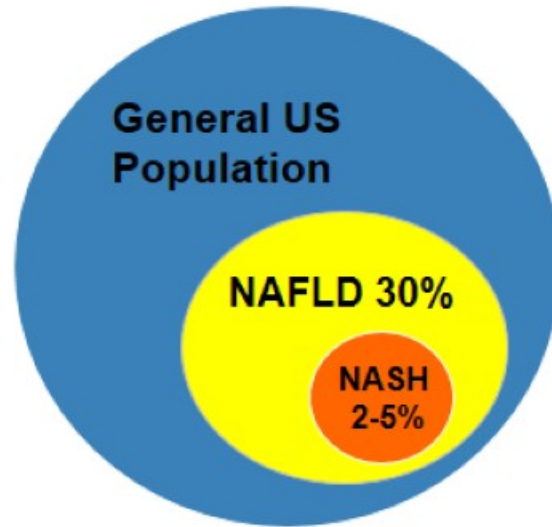
1. 5%
2. 15%
3. 30%
4. 50%

Global Prevalence of NAFLD

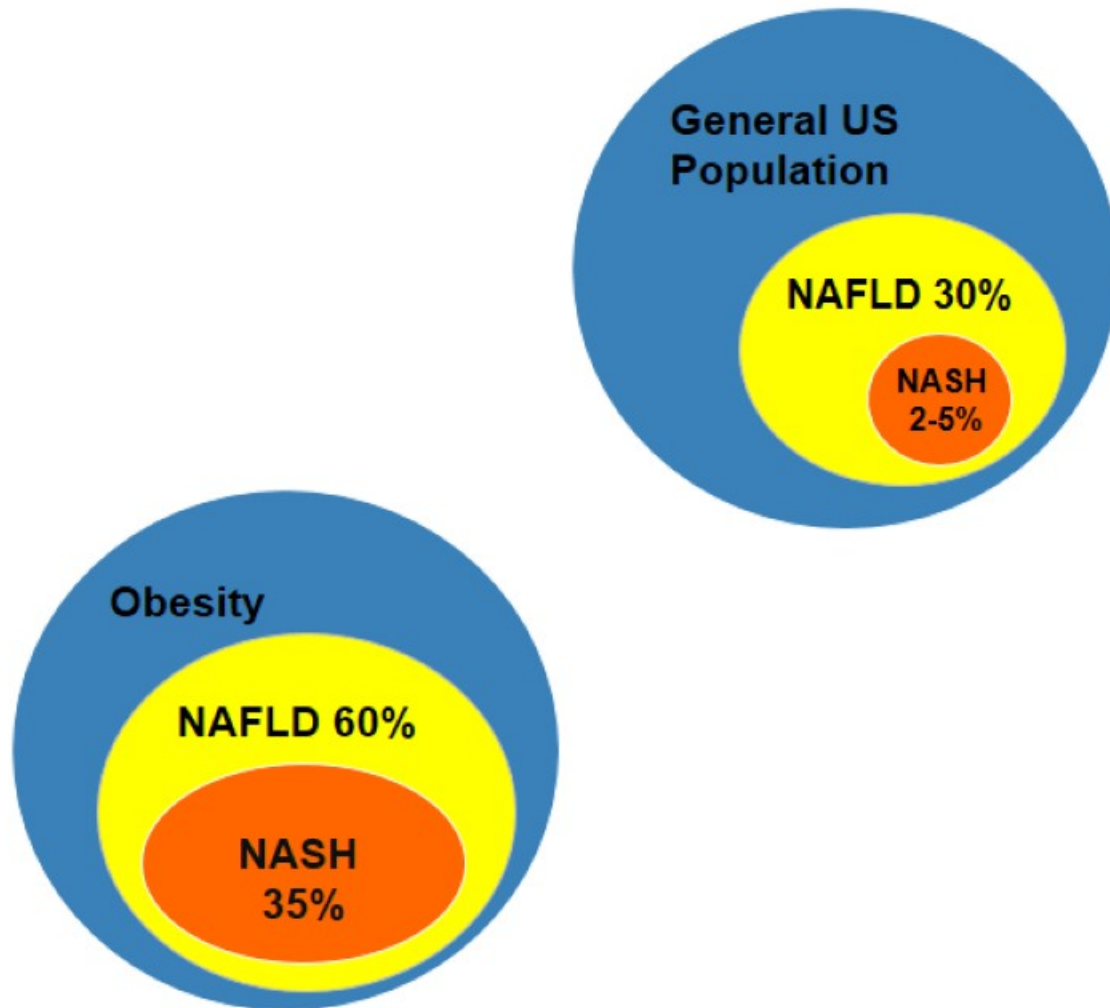
- Estimated global NAFLD prevalence: 25%
- Prevalence in US pop:
 - NAFLD: 30%
 - NASH: 2-5%
- Prevalence varies:
 - Population studied
 - Method used to assess NAFLD



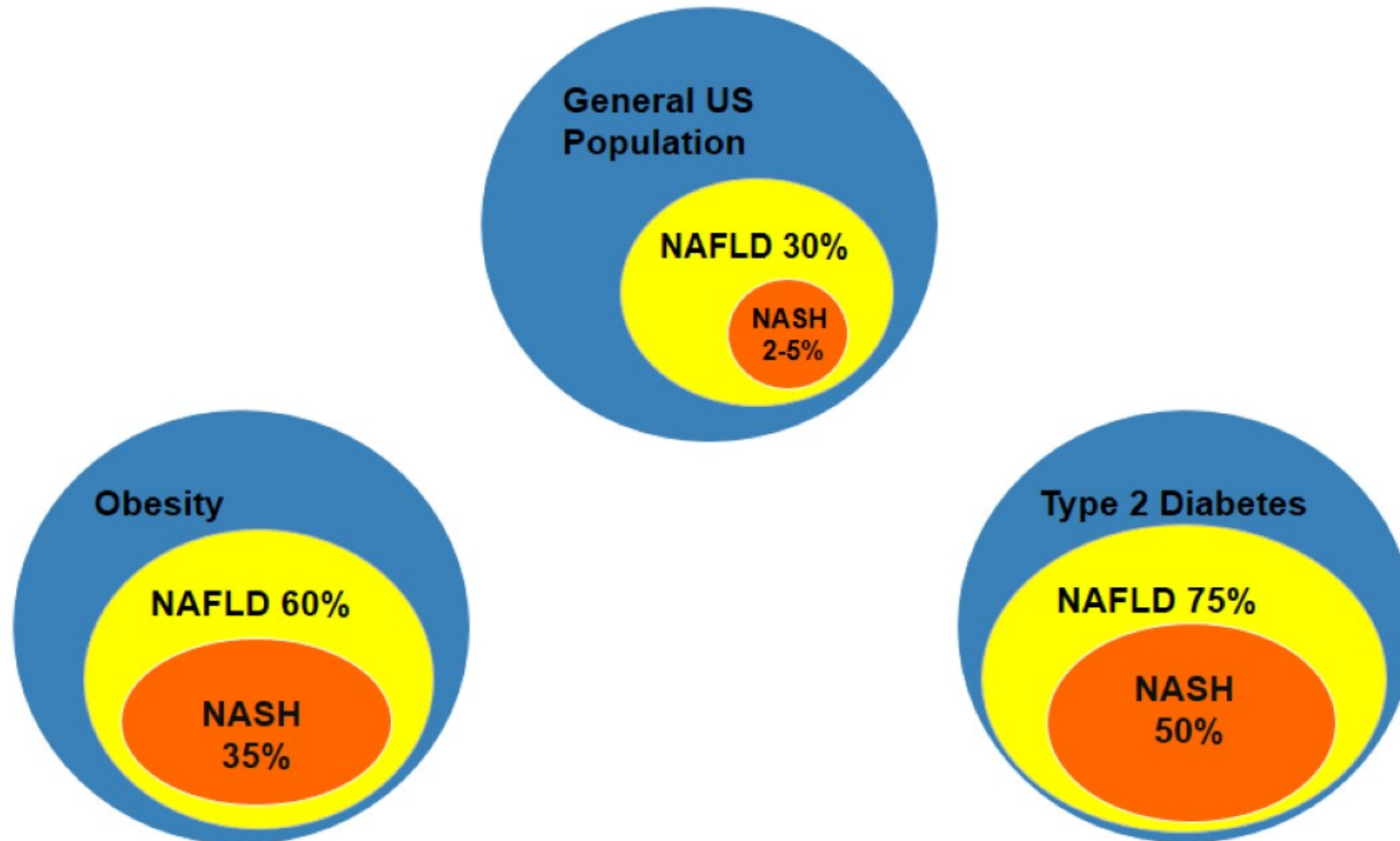
NAFLD prevalence varies by group studied



NAFLD prevalence varies by group studied



NAFLD prevalence varies by group studied



NAFLD Presentation

- Majority are asymptomatic
 - Fatigue is common

NAFLD Presentation

- Majority are asymptomatic
 - Fatigue is common
- Often detected incidentally
 - Elevated liver enzymes
 - Fatty infiltrate or hepatomegaly incidentally noted on abdominal imaging

NAFLD Presentation

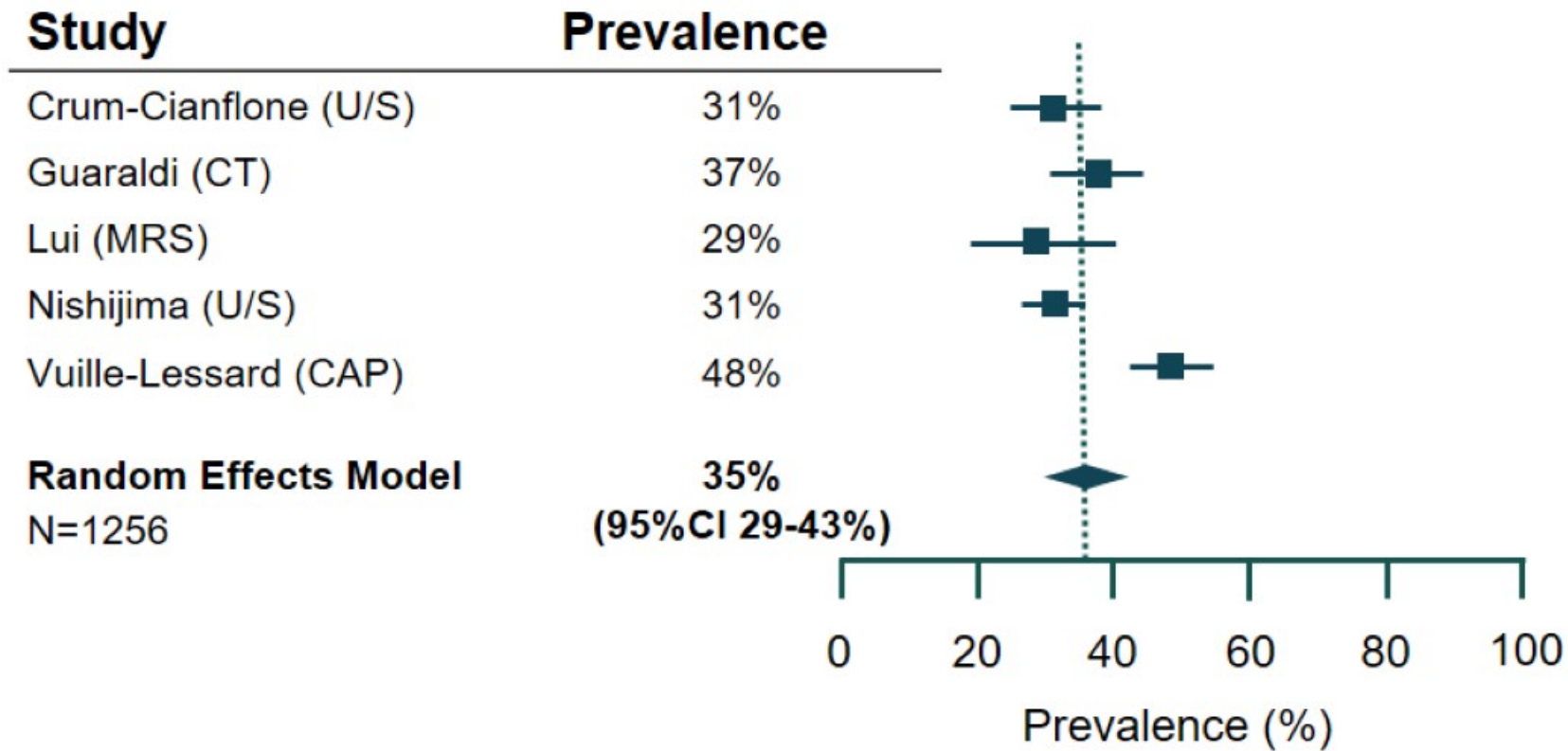
- Majority are asymptomatic
 - Fatigue is common
- Often detected incidentally
 - Elevated liver enzymes
 - Fatty infiltrate or hepatomegaly incidentally noted on abdominal imaging
- Liver enzymes are often normal
 - Not sensitive for NAFLD
 - Correlate poorly with histologic severity

NAFLD prevalence in HIV infection

Study (year)	Country	Number of subjects	Steatosis assessment	Prevalence of NAFLD
Hadigan, C (2007)	USA	33	MR spectroscopy	42%
Moreno-Torres, A (2007)	Spain	29	MR spectroscopy	58%
Mohammed, SS (2007)	Canada	26	Liver biopsy	45%
Guaraldi, G (2008)	Italy	225	CT	37%
Crum-Cianflone, P (2009)	USA	216	Ultrasound	31%
Ingiliz, P (2009)	France	30	Liver biopsy	60%
Nishijima, T (2014)	Japan	435	Ultrasound	31%
Price, JC (2014)	USA	465*	CT	13%
Macias, J (2014)	Spain	505*	CAP**	40%
Lui, G (2016)	Japan	80	MR spectroscopy	29%
Lombardi, R (2016)	Greece	125	Ultrasound	55%
Vuille-Lessard, E (2016)	Canada	300	CAP	48%
Price, JC (2017)	USA	122	MR spectroscopy	28%
Kirkegaard-Klitbo, DM (2020)	Denmark	453	CT	9%

*Includes HIV + HCV or HBV; **CAP= controlled attenuation parameter, obtained with Fibroscan

NAFLD prevalence in HIV infection



Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor

Factors associated with NAFLD in PLWH

Variable	Mean Difference (MD) or Odds Ratio (OR) (95% CI)	P-value
BMI	MD 2.9 (2.4 to 3.7)	p<0.001
Waist circumference	MD 8.0 (5.5 to 10.6)	p<0.001
Type 2 diabetes	OR 1.6 (1.1 to 2.4)	p=0.02
Fasting glucose	MD 0.4 (0.2 to 0.7)	p<0.001
Hypertension	OR 1.8 (1.3 to 2.4)	p=0.001
Triglycerides	MD 62 (24 to 99)	p=0.001
Total cholesterol	MD 6.2 (0.9 to 11.5)	p=0.02
HDL	MD -4.2 (-6.8 to -1.6)	p=0.002
LDL	MD 5.8 (2.0 to 9.6)	p=0.003

6 studies in HIV-monoinfected patients with sufficient data to include in risk factor meta-analysis

Factors associated with NAFLD in PLWH

Variable	Mean Difference (MD) or Odds Ratio (OR) (95% CI)	P-value
Suppressed HIV viral load	OR 1.1 (0.8 to 1.6)	p=0.41
Duration of HIV infection	MD 0.6 (-0.7 to 1.8)	p=0.39
Duration of HAART	MD -15 (-33 to 3.5)	p=0.11
CD4 count	MD 55 (12 to 98)	p=0.01
CD4 nadir	MD -11 (-41 to 20)	p=0.50

- Higher CD4 count associated with NAFLD
 - Well-treated HIV+ patients may have higher risk
 - Age and HAART exposure not associated
 - Insufficient data to meta-analyze exposure by drug class
- Study by Guaraldi found association with cumulative NRTI exposure (may have included D-drug exposure)

Factors associated with NAFLD in PLWH

Factors associated with NAFLD in HIV+ men in MACS (N=465)

	Fatty Liver OR*	p
Abdominal VAT (per 10 cm ²)	1.1 (1.0, 1.1)	<0.01
PNPLA3 (rs738409) non-CC	3.3 (1.7, 6.6)	<0.01
ALT >40 U/L	2.5 (1.2, 5.4)	0.02
HOMA-IR ≥4.9	2.5 (1.2, 5.2)	0.01
Cumulative dideoxynucleoside** (per 5 year exposure)	1.4 (1.1, 2.0)	0.02

*Also adjusted for age, MACS site, HCV status, and raced

**Dideoxynucleoside= didanosine, zidovudine, stavudine, or zalcitabine

Factors associated with NAFLD in PLWH

Factors associated with NAFLD in HIV+ men in MACS (N=465)

	Fatty Liver OR*	p
Abdominal VAT (per 10 cm ²)	1.1 (1.0, 1.1)	<0.01
PNPLA3 (rs738409) non-CC	3.3 (1.7, 6.6)	<0.01
ALT >40 U/L	2.5 (1.2, 5.4)	0.02
HOMA-IR ≥4.9	2.5 (1.2, 5.2)	0.01
Cumulative dideoxynucleoside** (per 5 year exposure)	1.4 (1.1, 2.0)	0.02

*Also adjusted for age, MACS site, HCV status, and raced

**Dideoxynucleoside= didanosine, zidovudine, stavudine, or zalcitabine

Association of 2 SNPs in PNPLA3 in HIV-monoinfected adults with elevated liver enzymes (N=62)

	NASH OR (versus nonspecific changes)	p
PNPLA3 (rs738409) non-C	3.9 (1.6, 9.3)	0.003
PNPLA3 (rs2281135) non-G	3.9 (1.5, 10.1)	0.004

Primary NAFLD vs HIV-associated NAFLD

- PLWH with biopsy-confirmed NAFLD had lower BMI and were more physically active compared to HIV-

TABLE 7. Anthropometry and Body Composition

	HIV-Negative (n = 24)	HIV-Positive (n = 25)	P
BMI (kg/m ²)	30.2 ± 1.0	26.3 ± 0.5	0.001
Weight (kg)	93.4 ± 3.7	82.6 ± 1.9	0.012
Height (cm)	175.7 ± 2.0	177.3 ± 1.4	0.510
Waist circumference (cm)	99.1 ± 2.5	94.0 ± 1.7	0.103
WHR	0.95 ± 0.01	0.95 ± 0.01	0.403
Normal: <0.90			
AMA (cm ²)	46.1 ± 3.4	54.8 ± 4.2	0.115
BIA fat mass (%)	22.7 ± 1.2	19.4 ± 0.9	0.026
Low: 6% to 10%			
Optimal: 11% to 17%			
Moderate: 18% to 20%			
Overweight: 20.1% to 24.9%			
Obesity: >25%			
Lipodystrophy score (Range: 1 [very mild] to 8)	N/A	6.0	N/A

Results are reported as mean ± SEM.
N/A indicates not available.

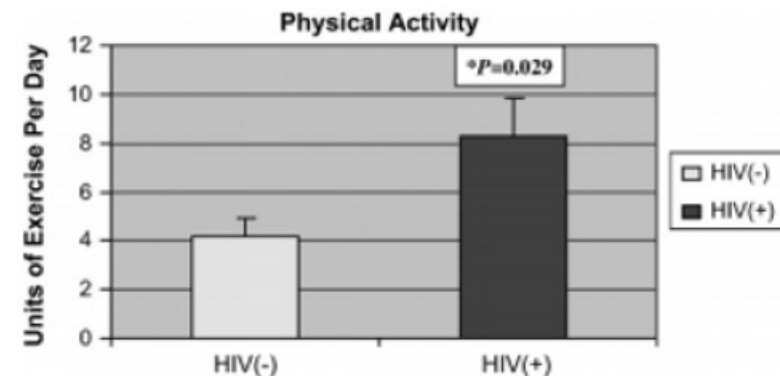
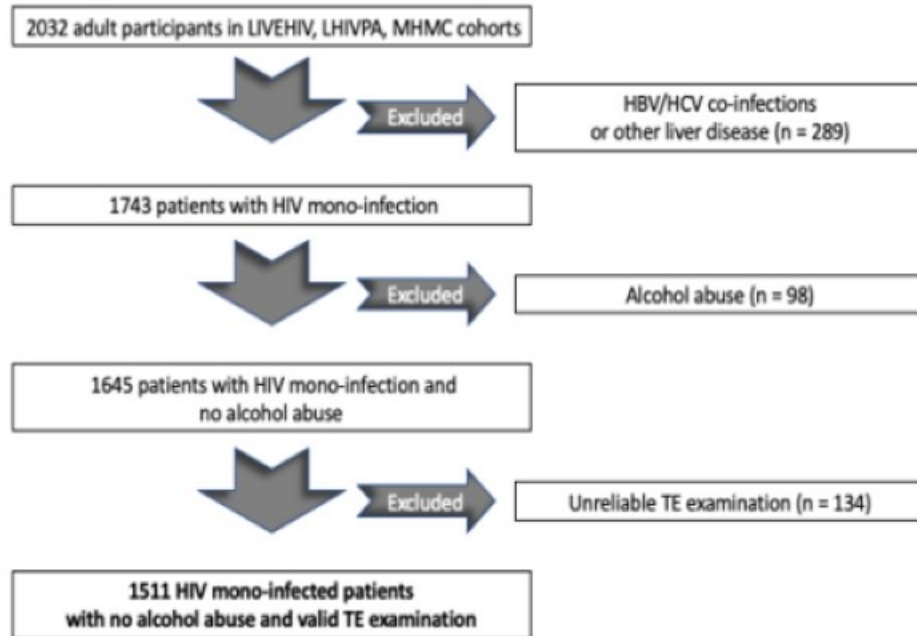
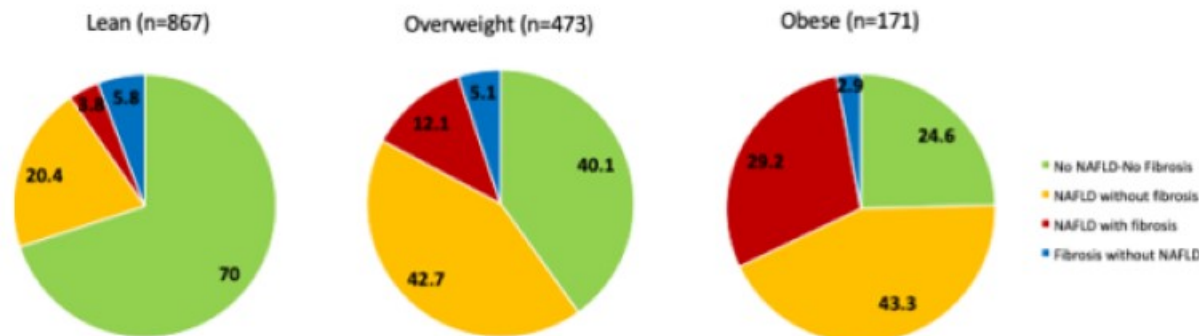


FIGURE 1. Physical activity was measured in units of exercise per day in male HIV-negative and HIV-positive liver biopsy-proven patients with NAFLD and was significantly different between the 2 groups.

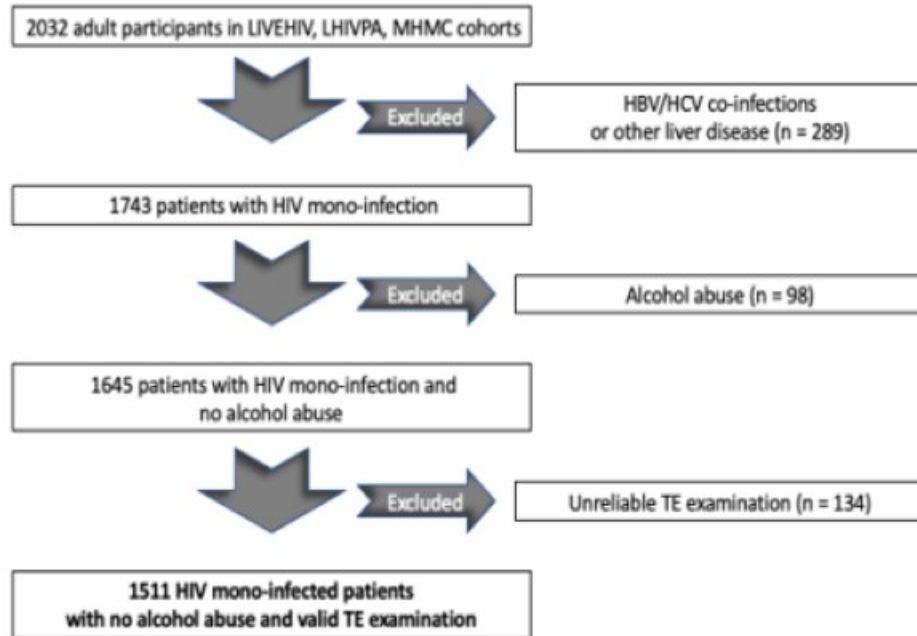
Prevalence of “Lean” NAFLD among PLWH



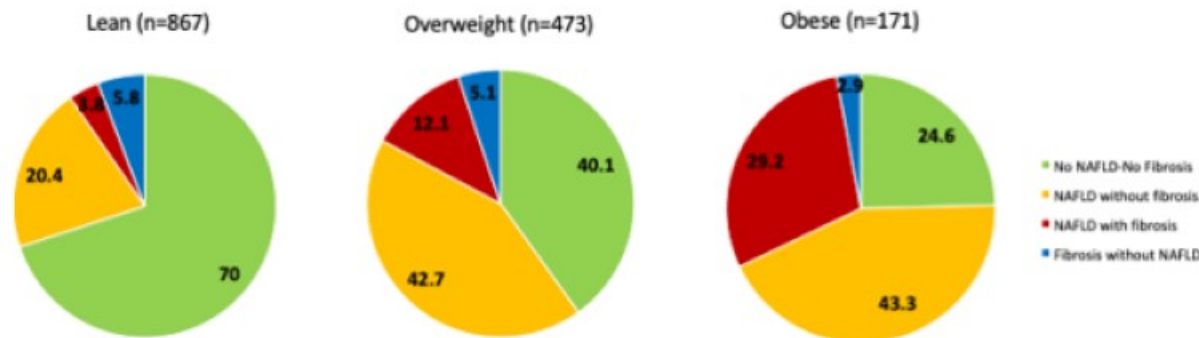
- Lean (BMI < 25 kg/m²): 57%
- Overweight (BMI 25-30 kg/m²): 31%
- Obese (BMI ≥ 30 kg/m²): 11%



Prevalence of “Lean” NAFLD among PLWH



- Lean (BMI < 25 kg/m²): 57%
 - 24% with NAFLD
- Overweight (BMI 25-30 kg/m²): 31%
 - 55% with NAFLD
- Obese (BMI ≥ 30 kg/m²): 11%
 - 73% with NAFLD



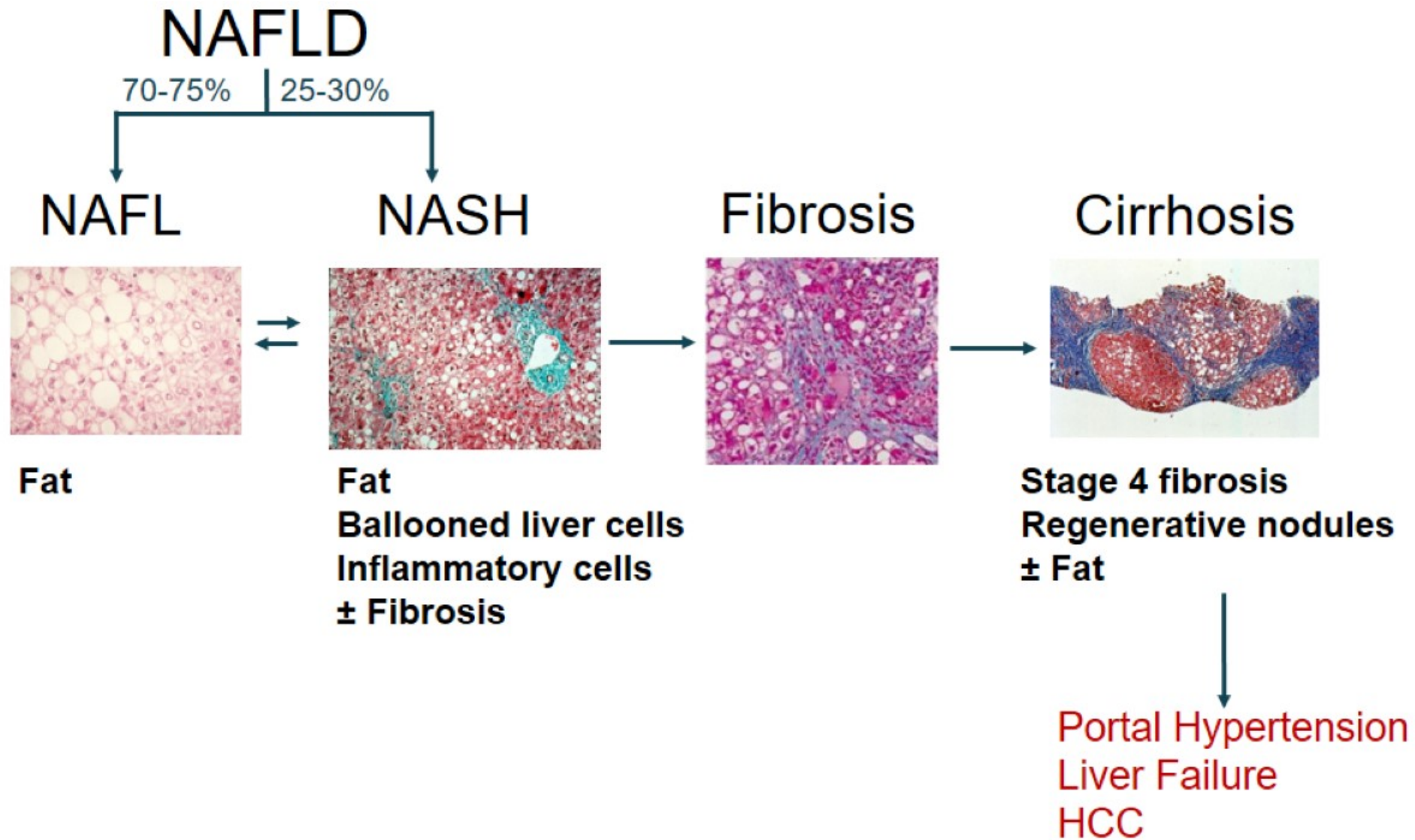
Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor

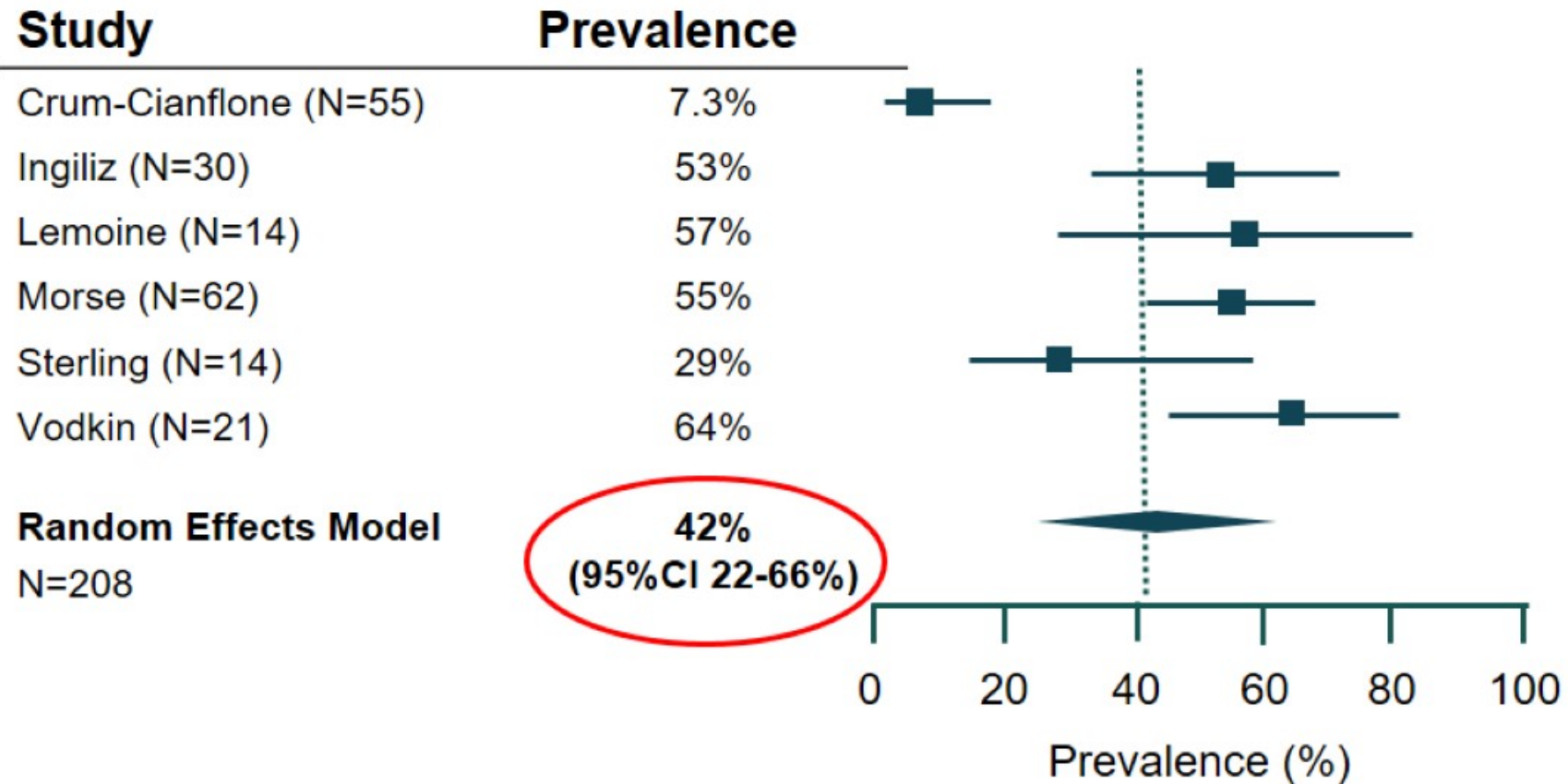
Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor
NAFLD Risk Factors	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic NAFLD at lower BMI's HIV-specific: older NRTI's, "D-drugs", early generation PI's, lipodystrophy

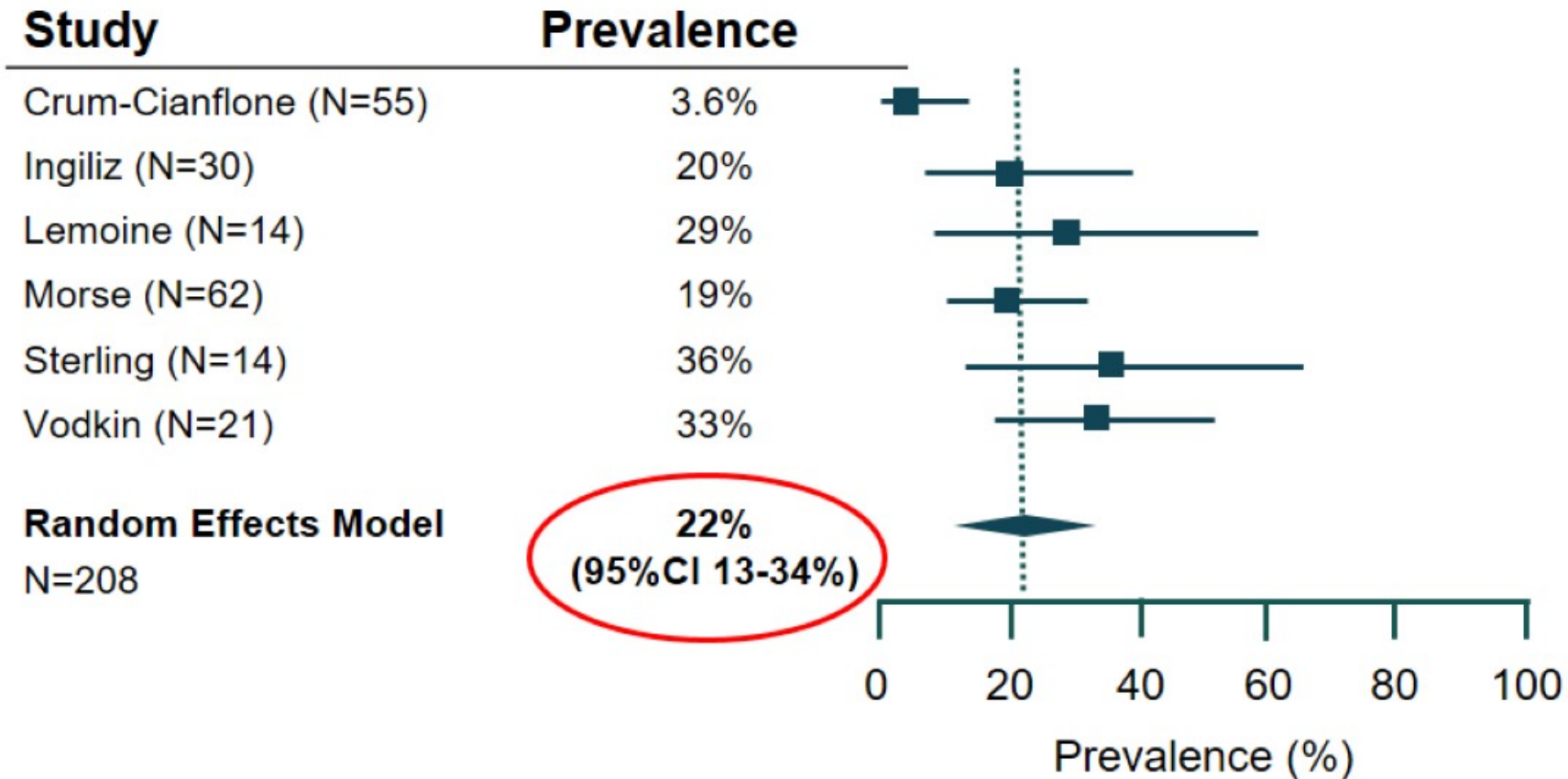
Histologic Spectrum of NAFLD



NASH prevalence in HIV infection

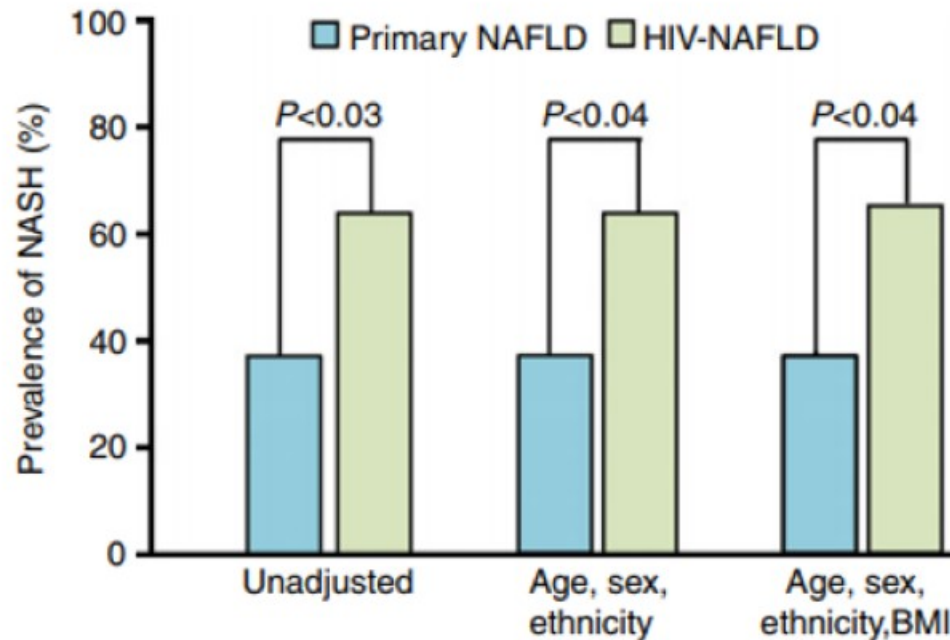


Fibrosis prevalence in HIV infection (F2)



Primary NAFLD vs HIV-associated NAFLD

- Case-control study of HIV+ patients with biopsy-proven NAFLD (N=33) and age-sex-matched HIV- controls with biopsy-proven NAFLD (N=33)



Prevalence of NASH:
64% in HIV+
36% in HIV-

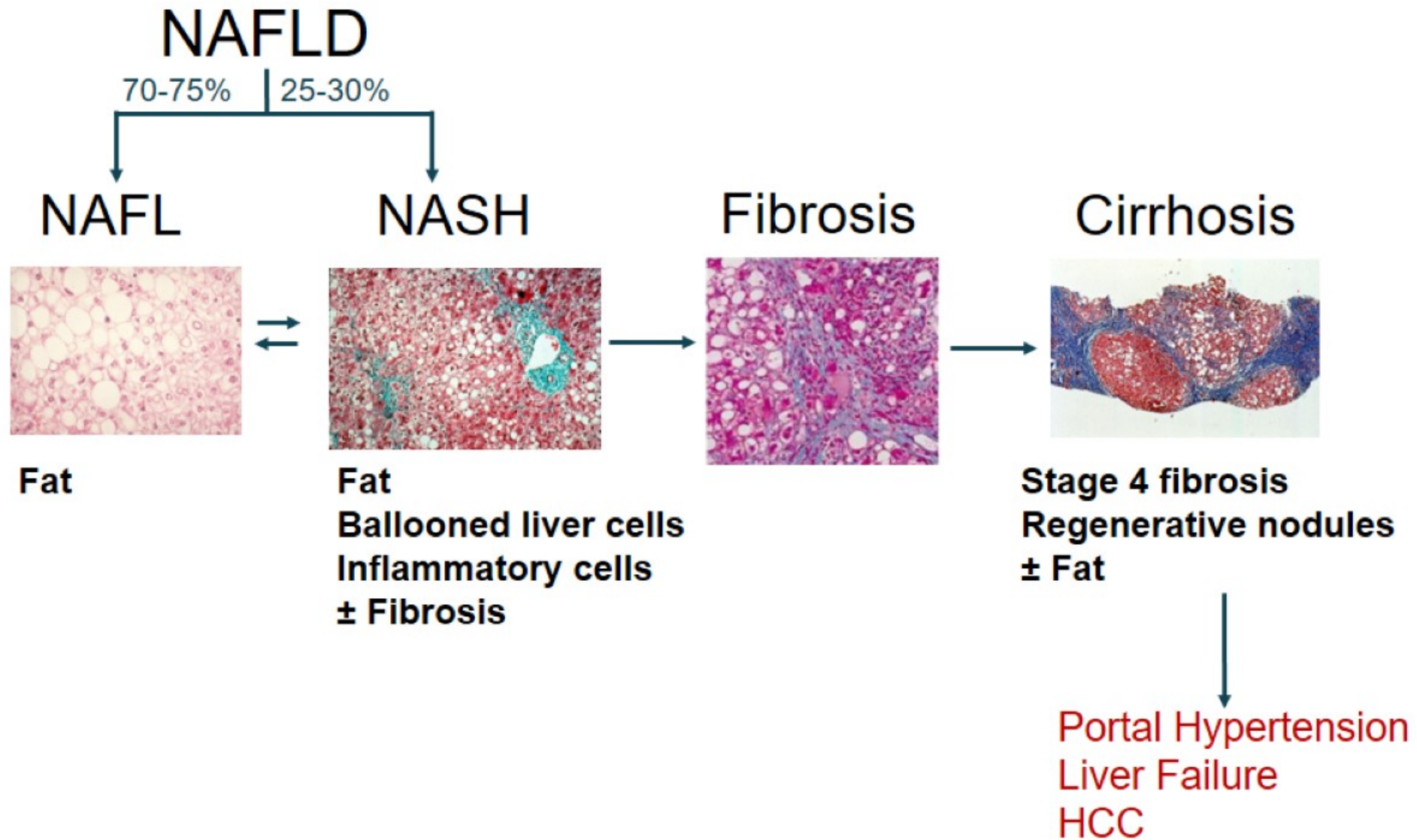
Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor
NAFLD Risk Factors	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic NAFLD at lower BMI's HIV-specific: older NRTI's, "D-drugs", early generation PI's, lipodystrophy

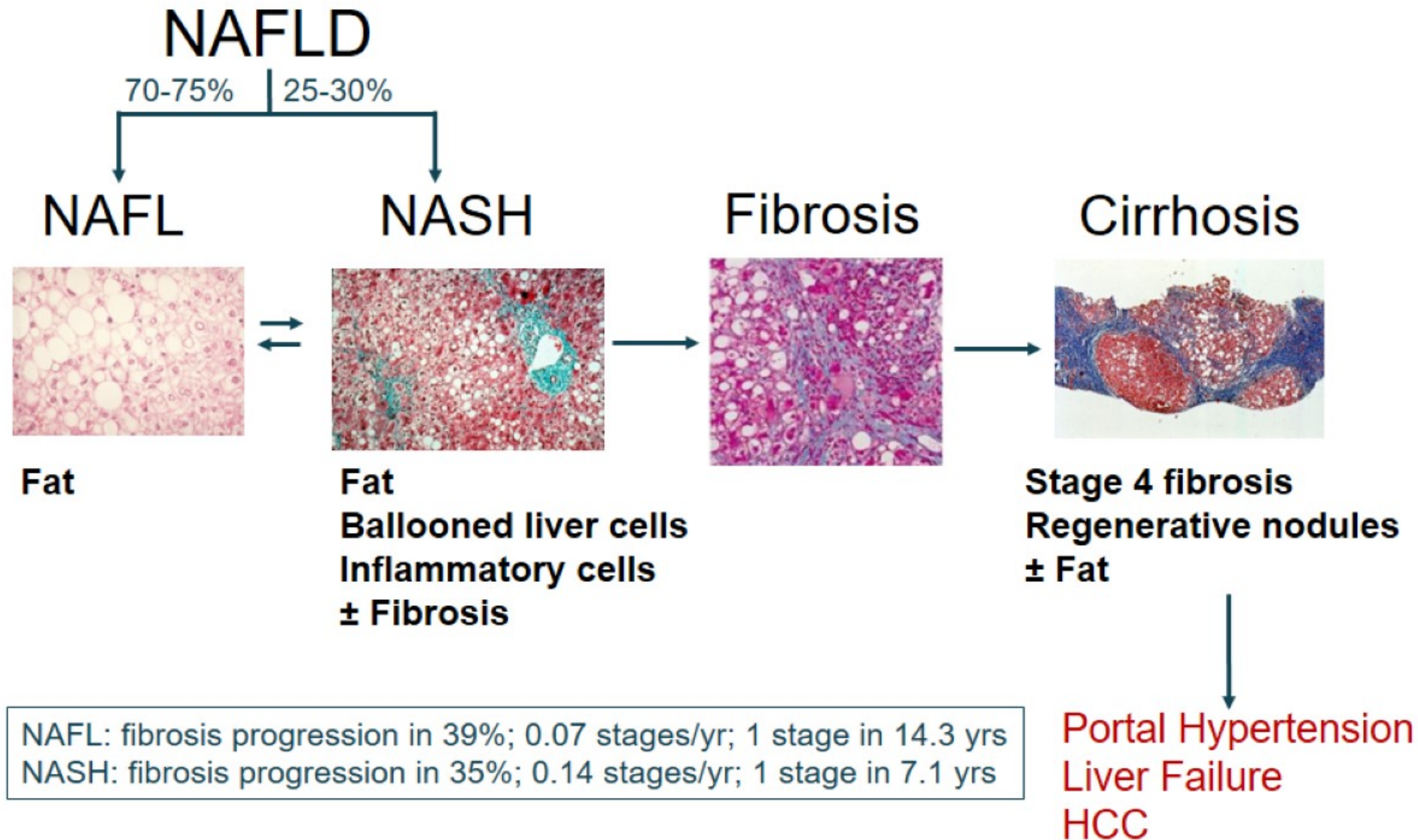
Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor
NAFLD Risk Factors	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic NAFLD at lower BMI's HIV-specific: older NRTI's, "D-drugs", early generation PI's, lipodystrophy
NASH Prevalence	25-30% of NAFLD patients with liver biopsy	42% of NAFLD patients with liver biopsy

Natural history of NAFLD

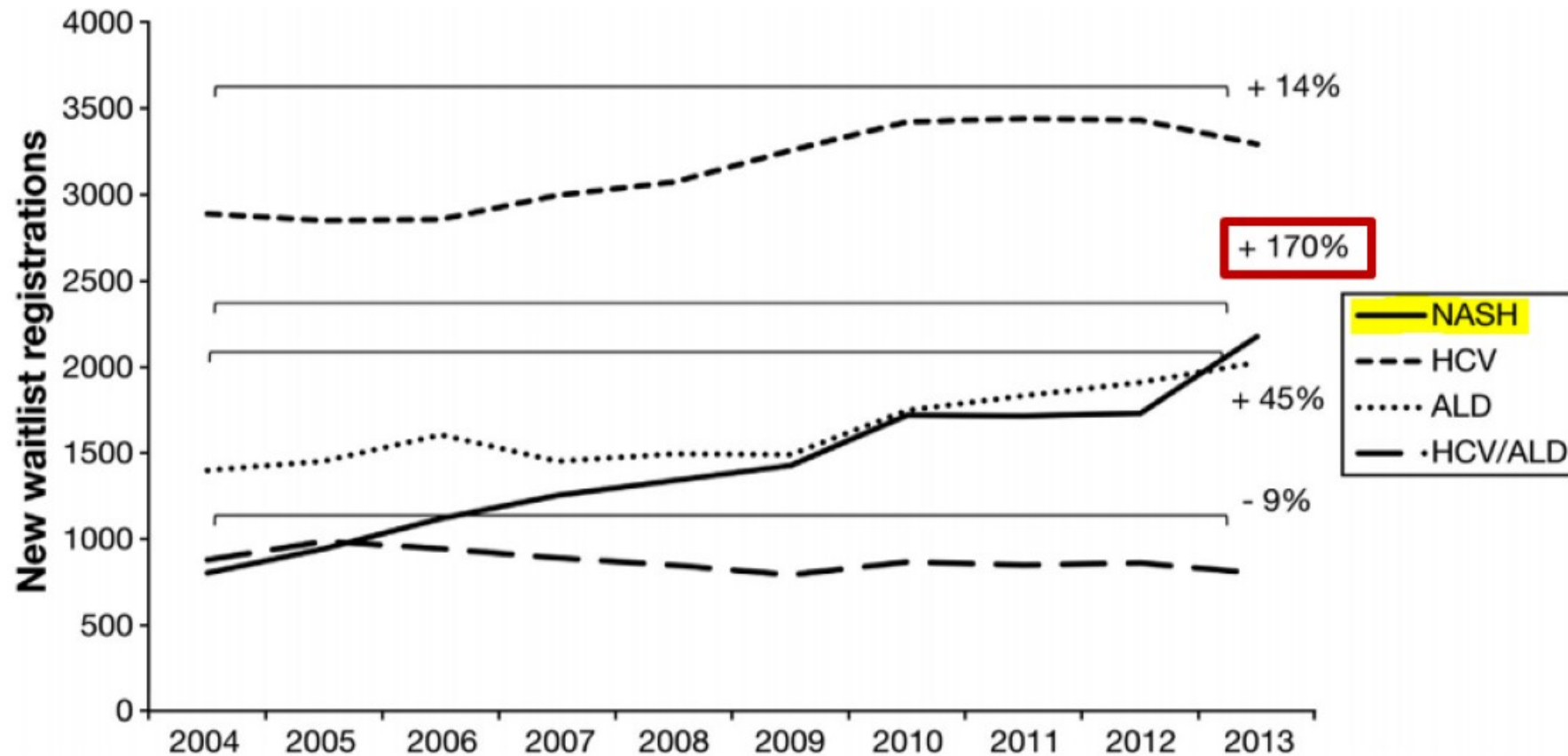


Natural history of NAFLD



Natural history of NAFLD

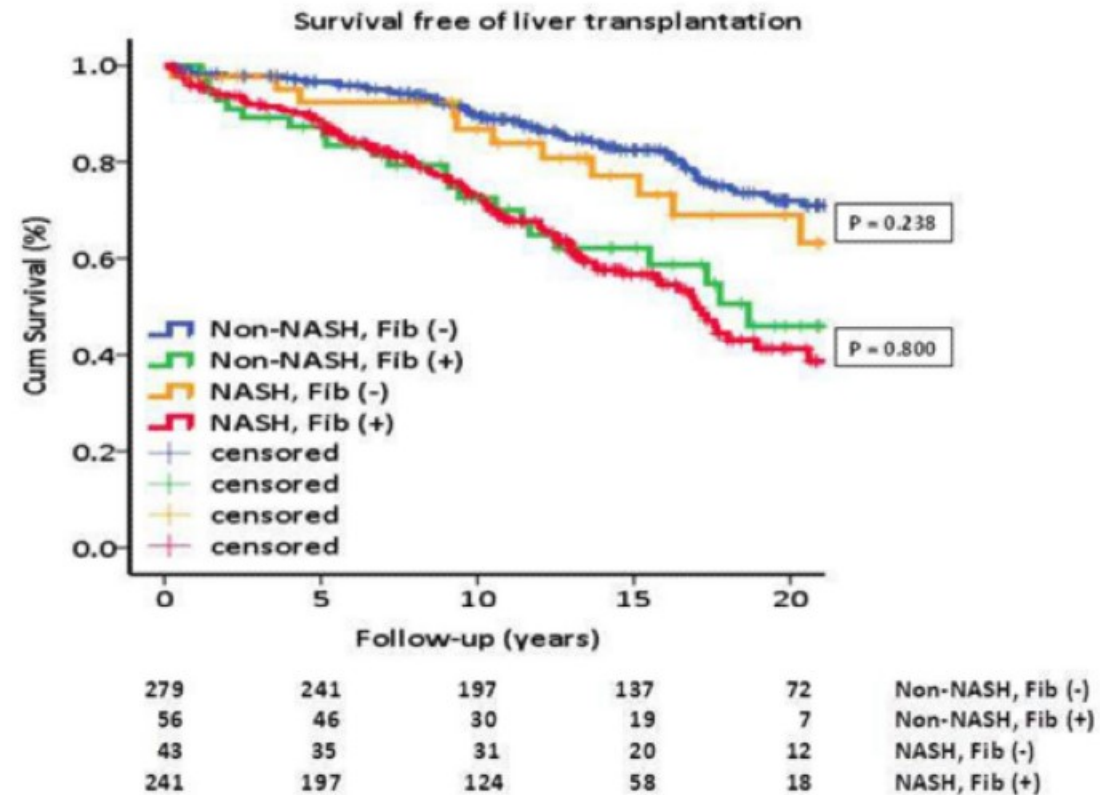
- NASH is rising as an indication for liver transplant; now #2 behind HCV



Natural history of NAFLD

- Liver fibrosis is the strongest predictor of adverse outcomes in NAFLD

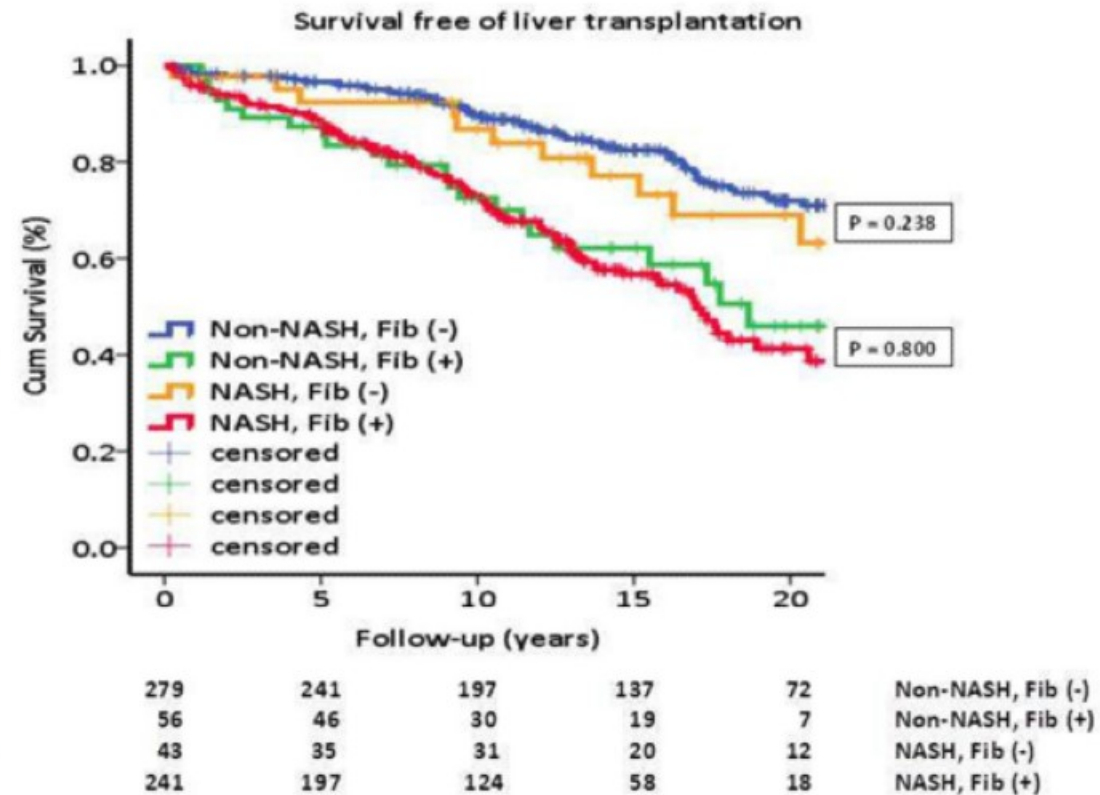
- 619 patients
- Median f/u 12.6 yrs
- 193 (33%) death or liver transplant



Natural history of NAFLD

- Liver fibrosis is the strongest predictor of adverse outcomes in NAFLD
- 619 patients
- Median f/u 12.6 yrs
- 193 (33%) death or liver transplant

Patients with Fibrosis, regardless of NASH, had shorter survival times than without fibrosis



Natural history of NAFLD

▪ Meta-analysis of 5 cohort studies with N = 1495 pts with NAFLD followed for 17,452 pt-yrs

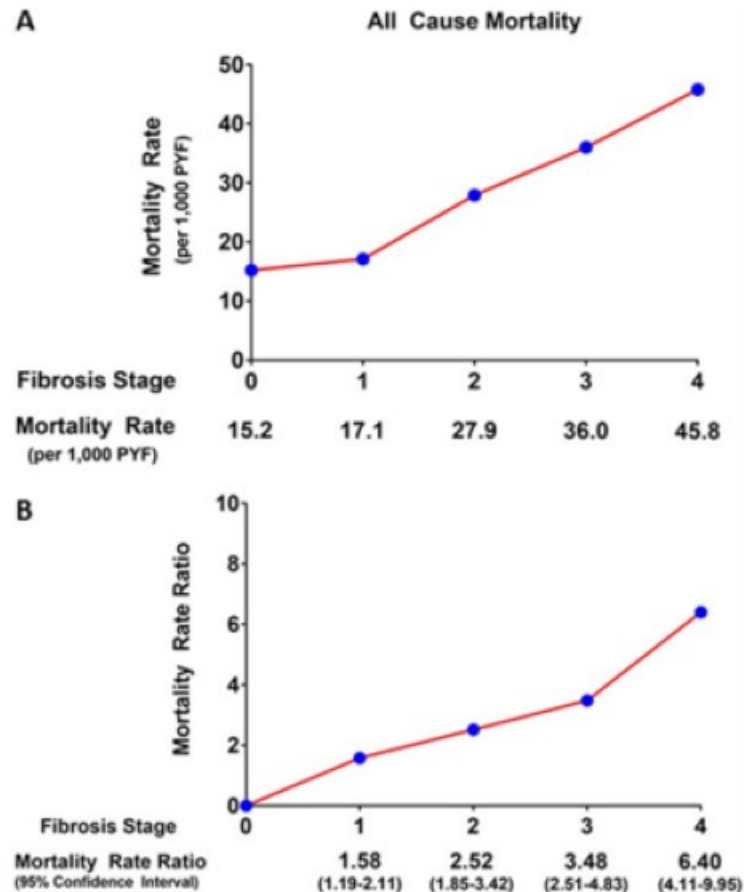


FIG. 2. Fibrosis stage-specific all-cause mortality rate and MRR. (A) Crude all-cause mortality rate by fibrosis stage. (B) All-cause MRR with 95% CIs by fibrosis stage.

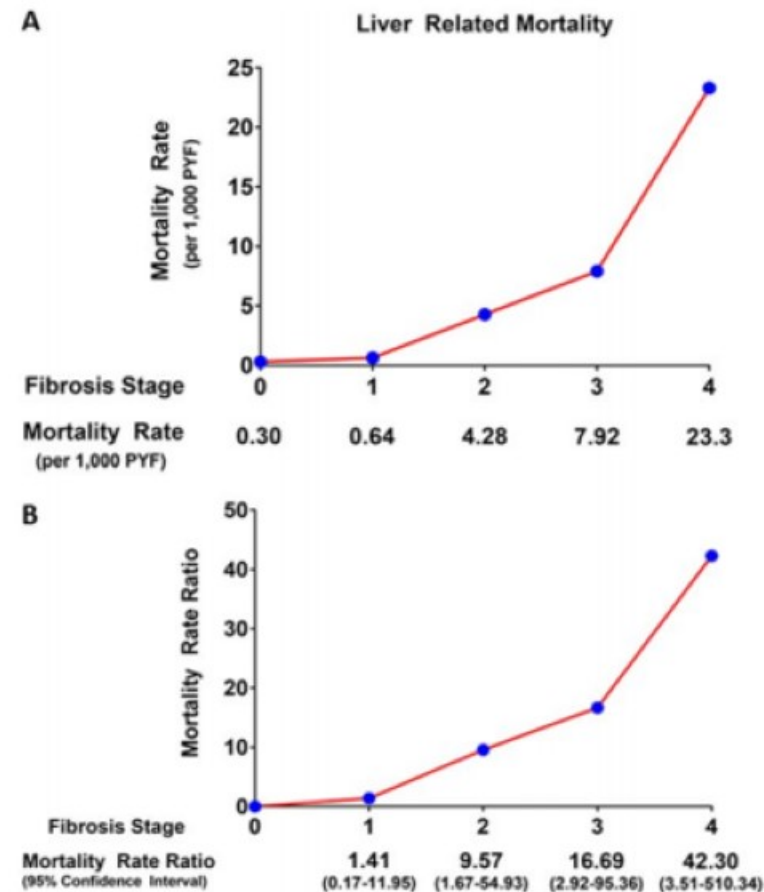


FIG. 4. Fibrosis stage-specific liver-related mortality rate and MRR. (A) Crude liver-related mortality rate by fibrosis stage. (B) Liver-related MRR with 95% CIs by fibrosis stage.

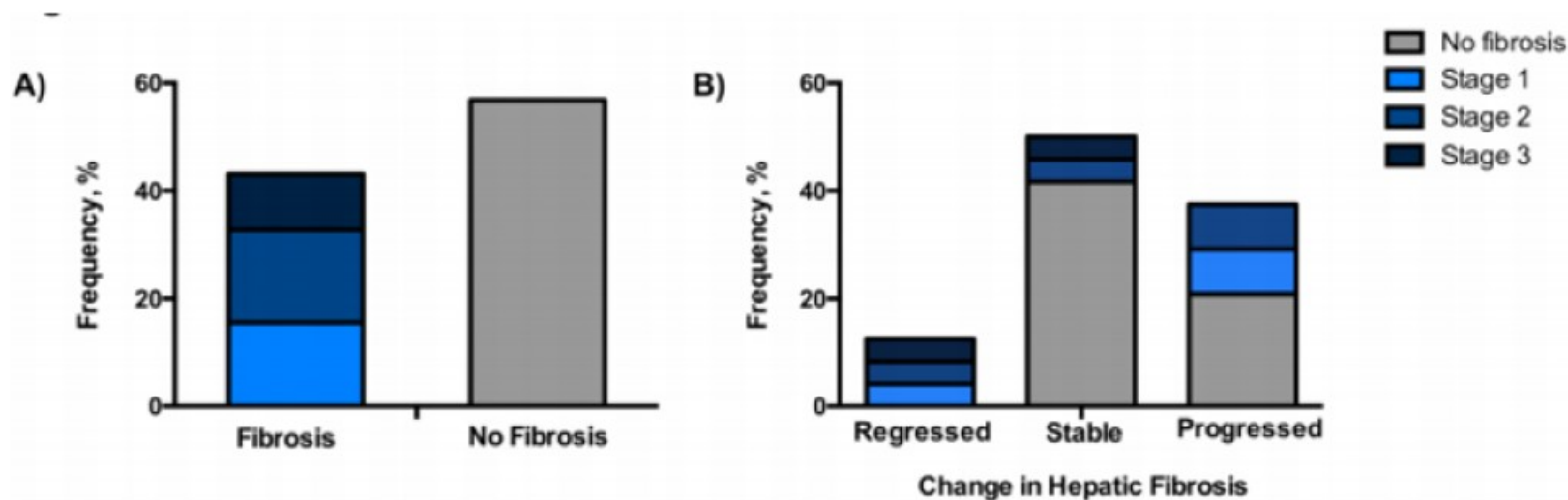
Natural history of NAFLD in PLWH

- 61 participants with HIV-associated NAFLD in RCT of tesamorelin or placebo
- 43% with fibrosis on baseline biopsy



Natural history of NAFLD in PLWH

- 61 participants with HIV-associated NAFLD in RCT of tesamorelin or placebo
- 43% with fibrosis on baseline biopsy



- 24 placebo-treated participants with paired biopsies
 - 38% had fibrosis progression over 12 months
 - Higher visceral fat at baseline increased odds of fibrosis progression by 37% (OR 1.37, 95% CI 1.03,2.07)

Pathogenesis of NAFLD in PLWH

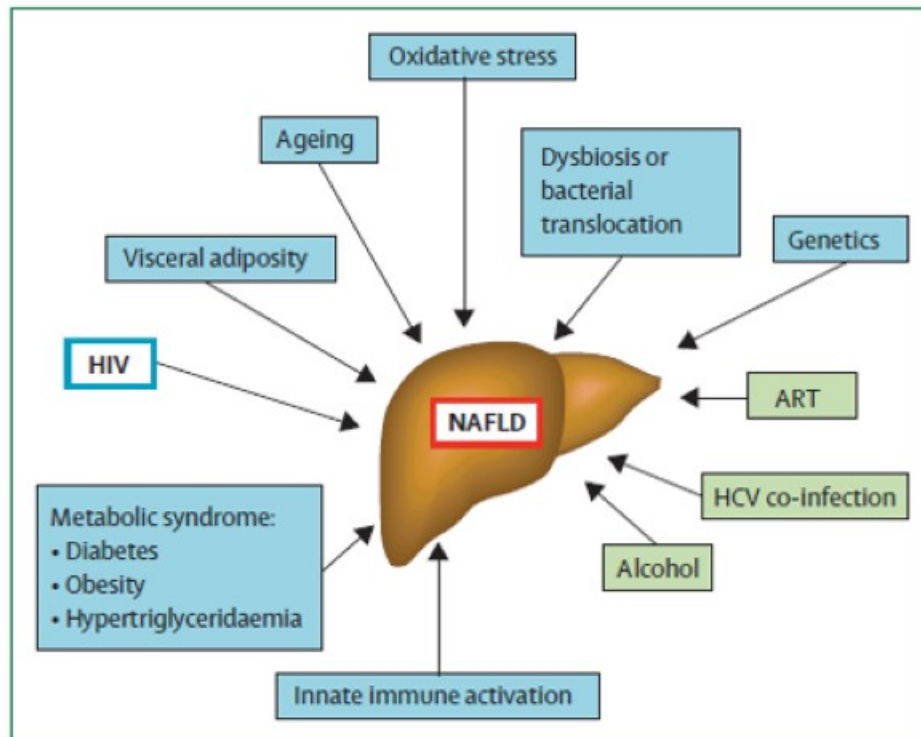


Figure 1: Diagram of the multifactorial pathogenesis of NAFLD in patients with HIV

Blue indicates primary causes and green indicates secondary causes. ART=antiretroviral therapy. HCV=hepatitis C virus. NAFLD=non-alcoholic fatty liver disease.

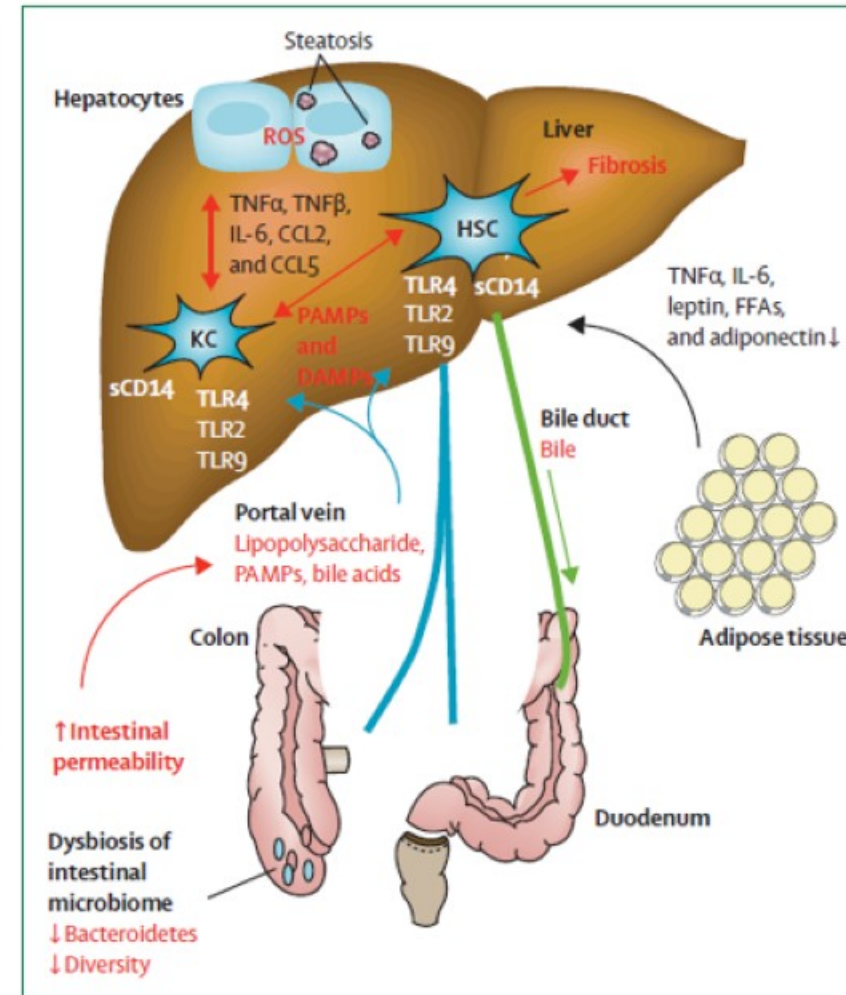


Figure 2: The gut-liver axis in the pathogenesis of non-alcoholic fatty liver disease

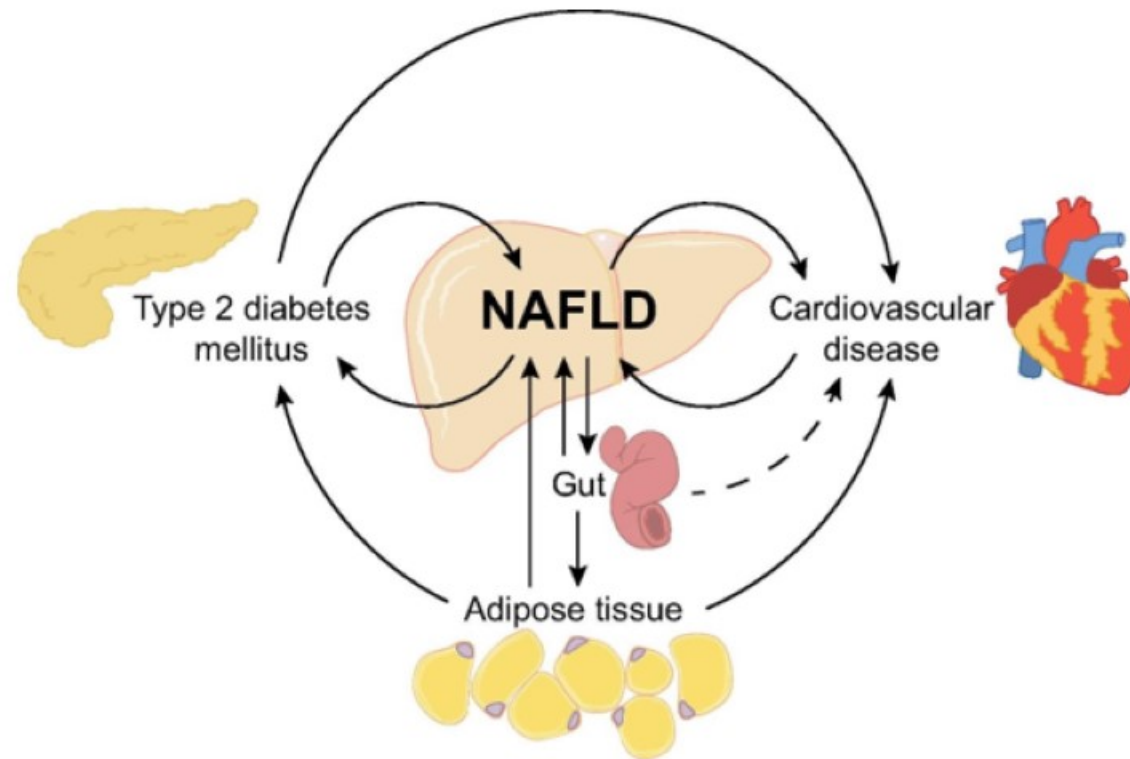
Audience Response Question #2

What is the leading cause of death in patients with NAFLD?

1. Malignancy
2. Cardiovascular disease
3. Liver disease
4. End-stage renal disease

Cardiovascular disease in NAFLD

- Cardiovascular disease is the #1 cause of death in patients with NAFLD (Malignancy #2, Liver #3)
- NAFLD is *independently* associated with subclinical and clinical CVD



Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor
NAFLD Risk Factors	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic NAFLD at lower BMI's HIV-specific: older NRTI's, "D-drugs", early generation PI's, lipodystrophy
NASH Prevalence	25-30% of NAFLD patients with liver biopsy	42% of NAFLD patients with liver biopsy

Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor
NAFLD Risk Factors	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic NAFLD at lower BMI's HIV-specific: older NRTI's, "D-drugs", early generation PI's, lipodystrophy
NASH Prevalence	25-30% of NAFLD patients with liver biopsy	42% of NAFLD patients with liver biopsy
Fibrosis Progression	35-40% progress 1 stage in 7 yrs for NASH	??

Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	Similarly high, HIV not independent risk factor
NAFLD Risk Factors	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic	Obesity, type 2 diabetes, dyslipidemia, metabolic syndrome, hereditary/genetic NAFLD at lower BMI's HIV-specific: older NRTI's, "D-drugs", early generation PI's, lipodystrophy
NASH Prevalence	25-30% of NAFLD patients with liver biopsy	42% of NAFLD patients with liver biopsy
Fibrosis Progression	35-40% progress 1 stage in 7 yrs for NASH	??
Long-term outcomes	Increased CVD risk Increased liver-related and all-cause mortality	Emerging evidence of independent a/w CVD, scant data on long-term outcomes

NAFLD Diagnostic Criteria

- Diagnostic criteria
 - Hepatic steatosis on imaging or liver biopsy
 - No “significant” alcohol intake
 - Absence of other causes of liver disease
 - No medications known to cause hepatic steatosis

NAFLD Diagnostic Criteria

- Diagnostic criteria
 - Hepatic steatosis on imaging or liver biopsy
 - No “significant” alcohol intake
 - Absence of other causes of liver disease
 - No medications known to cause hepatic steatosis

NAFLD is a diagnosis of exclusion

Evaluation of Suspected NAFLD

- Liver tests
- Abdominal ultrasound
- Other serologic evaluation:
 - HBsAg, sAb, cAb
 - HCV Ab

 - [AMA, IgM (for PBC)]
 - ASMA, ANA, IgG
 - A1AT phenotype
 - Iron, Tsat, ferritin
 - Ceruloplasmin age < 45
 - HAV Ab (for vaccination status)

Audience Response Question #3

How can you distinguish between NAFL and NASH?

1. Fibroscan
2. MR Elastography
3. Liver Biopsy

Diagnosis and Staging of NAFL vs NASH

Liver biopsy is the only method to reliably distinguish between NAFL and NASH

Serum markers of fibrosis in NAFLD

▪AST:ALT ratio AST/ALT

▪AST-to-plt ratio index (APRI) $\frac{\text{AST/ upper limit of nl}}{\text{Platelet count (10}^9\text{/L)}} \times 100$

▪FIB-4 $\frac{\text{Age (years) x AST}}{\text{Platelet count (10}^9\text{/L) x } \sqrt{\text{ALT}}}$

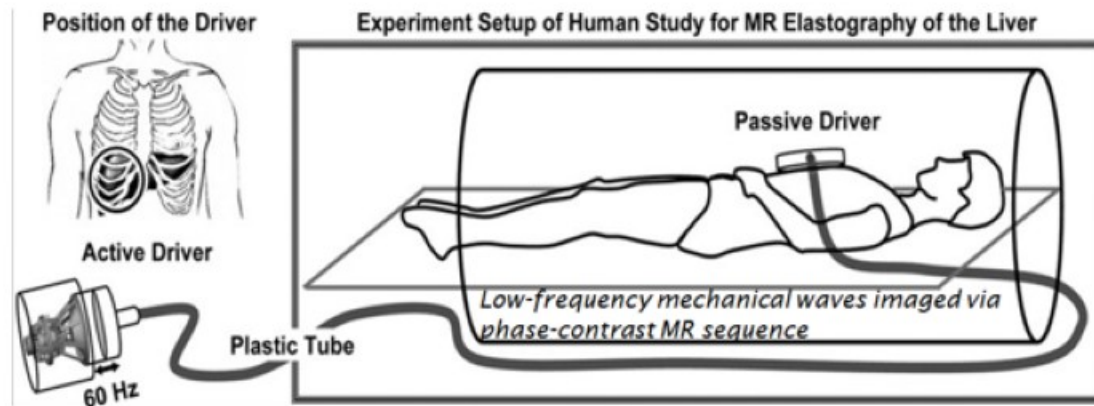
▪NAFLD fibrosis score nafldscore.com

Age (years)	<input type="text"/>
BMI (kg/m ²)	<input type="text"/>
IGF/diabetes	<input type="checkbox"/>
AST	<input type="text"/>
ALT	<input type="text"/>
Platelets (x10 ⁹ /l)	<input type="text"/>
Albumin (g/l)	<input type="text"/>
	<input type="button" value="calculate score"/>

Giannini E, Arch Intern Med, 2003. Wai CT, Hepatology, 2003. Sterling RK, Hepatology, 2006. Angulo P, Hepatology, 2007.

Non-invasive imaging of fibrosis in NAFLD

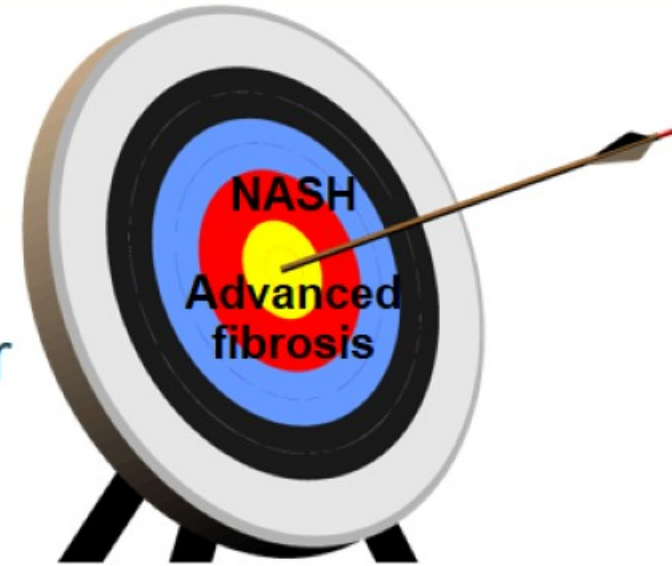
- Vibration controlled transient elastography (VCTE)
- Magnetic resonance elastography (MRE)



Fibrosis test	AUROC \geq F2 HIV- (N=104)	AUROC \geq F2 HIV+ (N=59)
VCTE	0.86 (0.77-0.95)	0.93 (0.85-0.99)
MRE	0.89 (0.83-0.96)	

Indications for Liver Biopsy

- Suspicious for NASH
 - Significant liver enzyme elevation
 - Diabetes
- Suspicious for advanced fibrosis or cirrhosis
 - Thrombocytopenia
 - Imaging (e.g., splenomegaly)
 - Noninvasive assessment: FIB-4, Fibroscan
 - Diabetes
 - Older age
- Unable to rule out other diseases



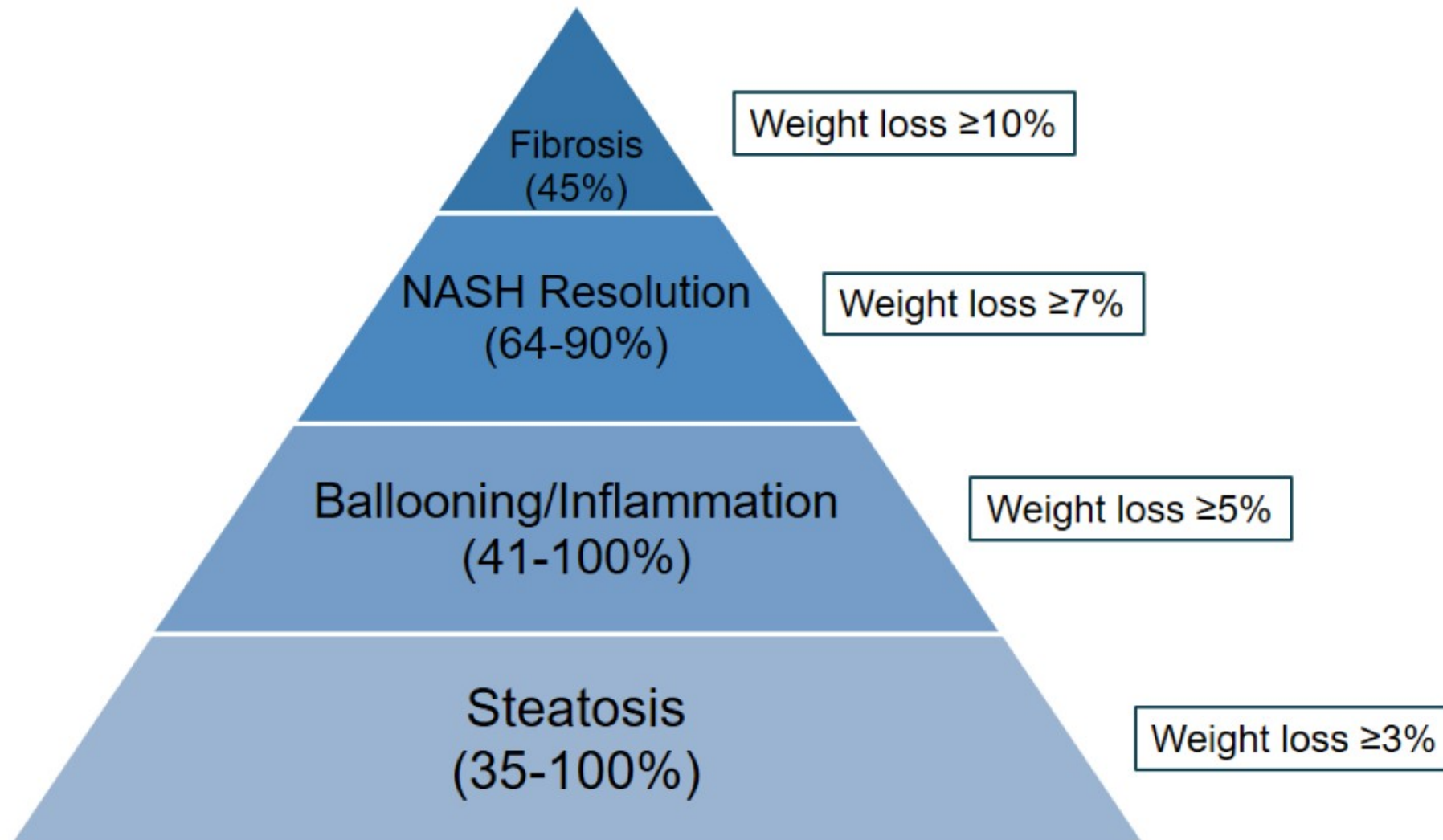
Chalassani N, Hepatology, 2012. Chalassani N, Hepatology, 2017.

Weight loss and NAFLD

- Diet and exercise combination is best
- Avoid fructose-sweetened beverages, added sugars
- Loss of >7-10% weight improves NASH + fibrosis
- Exercise alone reduces liver fat
 - Aerobic >150-250 min/week
 - Resistance training 45 min/day for 3 days/week

Harrison S, Hepatology, 2009. Promrat K, Hepatology, 2010. Vilar-Gomez E, Gastro, 2015.
Chalasani N, Hepatology, 2012

Weight loss impact on NAFLD



Treatment of Metabolic Syndrome in NAFLD

- Statins

- **Safe for use in NAFLD**

- Potential benefits of NAFLD/liver enzyme improvement and reduced risk of liver death or HCC

- Not proven in randomized controlled trials for NAFLD treatment

Treatment of Metabolic Syndrome in NAFLD

- Statins

- Safe for use in NAFLD

- Potential benefits of NAFLD/liver enzyme improvement and reduced risk of liver death or HCC

- Not proven in randomized controlled trials for NAFLD treatment

- Metformin

- Safe for use in NAFLD

- Some studies show improvement in liver biopsy and liver enzymes

- Not proven in randomized controlled trials for NAFLD treatment

Summary of NAFLD in PLWH

- NAFLD is common in PLWH
 - Prevalence is likely to increase with aging HIV+ population

Summary of NAFLD in PLWH

- NAFLD is common in PLWH
 - Prevalence is likely to increase with aging HIV+ population
- Similarities with primary NAFLD
 - Main risk factors are metabolic, genetic/hereditary

Summary of NAFLD in PLWH

- NAFLD is common in PLWH
 - Prevalence is likely to increase with aging HIV+ population
- Similarities with primary NAFLD
 - Main risk factors are metabolic, genetic/hereditary
- Differences from primary NAFLD
 - At higher risk for “lean” NAFLD
 - Steatogenic and fibrotic effects of HIV/ART likely impact the natural history: potentially more NASH and fibrosis

Summary of NAFLD in PLWH

- NAFLD is an umbrella term that encompasses the full spectrum of disease
 - NASH >>> NAFL has risk of progression to cirrhosis
 - Biopsy is needed to distinguish NASH vs NAFL

Summary of NAFLD in PLWH

- NAFLD is an umbrella term that encompasses the full spectrum of disease
 - NASH >>> NAFL has risk of progression to cirrhosis
 - Biopsy is needed to distinguish NASH vs NAFL
- Management hinges weight loss, exercise, avoiding added carbohydrates, and metabolic syndrome control

Summary of NAFLD in PLWH

- NAFLD is an umbrella term that encompasses the full spectrum of disease
 - NASH >>> NAFL has risk of progression to cirrhosis
 - Biopsy is needed to distinguish NASH vs NAFL
- Management hinges weight loss, exercise, avoiding added carbohydrates, and metabolic syndrome control
- Key knowledge gaps exist in HIV-associated NAFLD
 - Rate of and risk factors for fibrosis progression
 - Long-term outcomes
 - Pharmacologic management

Posttest Question #1

What is the estimated prevalence of NAFLD in the general US population?

1. 5%
2. 15%
3. 30%
4. 50%

Posttest Question #2

What is the leading cause of death in patients with NAFLD?

1. Malignancy
2. Cardiovascular disease
3. Liver disease
4. End-stage renal disease

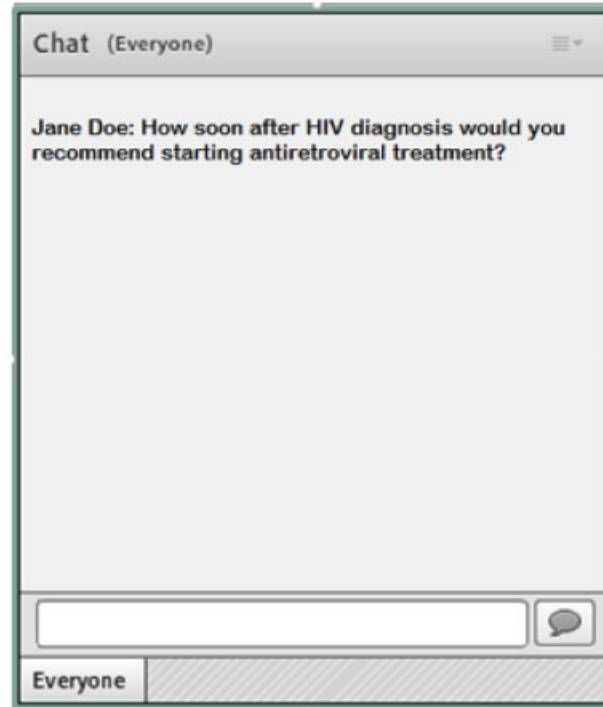
Posttest Question #3

How can you distinguish between NAFL and NASH?

1. Fibroscan
2. MR Elastography
3. Liver Biopsy

QUESTION-AND-ANSWER SESSION

Please type your questions into the CHAT BOX.



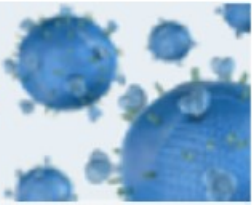
The webinar will be available for on-demand viewing and CME credits at <https://www.iasusa.org/activities/webinars/archived-cme-webinars/>

CME credit cannot be claimed for **both** the live and on-demand versions of the same webinar.

Evaluations, and information on how to claim CME, pharmacy, nursing, or pharmacotherapy credits, and certificate of participation, will be **emailed by 5 PM PT tomorrow.**

Not Receiving Our Emails?

Check the FAQ section on the IAS-USA website for more information



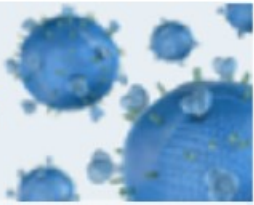
IAS-USA **VIRTUAL Update on HIV:
A Focus on Antiretroviral Therapy, New ART Drugs and
Strategies, and the Intersection of COVID-19 and HIV**



West Coast

Monday, June 29
10:00 AM - 3:15 PM PT

To register, visit <https://www.iasusa.org/>



IAS-USA **VIRTUAL Update on HIV:
A Focus on Antiretroviral Therapy, New ART Drugs and
Strategies, and the Intersection of COVID-19 and HIV**



West Coast

Monday, June 29
10:00 AM - 3:15 PM PT



East Coast

Tuesday, July 14
10:00 AM - 2:50 PM PT

To register, visit <https://www.iasusa.org/>



IAS-USA **VIRTUAL Update on HIV:
A Focus on Antiretroviral Therapy, New ART Drugs and
Strategies, and the Intersection of COVID-19 and HIV**



West Coast

Monday, June 29
10:00 AM - 3:15 PM PT



East Coast

Tuesday, July 14
10:00 AM - 2:50 PM PT



Midwest

Thursday, July 30
10:00 AM - 2:45 PM PT

To register, visit <https://www.iasusa.org/>

COVID-19: What We Know Today That We Didn't Know Yesterday and Other Scientific Conversations

An IAS-USA roundtable series that will go over updates regarding COVID-19



Paul A. Volberding, MD
George Rutherford, MD
Early June
TBD



Jeanne M. Murrain, MD
Judith S. Currier, MD
Wednesday, June 17
4:00 PM – 5:00 PM PT

More details will be release on <https://www.iasusa.org/>

<https://www.iasusa.org/activities/webinars/upcoming-webinars/>

HIV Infection and the Kidney in 2020

Christina M. Wyatt, MD
Tuesday, June 23, 2020

**HIV 101: Fundamentals of HIV Infection and
Applications of Antiretroviral Therapy**

Michael S. Saag, MD
Rajesh T. Gandhi, MD
Tuesday, June 30, 2020

**Weigh Gain: A Growing Issue in
Antiretroviral Therapy**

John R. Koethe, MD
Tuesday, July 21, 2020

**Physical Function and Frailty in HIV: What
Does It Mean, How Do We Measure It, Why
Should We Care, and What Can We Do?**

Kristine M. Erlandson, MD MS
Tuesday, July 28, 2020

**Management and Prevention of HIV Infection
Among Transgender Adults**

Asa E. Radix, MD
Tuesday, August 18, 2020

Liver Transplant Among People With HIV

Christine M. Durand, MD
Tuesday, August 25, 2020

**PEP to PrEP Transitions: Evidence and
Innovations**

Douglas S. Krakower, MD
Tuesday, October 13, 2020

*Register
Now!*

<https://www.iasusa.org/activities/webinars/upcoming-webinars/>

HIV Infection and the Kidney in 2020

Christina M. Wyatt, MD
Tuesday, June 23, 2020

HIV 101: Fundamentals of HIV Infection and Applications of Antiretroviral Therapy

Michael S. Saag, MD
Rajesh T. Gandhi, MD
Tuesday, June 30, 2020

Weigh Gain: A Growing Issue in Antiretroviral Therapy

John R. Koethe, MD
Tuesday, July 21, 2020

Physical Function and Frailty in HIV: What Does It Mean, How Do We Measure It, Why Should We Care, and What Can We Do?

Kristine M. Erlandson, MD MS
Tuesday, July 28, 2020

Management and Prevention of HIV Infection Among Transgender Adults

Asa E. Radix, MD
Tuesday, August 18, 2020

Liver Transplant Among People With HIV

Christine M. Durand, MD
Tuesday, August 25, 2020

PEP to PrEP Transitions: Evidence and Innovations

Douglas S. Krakower, MD
Tuesday, October 13, 2020

4-PART Webinar Series on Pain and Addiction:

PART 1—Chronic Pain in People With HIV: An Evidence-Based, Practical

Jessica Merlin, MD, PhD, MBA
Tuesday, September 1, 2020

PART 2—Medical Cannabis in People With HIV: What's the Evidence?

Jessica Merlin, MD, PhD, MBA
Tuesday, October 6, 2020

PART 3—Opioid Use and HIV/Hepatitis C Made Easy: A Practical Implementation of the Evidence

R. Douglas Bruce, MD, MA, MSc
Tuesday, November 3, 2020

PART 4—More Than One Problem: Mental Illness as a Contributing Factor of Pain and Substance Use in People With HIV

R. Douglas Bruce, MD, MA, MSc
Tuesday, December 1, 2020

Thank You

- To our presenter, Dr Jennifer C. Price, MD
- To the audience for your participation
- To the heroic medical community working 24/7 in untenable environments and situations in response to the COVID-19 pandemic