



INTERNATIONAL CONFERENCE ON
VIRAL HEPATITIS

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NASH - The New Epidemic in HIV-Coinfected Patients?

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Outline:

- Case definition and HIV effects
- Epidemiology
- Diagnostic modalities- CAP considerations
- Practical management implications for HIV providers
- Issues on ART management

September 2015: The Intake appointment

47 yo MSM diagnosed with HIV in 1996 in Spain. Health care worker. Denied any prior AIDS defining illnesses. Denied Drugs or alcohol.

HIV history:

- 2002-2006: TDF + 3TC + Lopinavir/ritonavir
- 2007-2014: coformulated Atripla
- 2014-present: truvada + raltegravir. **Current CD4: 700 (39%) and HIV VL undetectable.**

Physical Exam:

BP 133/85 mmHg | Pulse 88 | Temp 96.8 F (36 C) | Resp 18 | Ht 5' 10" (1.778 m) |
Wt 97.523 kg (215 lb) | BMI 30.85 kg/m²

Besides mild central fat accumulation his physical exam was unremarkable.

Main laboratory intake results

Metabolic profile

- Total cholesterol: 152 mg/dl
- **Triglycerides: 217 mg/dl (H)**
- Direct LDL: 102 mg/dl
- Glucose: 80
- SCr: 1.00

Liver profile

- Albumin: 4.40
- T. Bilirubin: 0.5
- ALP: 77
- **AST: 53 (H)**
- **ALT: 111 (H)**

General hematologic parameters

- WBC: 5.7
- HGB: 15.90
- PLT: 267
- INR: 1.0

Common causes of infectious hepatitis part of routine HIV intake labs

- Hepatitis A Ab IgG: Reactive
- Hepatitis C Ab: Non-reactive
- Hepatitis B Ig Core: Non-reactive
- Hepatitis B s Antigen: Non-reactive
- Hepatitis B s Ab: Reactive (164)
- Syphilis EIA: Non-reactive

November 2015: Liver ultrasound

The liver measures 16.6 cm in long axis. It is increased in echogenicity. There is no intra or extra hepatic bile duct dilation. The common bile duct measures for 9 mm. The gallbladder is normal with no calculi, sludge or wall thickening. No ascites is seen.

The visualized aorta and inferior vena cava are within normal limits.

IMPRESSION:

Mild hepatomegaly with fatty infiltration of the liver.

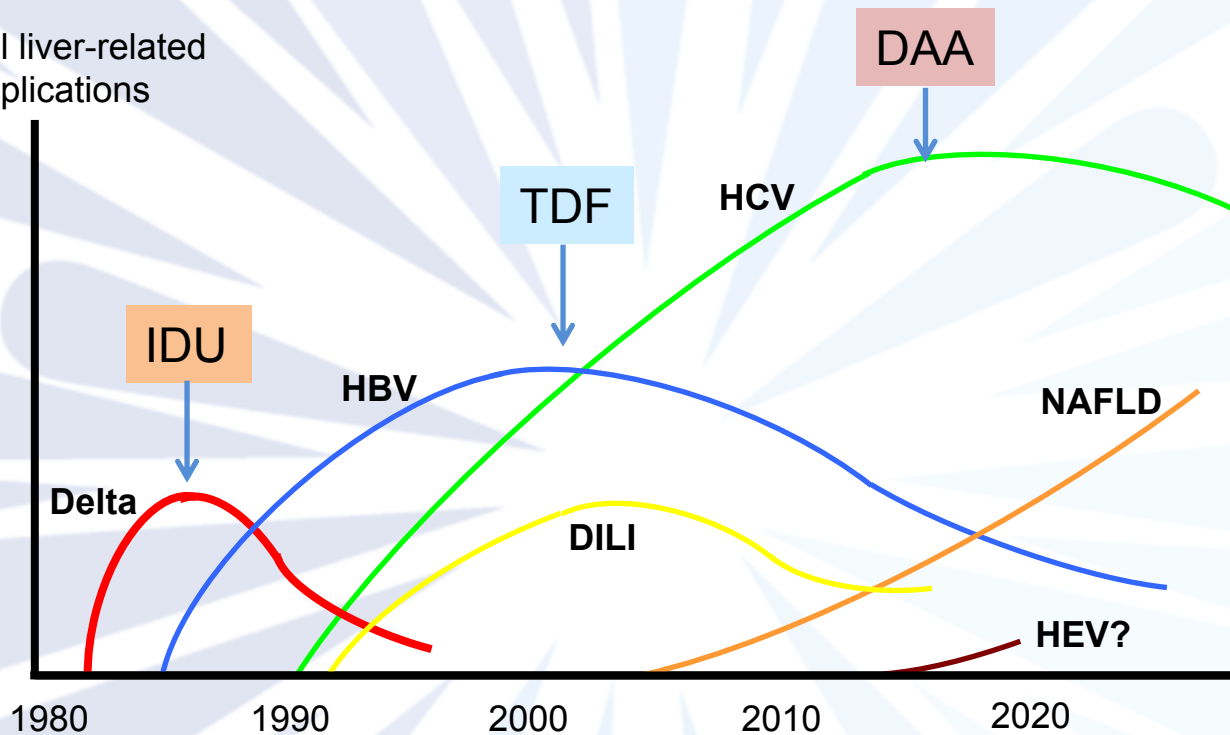
Does this case remind you of what you are seeing in your clinical practice?

NAFLD definition

- A clinicopathologic disorder defined by the presence of fat in $>5\%$ of hepatocytes in the absence of other secondary causes (e.g. alcohol use, hereditary disorders, **steatogenic medications**, or viral hepatitis)

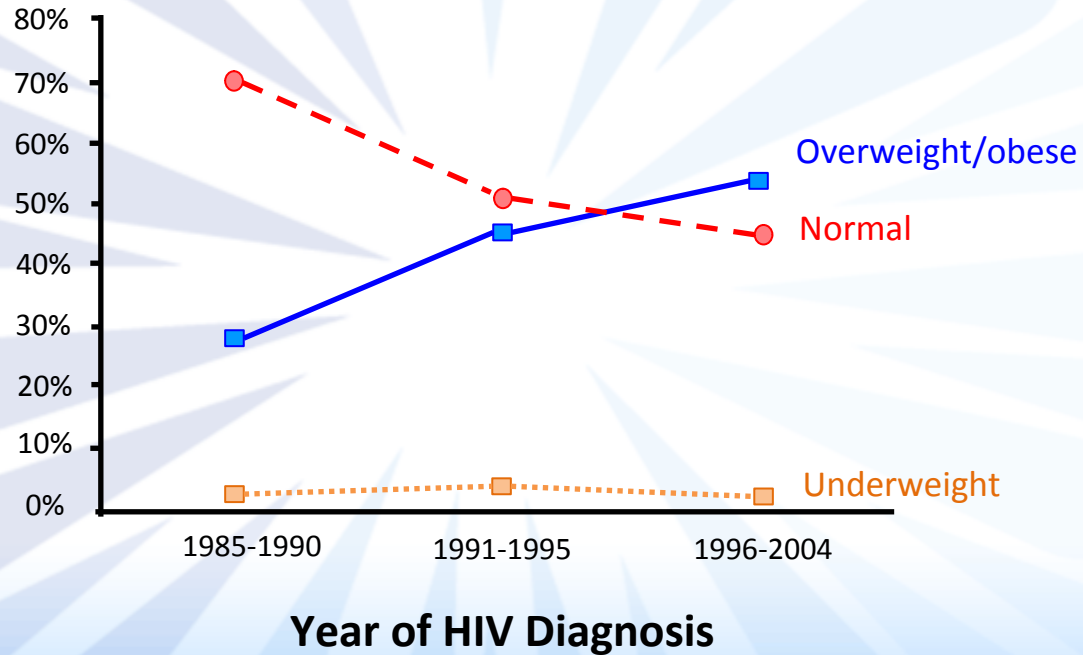
The changing epidemiology of Liver Disease in HIV patients

Clinical liver-related complications



More than 50% of Persons Living with HIV are overweight during the ART era.

Trends in Weight Categories at HIV Diagnosis during the HIV Epidemic.



Risk factors for NAFLD

- **Ethnic predisposition**
 - More common in Asian Indians>Hispanics>Caucasians>African Americans
- **Risk factors include metabolic syndrome**
 - Obesity, hypertension, hypertriglyceridemia, insulin resistance and diabetes
 - PNPLA3 genotype

Are the metabolic consequences of obesity different in HIV+ patients?

Consistent:

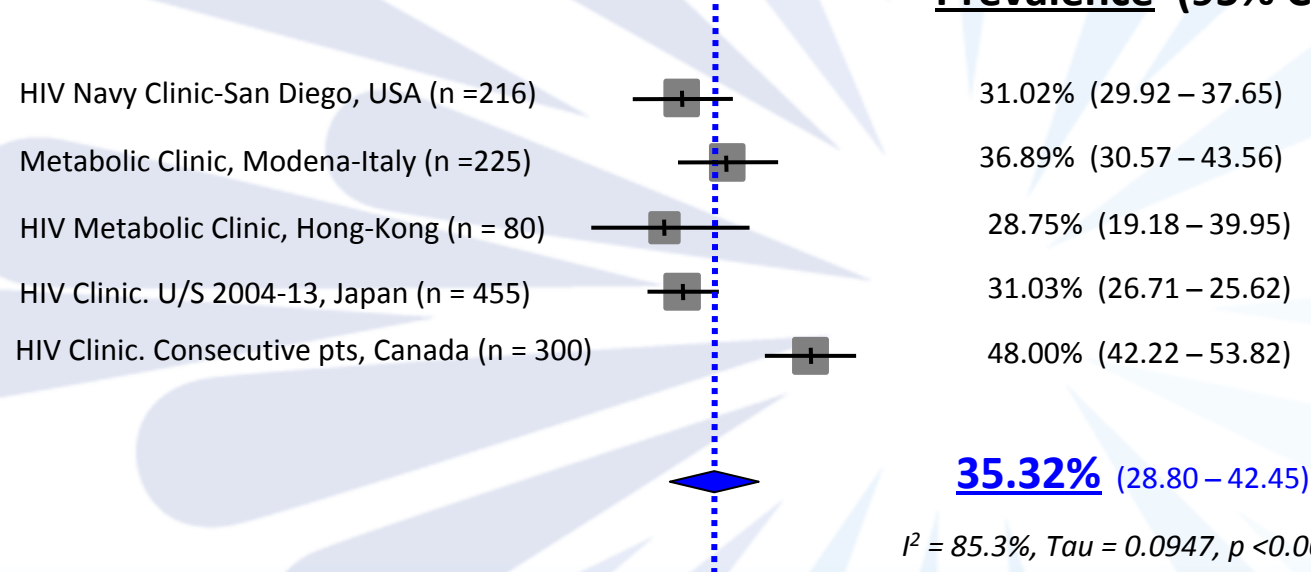
- obese HIV+ subjects have a higher trunk-to-appendicular fat ratio, a predictor of cardiovascular disease, compared to obese non-HIV controls.
- Higher calculated visceral fat.

Variable:

- Severity of peripheral resistance to the insulin
- Magnitude of lipid elevation
- Effects of biomarker and endovascular inflammation: ICAM-1, sCD14, TNF α R2

NAFLD prevalence

Prevalence (95% CI)

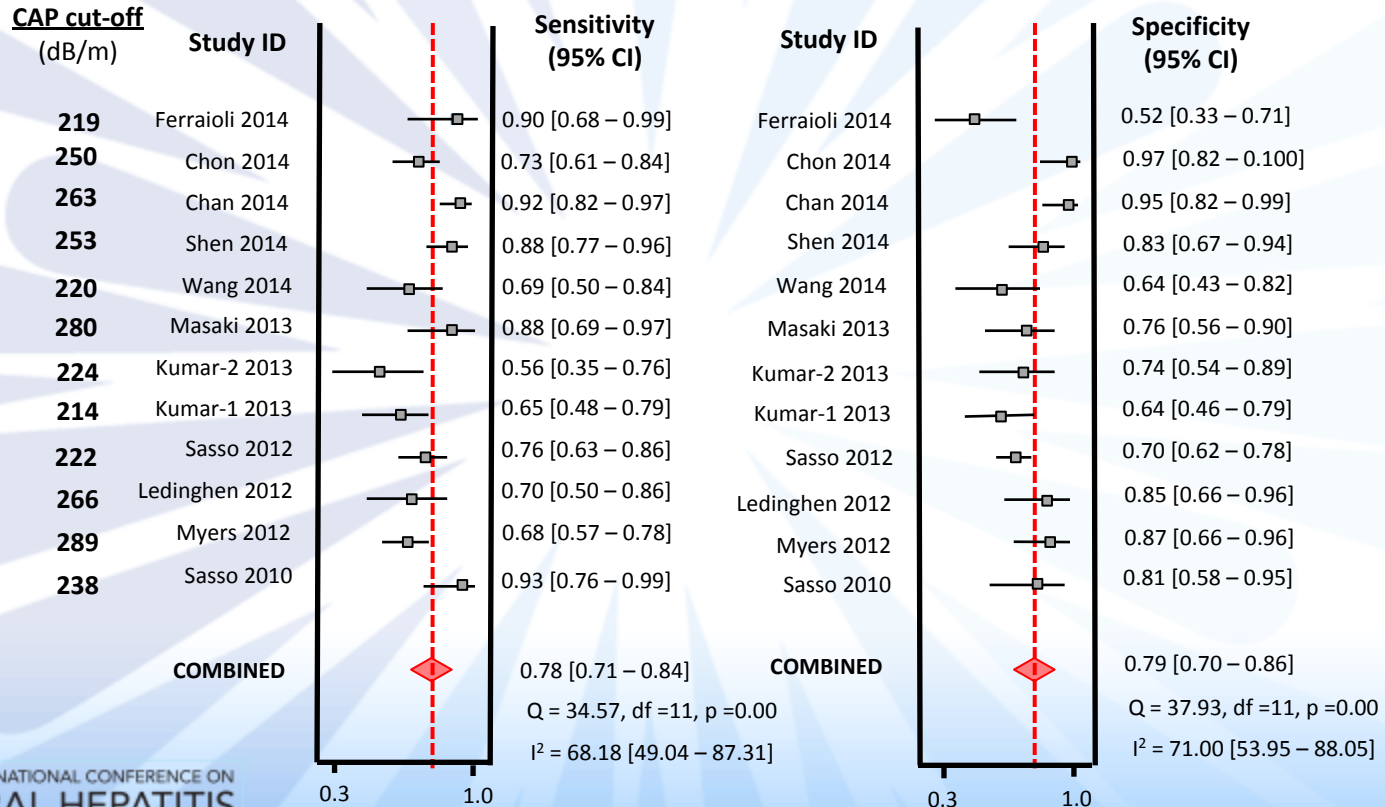


Prevalence (%)

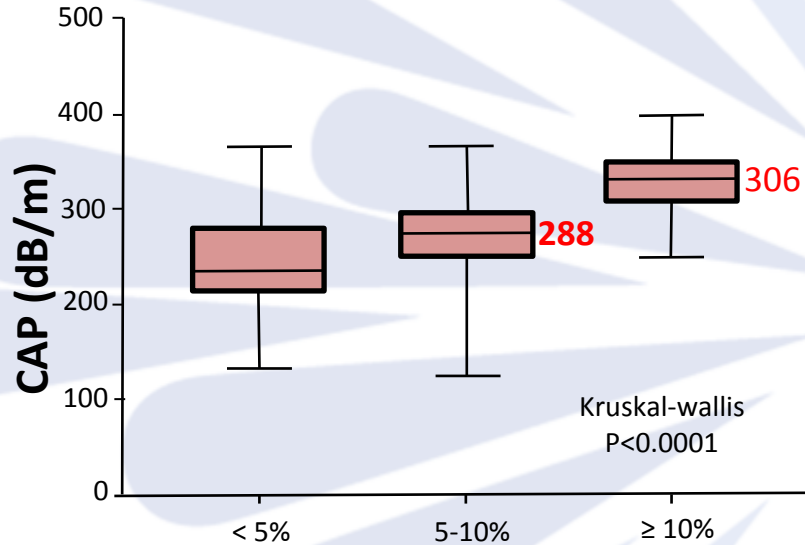
How to diagnose it?

- Liver biopsy: Invasive, observer variation, heterogeneous fat distribution
- Liver ultrasound: Low sensitivity-threshold 30%.
- Fibroscan- Controlled Attenuated parameter -
Caveats
- MRI

Forest plots of sensitivity and specificity of controlled attenuation parameter (CAP) for the detection of stage 1 (S1) hepatic steatosis

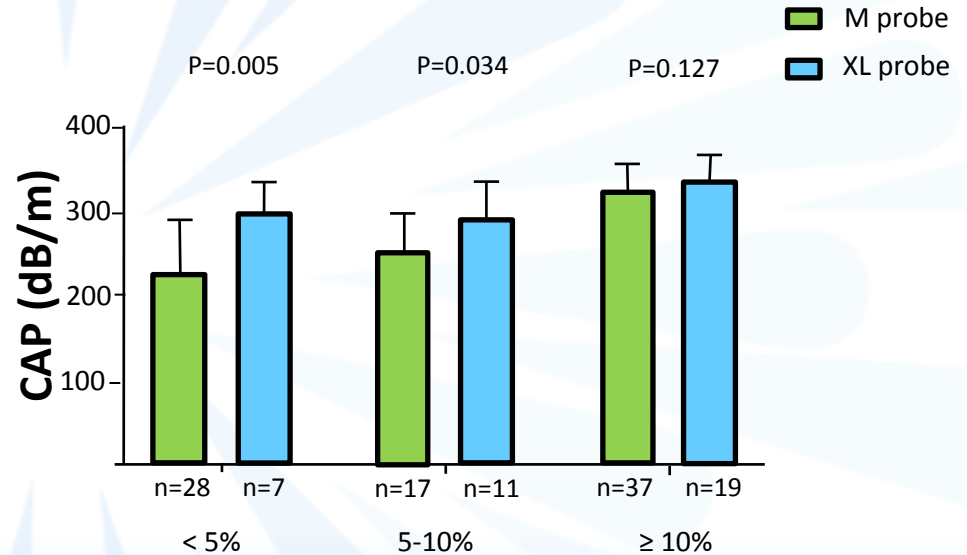


Distribution of CAP measurements stratified by hepatic fat content



MRI-FDFF

Higher CAP value using XL compared to M probe when MRI < 10%



MRI-FDFF %

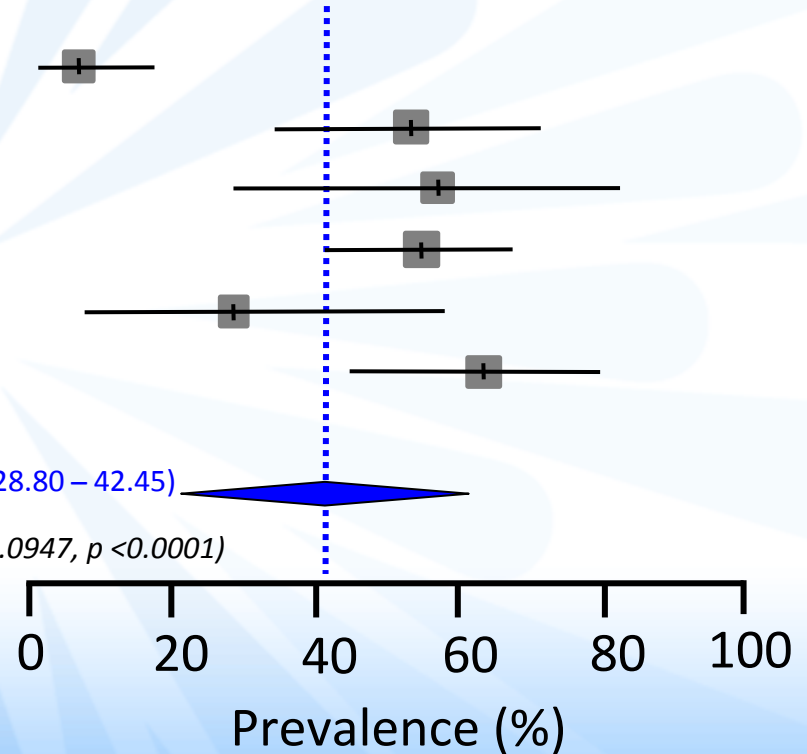
NASH prevalence

Prevalence (95% CI)

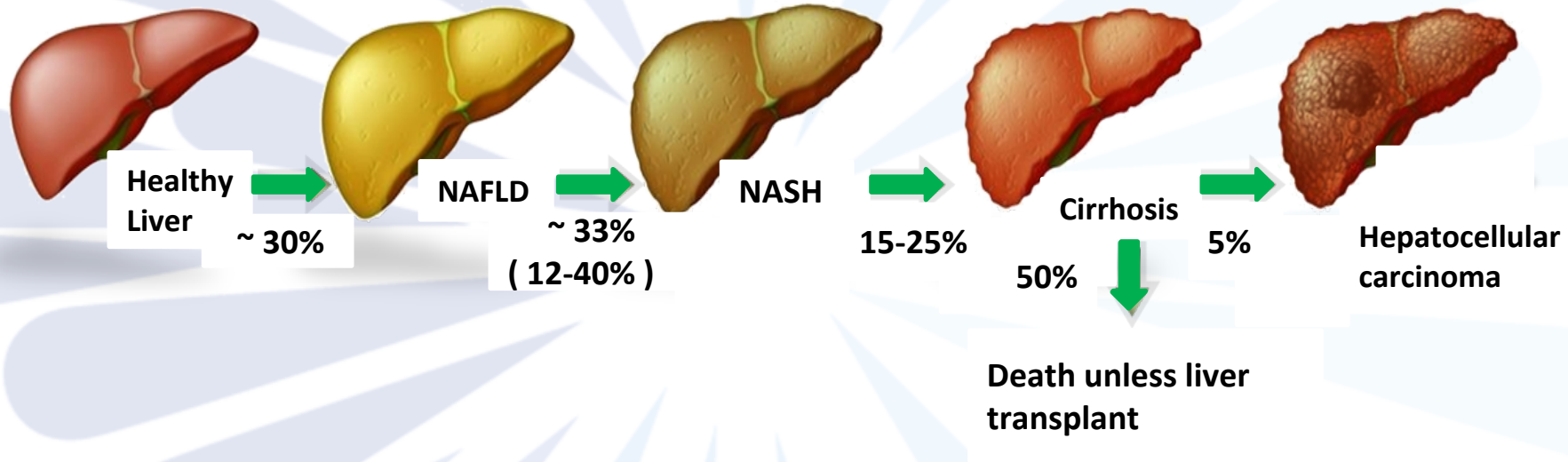
HIV Navy Clinic-San Diego, USA (n = 55)	7.27% (2.02 – 17.59)
Metabolic Clinic, Modena-Italy (n =225)	36.89% (30.57 – 43.56)
HIV Metabolic Clinic, Hong-Kong (n = 80)	28.75% (19.18 – 39.95)
HIV Clinic. U/S 2004-13, Japan (n = 455)	31.03% (26.71 – 35.36)
HIV Clinic. Consecutive pts, Canada (n = 300)	48.00% (42.22 – 53.82)

35.32% (28.80 – 42.45)

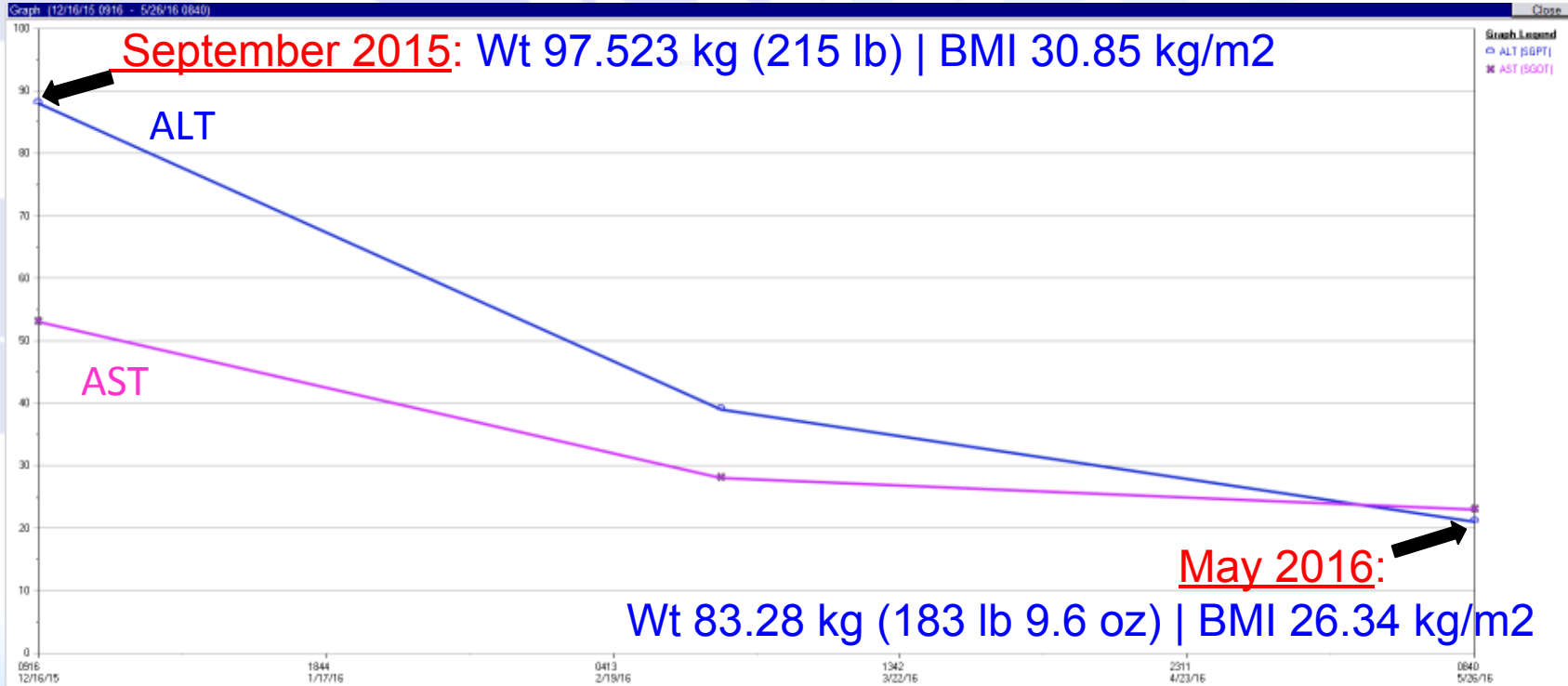
$I^2 = 85.3%$, $\tau = 0.0947$, $p < 0.0001$)



Natural history of NAFLD



May 2016: our patient modified his diet and has started exercising!





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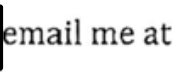
Aramchol for HIV-associated nonalcoholic fatty liver disease and lipodystrophy

Dear 

Please find enclosed your MRI results from your recent visit.

The fat fraction of your liver was 2.92%, MR elastography 3.64kPa of and fibroscan 25.4kPa.

A fat fraction >5% is indicative of fatty liver disease, and Fibroscan score of > 7 kPa is indicative of fibrosis, >14 may suggest cirrhosis. MR elastography > 3.0 kPa may suggest advanced cirrhosis. Please show these results to your Primary Care provider.

If you have any questions, please feel free to call me at  email me at 

Thanks,



Management implications for HIV providers

- Staging for complications of portal Hypertension: EGD
- HCC screening
- Verify immunization status:
 - + Viral hepatitis HAV, HBV
 - + Invasive pneumococcal infections
- * Counseling: Behavioral, medications, life-style

Non-invasive online tools for liver fibrosis: practical tips.

metabolic and cardiovas... The Metabolic and Cardiovas... Volume 65 Issue 5 | Clinical Inf...

NAFLD fibrosis score Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)

BMI (kg/m²)

IGF/diabetes

AST

ALT

Platelets (x10⁹/l)

Albumin (g/l)

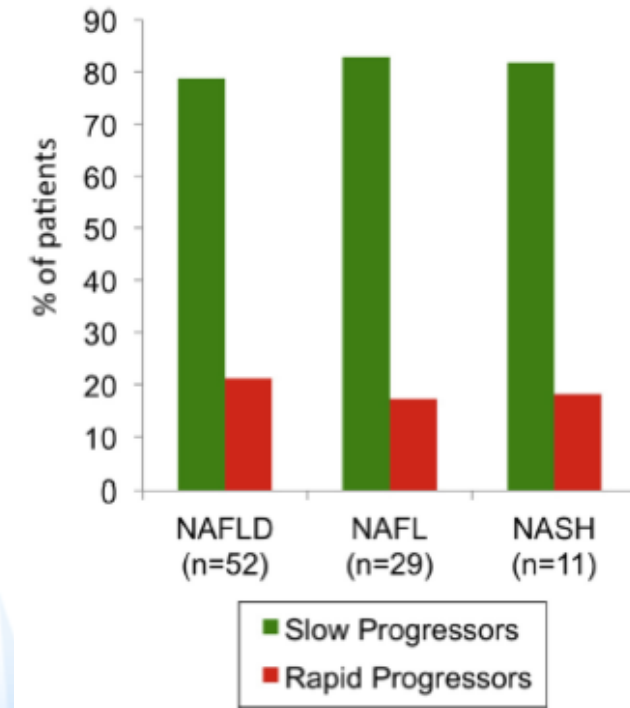
Score

< -1.455: predictor of **absence** of significant fibrosis (F0-F2 fibrosis)
≤ -1.455 to ≤ 0.675: Indeterminate score
> 0.675: predictor of **presence** of significant fibrosis (F3-F4 fibrosis)

BMI: body mass index
IGF: impaired fasting glucose

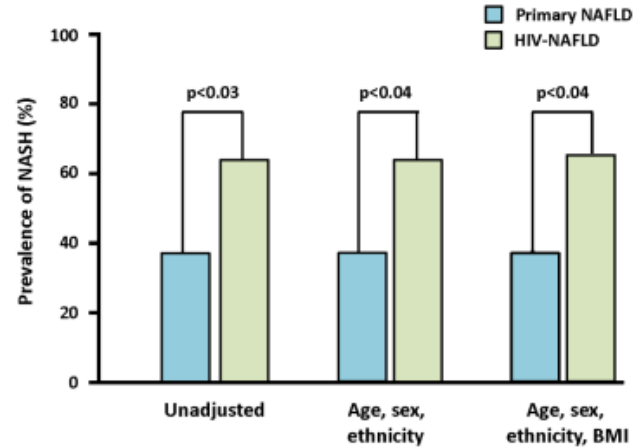
Fibrosis progression rate in NAFLD

- FPR in NAFL: 14 years/stage
- FPR in NASH: 7 years/stage
- 20% of those who progress are “Rapid Progressors”



Multivariable-adjusted risk of NASH in HIV-associated NAFLD

Risk of NASH is significantly higher in HIV than primary NAFLD independent of age, sex, ethnicity and BMI



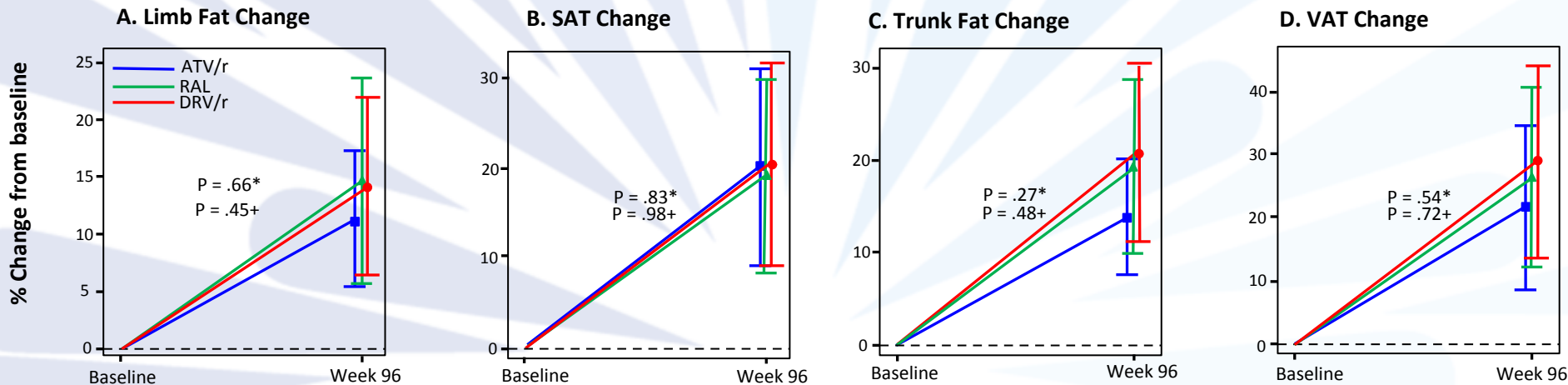
Are there HIV predictors of NASH and Fibrosis ?

HIV-related factors	Ishak Fibrosis Score on Liver biopsy		P	Biopsy Diagnosis		P
	< 2 (n = 47)	≥ 2 (n = 12)		Non-specific (n=22)	NASH (n = 34)	
Time from HIV Diagnosis	17.5 (2.3 -27.8)	17.1 (3.8 -24.8)	.72	18.2 (2.7 -24.7)	16.3 (2.3-27.8)	.37
Total CD4+	539 (105-1631)	592 (138 -1525)	.62	498 (1105-115)	580 (138-1631)	.4
CD4+ %	30 (7-49)	31 (8-47)	.67	31 (8-49)	28 (7-48)	.19
CD4+ nadir	195 (< 10-599)	160 (< 10-423)	.75	189 (12-561)	178 (6-599)	.41
History of opportunistic infections	21 (45%)	4 (33%)	.48	8 (36%)	17 (50%)	.59
ART duration at biopsy	12.4 (1.7 -22.8)	13.0 (2.7-21.6)	.96	12.9 (3.2-20.6)	11.1 (1.7-22.8)	.33

Adapted from Morse et al. CID 2015; 60: 1569-1578

Does it matter which antiretroviral regimen we choose?

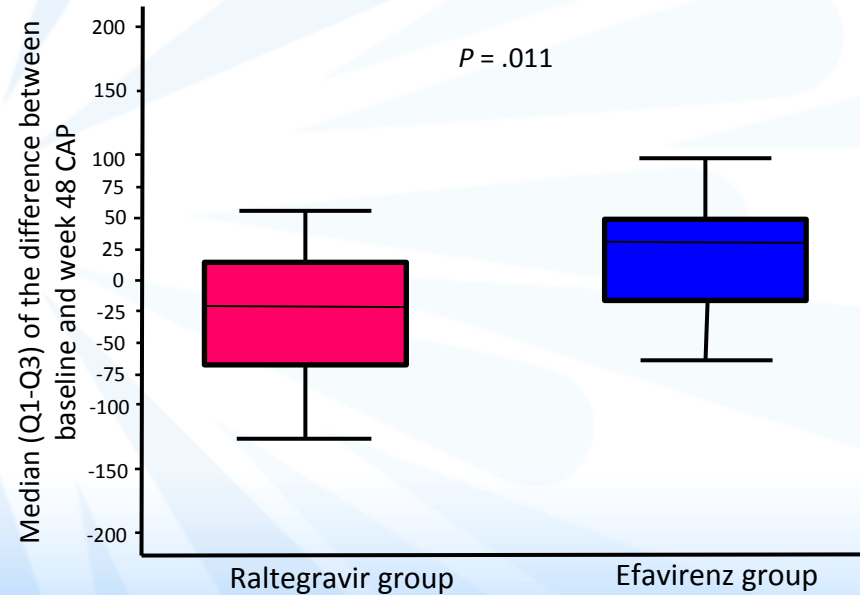
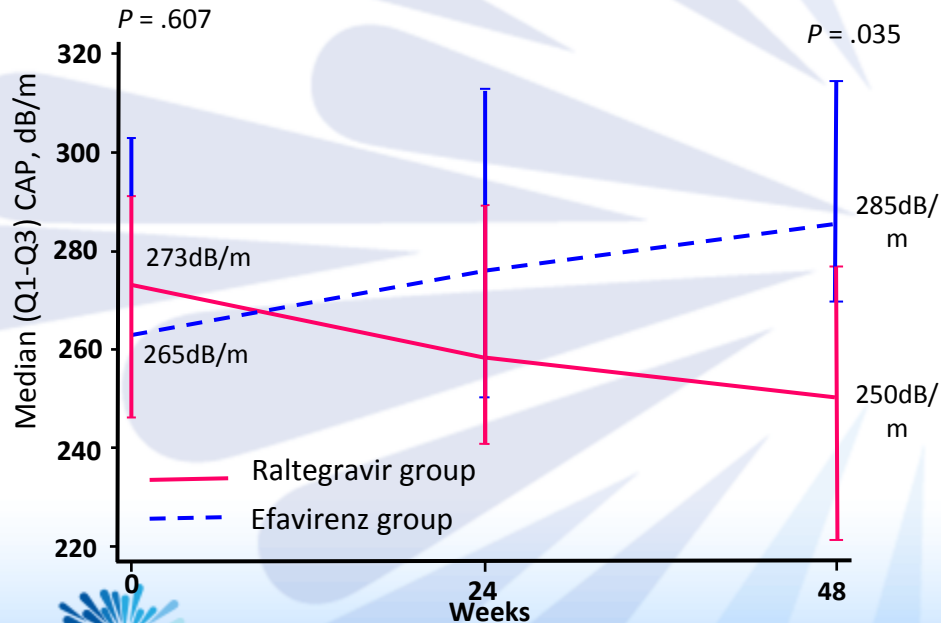
ACTG 5260s: Changes for all fat and lean outcomes PI vs Raltegravir



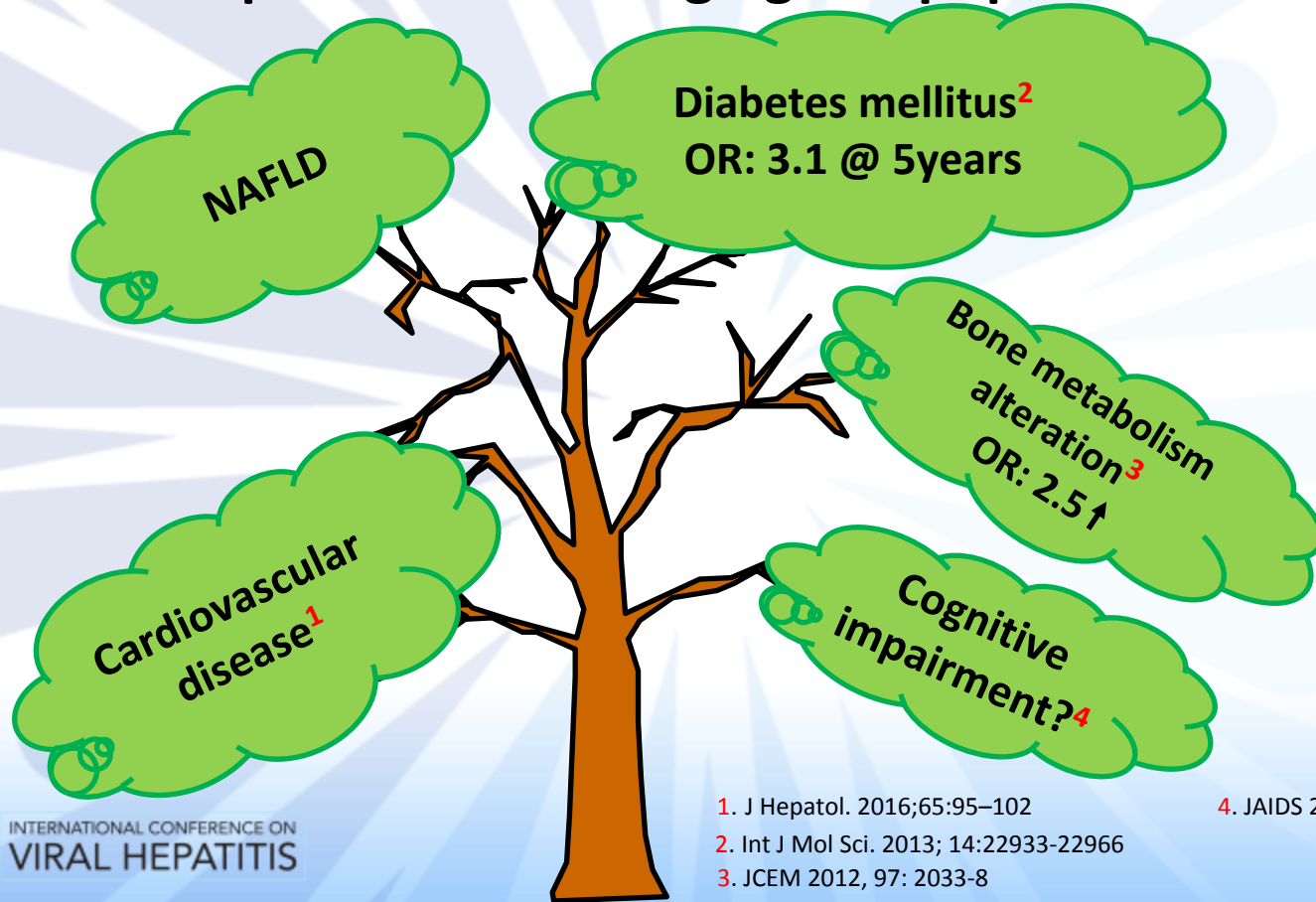
328 patients were randomized (90% male, 44% white non-Hispanic). Overall, at week 96, increases in limb fat (13.4%), subcutaneous (19.9%) and visceral abdominal fat (25.8%), trunk fat (18%), and lean mass (1.8%) were apparent ($P < .001$ for changes within each arm).

Changes for all fat and lean outcomes were not different between the PI arms or between the RAL and the combined PI arms.

What about after someone is diagnosed with NAFLD?



A window of opportunity: Liver fat as barometer of metabolic complications in an aging HIV population.



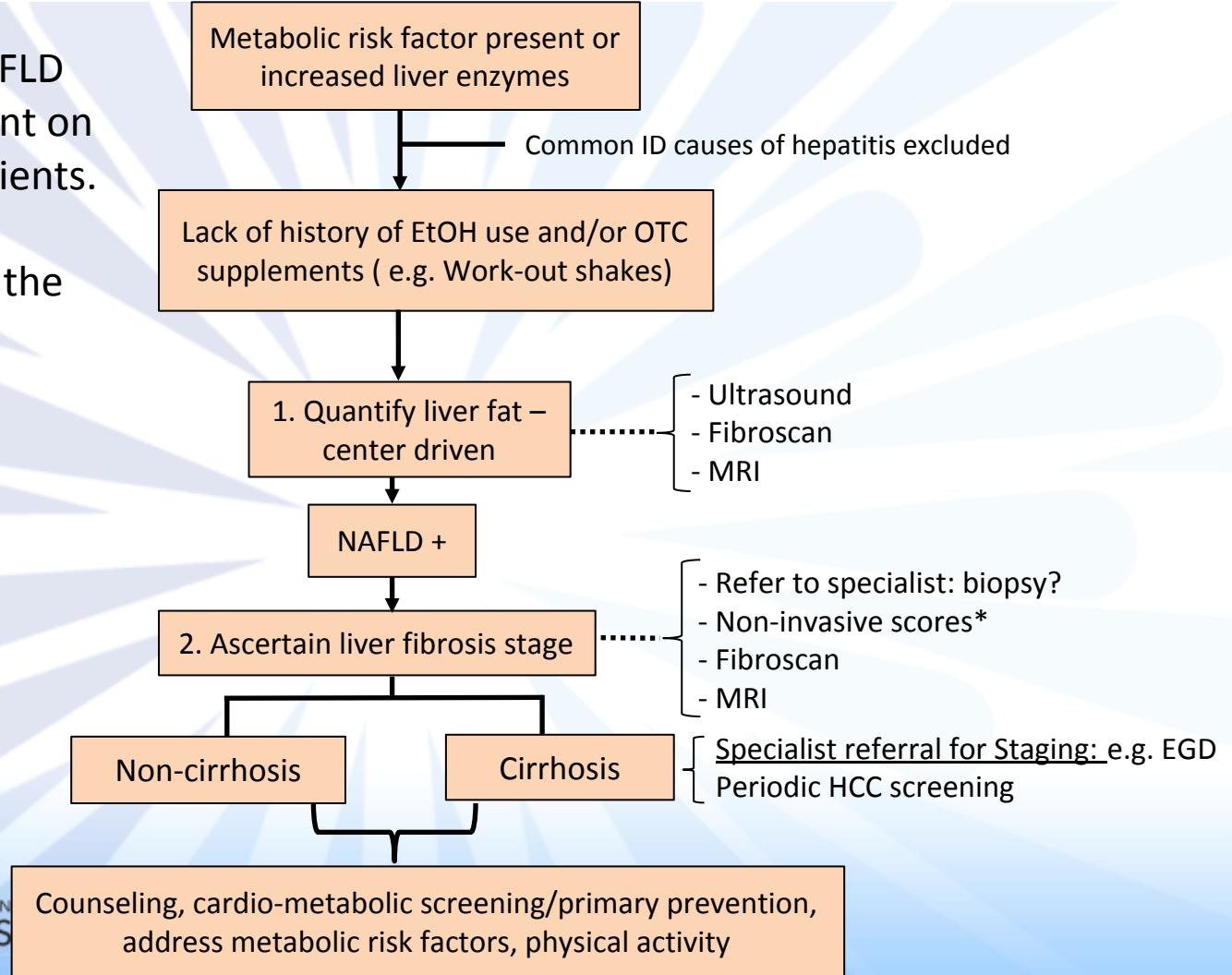
1. J Hepatol. 2016;65:95–102

2. Int J Mol Sci. 2013; 14:22933-22966

3. JCEM 2012, 97: 2033-8

4. JAIDS 2015, 28: 281-288

“The July 2017 AASLD NAFLD guidelines do not comment on unique needs of HIV+ patients. This is a practical, albeit incomplete algorithm for the HIV provider.”



Summary:

- Persons living with HIV (PLWH) are at high risk for developing NAFLD/NASH
- Following diagnosis of ‘fatty liver’ is also essential to investigate liver fibrosis stage
- In the absence of specific treatment for NASH, HIV providers must focus on preventive efforts addressing weight and insulin resistance
- Emerging data suggest that reassessing ARV class might be a consideration for management of NAFLD in PLWH
- Think of NAFLD/NASH not only a marker but also as a mediator, for multiple future adverse health outcomes

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