La Steatosi epatica nel paziente con infezione da HIV

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8° WORKSHOP NAZIONALE CISAI

PERUGIA, 30 - 31 MARZO 2017

Prevenzione e gestione delle co-morbidità associate all'infezione da HIV

Introduction/Background

- Definition
- Causes of secondary Hepatic steatosis

Definitions (NAFLD or NASH?)

- Non Alcoholic Fatty Liver Disease (**NAFLD**): presence of FAT in >5% of hepatocytes in the absence of other secondary cause (eg, alcohol use, hereditary disorders, steatogenic medications or viral hepatitis)
- Nonalcoholic steato-hepatitis (**NASH**): presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis
- Virus Associated Fatty Liver Disease (**VAFLD**)

Chalasani N et al. Gastroenterology 2012; 142: 1592–609.

Common Causes of Secondary Hepatic Steatosis

- Macrovesicular steatosis

Excessive alcohol consumption - Hepatitis C (genotype 3) - Wilson's disease - Lipodystrophy - Starvation - Parenteral nutrition - Abetalipoproteinemia - Medications (e.g., amiodarone, methotrexate, tamoxifen, corticosteroids)

- Microvesicular steatosis

Reye's syndrome - Medications (e.g. valproate) - Acute fatty liver of pregnancy - HELLP syndrome - Inborn errors of metabolism (e.g., LCAT deficiency, cholesterol ester storage disease, Wolman disease)

Chalasani N et al. Hepatology 2012; 55: 2005–23

NAFLD and NASH

- Simple steatosis can progress to NASH and both conditions progress to advanced fibrosis, though this occurs at much slower pace for simple steatosis than NASH.

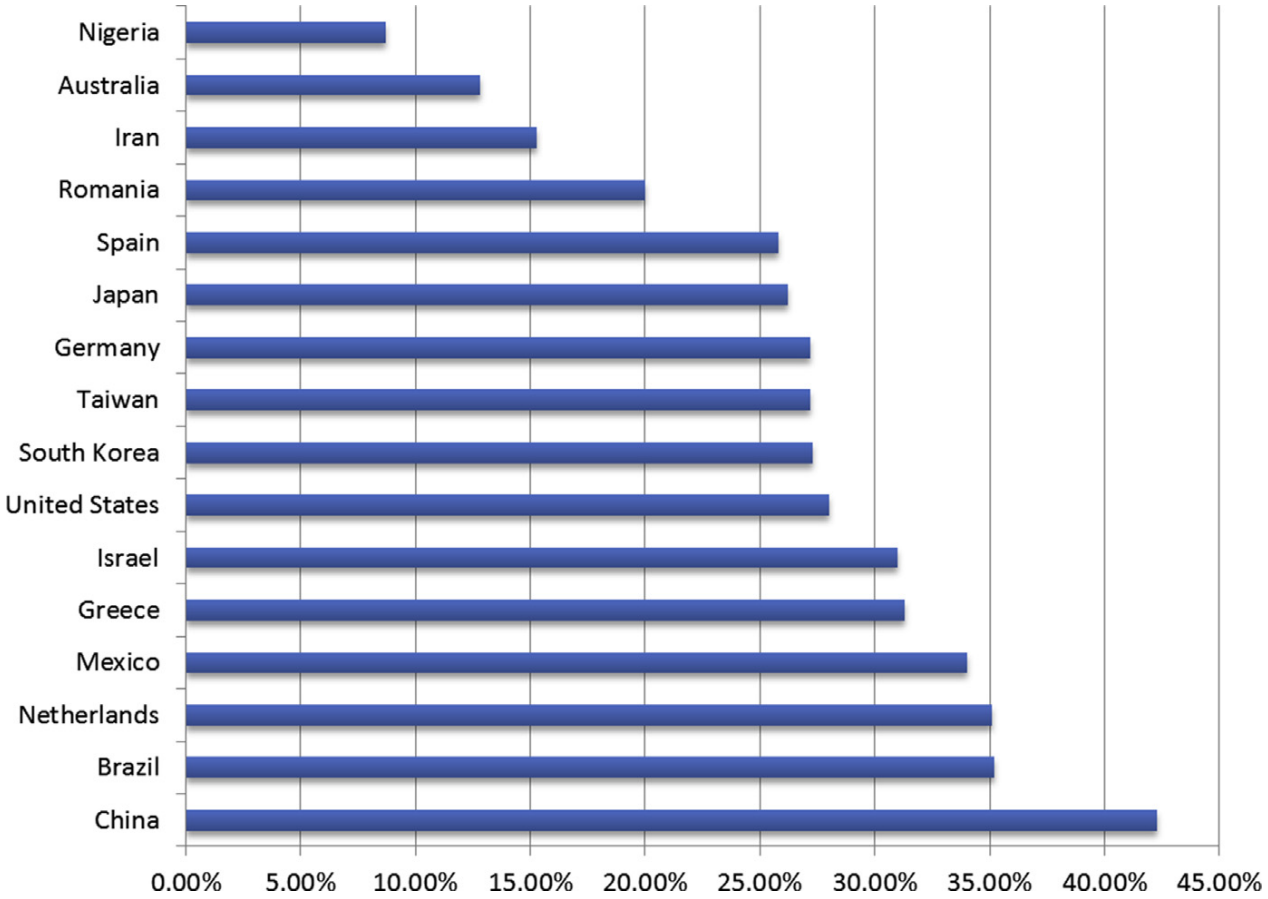
Singh S et al. Clin Gastroenterol Hepatol 2015; 13: 643-654.e1-9; Pais R et al. J Hepatol 2013; 59: 550-556 ; Wong VW et al. Gut 2010; 59: 969-974 ; McPherson S. J Hepatol 2015; 62: 1148-1155

Epidemiology/Prevalence (General population)

- NAFLD : 6.3-33%
- NASH: 3-5%

Vernon G et al. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and nonalcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34: 274-28

Epidemiology/prevalence



Sayiner M et al. Clin Liver Dis. 2016 May;20(2):205-14

Risk factors for NAFLD

Conditions with significant association:

- Obesity
- Type 2 diabetes mellitus
- Dyslipidemia
- Metabolic syndrome

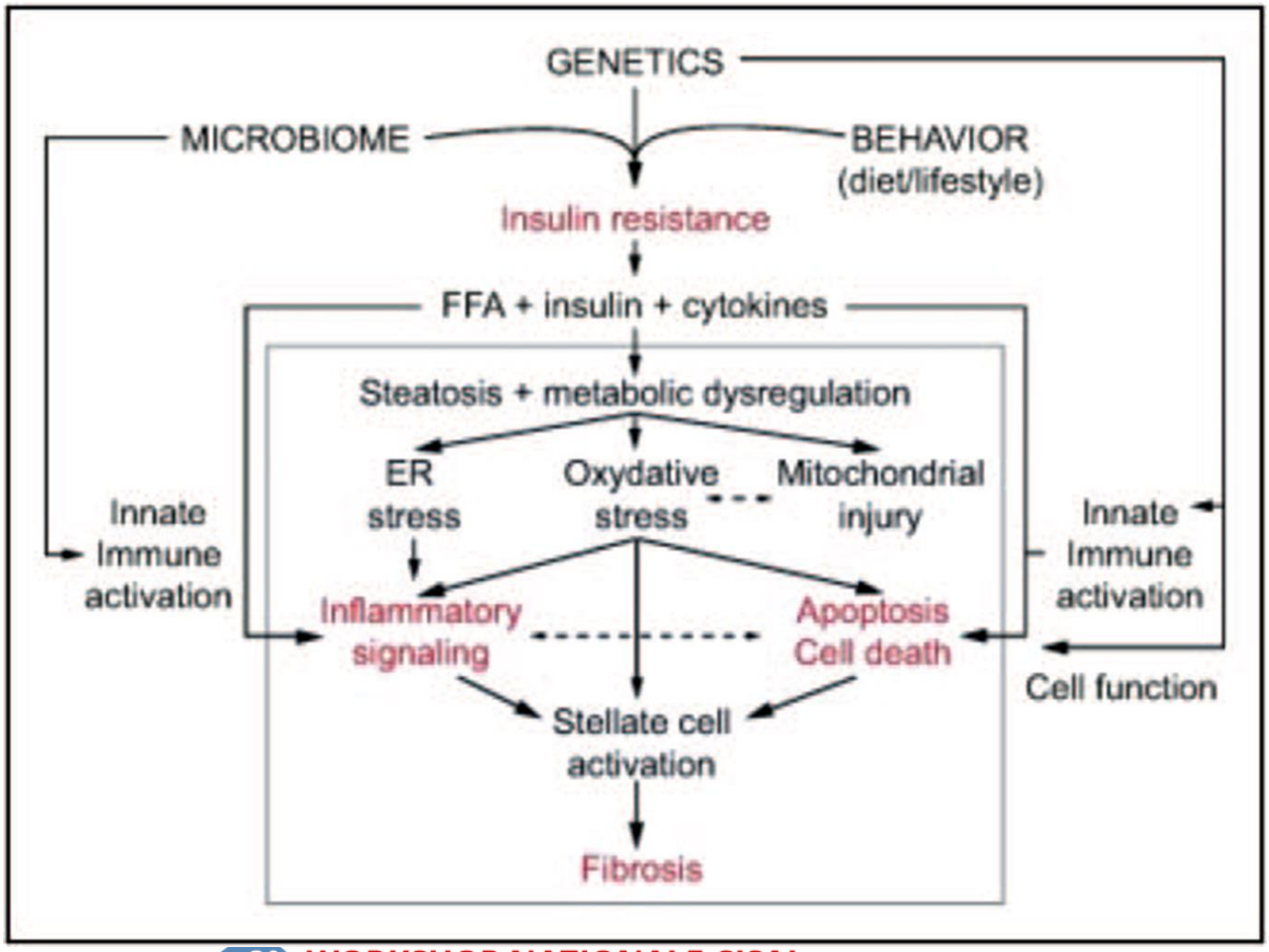
Conditions with a trend in association:

- Obstructive Sleep apnea, Polycystic ovary syndrome, Hypopituitarism, Hypogonadism , Pancreato-duodenal resection, Hypothyroidism, Hypertension.
- Male sex*/White race*

Adapted from Chalasani N et al. Hepatology 2012; 55: 20023

*debated

Pathogenesis



Tafesh ZH Curr Opin Infect Dis. 2017 Feb;30(1):12-20

Diagnosis

- Liver biopsy is the gold standard to diagnose NAFLD and NASH.
- Ultrasonography (US) is accurate in detecting moderate-severe steatosis (i.e. fat accumuation>30%) with a sensitivity >80% and specificity >95%

Webb M et al. AJR Am J Roentgenol 2009; 192: 909-914
Borges VF et al. J Clin Ultrasound 2013

Diagnosis

- **Transient Elastography with detection of controlled attenuation parameter (CAP),** has been recently validated for detection of hepatic steatosis. It has been strongly correlated with steatosis and sensitivity/specificity ≥ 90%.
- **Computed tomography (CT)** with calculation of Liver to spleen ratio <1.1 demonstrated a sensitivity =83% and specificity =82% for detection of moderate/severe steatosis.

Sasso M et al. Ultrasound Med Biol 2010; 36:1825–1835
Lee SS, J Hepatol 2010; 52: 579-585
Park SH, Radiology 2006; 239: 105-112

Diagnosis

- Magnetic resonance spectroscopy (MRS) is able to detect mild steatosis (fat accumulation >5%) with a sensibility and specificity >80%.
- It has been purposed as the gold standard for imaging methods for detecting hepatic steatosis because of the high accuracy and reproducibility.

Lee SS, J Hepatol 2010; 52: 579-585,
van Werven JR, Radiology 2010; 256: 159-168

Steatosi/NAFLD in HIV

Hepatic steatosis in HIV/Literature

- Inclusion criteria:
- HIV monoinfected group analyzed separetely

What is the prevalence?

Histologic studies

Authors	Sample	Population characteristics	Exclusion Criteria	Inclusion Criteria	NAFLD%	NASH%	Risk factors
Mohammed SS et al. JAIDS 2007	26 **HIV pos** *vs* 25 HIV neg	HIV neg con BMI >>	HBV, HCV, other causes of chronic hepatitis	ALT; AST >1.5 ULN, alcohol consumption<20 gr/day	**45** vs 55 ns	**54.8** vs 45.2 ns	HIV (?) cART (?)
Akhtar MA et al. Eur J Gastroenterol Hepatol 2008	21 **HIV pos**	Male S (90%) BMI 27(19-41)	Active viral hepatitis	Abnormal liver function test	**62 (23% ART induced)**	**57 (42% ART induced)**	cART (NRTIs)
Crum-Cianflone N et al. JAIDS 2008	55 **HIV pos biopsy vs** 216 **HIV pos** (only US)	BMI>> WC>> lipid lowering medic. >>	Chronic HBV/HCV Alcohol >20 gr/day (male) and > 10 gr (female)	Abnormal liver function test and/or US with steatosis	**36** vs 31% (US)	**20 (of proven NAFLD)**	White race/black race, BMI, WC, HDL, TRG,
Ingiliz et al. Hepatology 2009	**30 HIV pos**	97% male BMI= 23 (22-24)	Alcohol ≤20 gr/day, HBV, HCV, hemocromatosis, autoimmune hep	**ALT/AST elevation**	**60**	**53**	Insulin Resistance for NASH
Sterling RK et al. J Clin Gastroenterol 2013	14 **HIV pos**	Mean BMI=29.9±7.4 Male 71%	HBV, HCV, diabetes, alcohol>30 (men), >20 wormen	**1.25 to 5 ULN in AST, ALT, or alkaline** phosphatase (ALP),	**65**	**26**	GGT for steatosis, HOMA-IR for NASH.
Morse CG et al. CID 2015	62 **HIV pos**	BMI=27 Obese= 30% OvWeight=45% Diabetes=11% Male S(94%)	evidence of active viral hepatitis, hereditary or autoimmune LD, ongoing alcohol abuse	AST/ALT elevations	**72%**	**55**	IR, Obesity, 2 minor alleles in the PNPLA3

Hepatic Steatosis in HIV (US)

Sensitivity>90%/specificity >90%

Prevalence : 31-55%

Risk factors: TRG**, Tot Chol**, HOMA **, Male sex, Female sex, Age, GGT, BMI, Framingham risk score , ALT/AST ratio

Borges VF et al. J Clin Ultrasound 2013
Li Vecchi et al. Int J Infect. Dis. 2012;16:e397-402
Lombardi R. et al. Dig and Liver Dis 2016; 48:1471-1477
Nishijima T. et al. PLoS ONE 2014;9 :e87596
Guaraldi et al. Arch Med Res. 2011;42:690-7

Hepatic Steatosis in HIV (TE-CAP)

- Transient Elastography (Fibroscan) with CAP sensitivity/specificity ≥ 90%
- Prevalence: 39-51.5%

- Risk factors: BMI***, Diabetes , Hypertension

Sulyok M et al. Eur J Gastroenterol Hepatol. 2015;27:679-85
Macías J et al. AIDS. 2014 Jun 1;28(9):1279-87
Macías J et al. HIV Med. 2016;17:766-773

NAFLD in HIV (CT)

- Liver to spleen Ratio<1.1 sensitivity and specificity of 83.3 and 81.5, not able to detect mild steatosis
- Prevalence: 19-37%
- Risk factors: NRTI exposure**, ALT/AST ratio, male sex, WC , PNPLA3 (rs738409) non-CC genotype

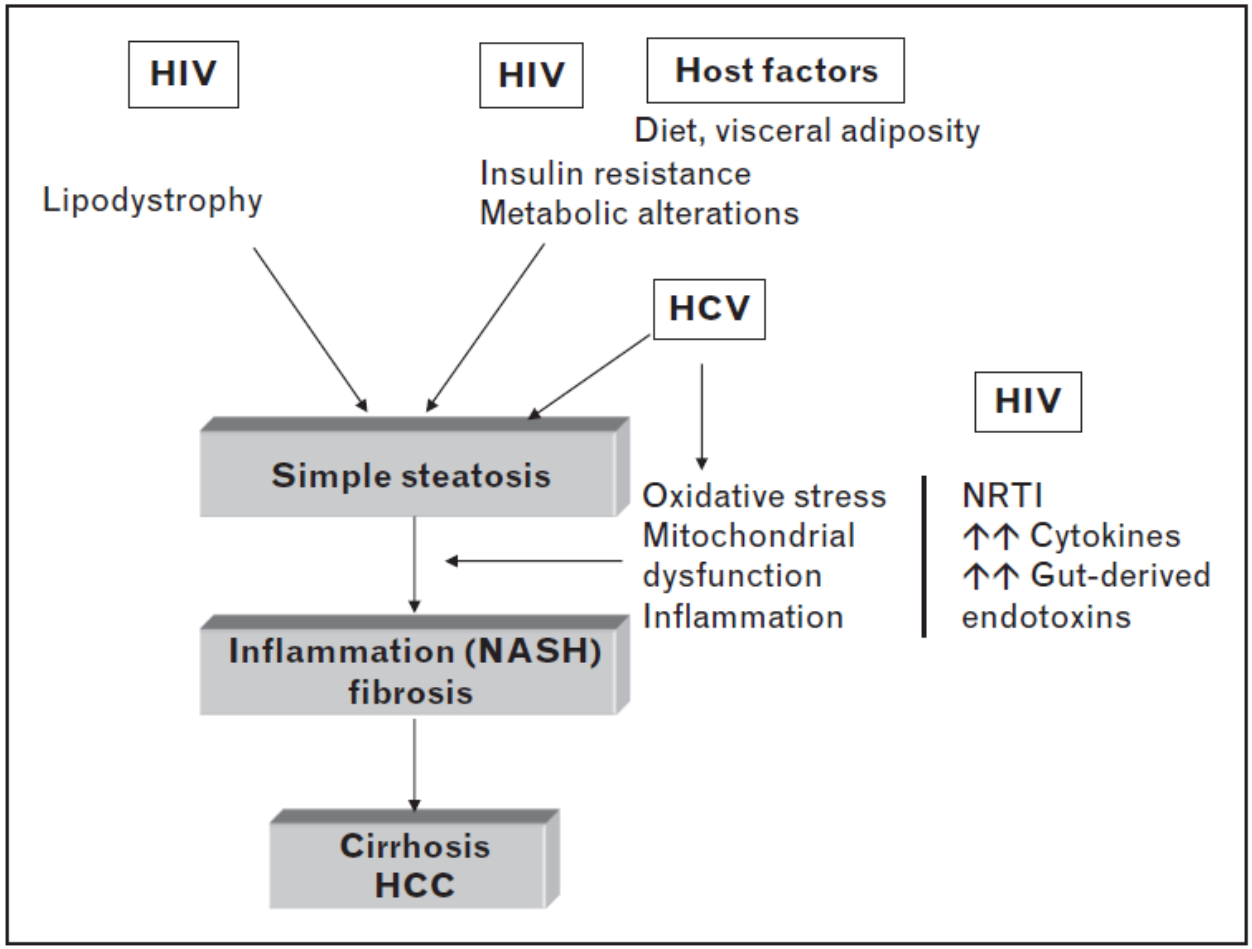
Iwasaki M et al. Transplantation 2004; 78:1501–5
Guaraldi G et al. Clin Infect Dis. 2008;47:250-7
Price JC et al. Am J Gastroenterol. 2014;109:695-704

Hepatic steatosis in HIV (MRS)

- Magnetic resonance Spectroscopy (sensitivity>80%; specificity>80% also for mild steatosis)
- Prevalence: 17% (women)- 28.7-58.6%
- Risk factors: HOMA-IR *****, visceral adiposity VAT ***, BMI, WC, Hispanic ethnicity, male sex, VLDL.

Hadigan C et al. J Acquir Immune Defic Syndr. 2007;46:312-7
Lui G et al. Aliment Pharmacol Ther 2016; 44: 411–421
Price JC et al. Hepatology. 2017;65:853-863
Kardashian A et al. AIDS. 2017;31:365-373
Moreno-Torres et al. Antiv. Ther. 2007;12:195-203

Pathogenesis



Lemoine M et al. Curr Opin Infect Dis. 2012 Feb;25(1):10-6

Is NAFLD more frequent in HIV?

Hepatic Steatosis in HIV pos vs HIV Neg

Less frequent in HIV pos vs HIV neg

MACS Cohort , *CT* (1)

WIHS/VAHH Cohorts, *MRS* (4,5)

No significant difference in HIV pos vs HIV neg

-Liver Biopsies (3)

-Hong Kong Cohort, *MRS* (2)

1. Price JC et al. Am J Gastroenterol. 2014;109:695-704
2. Lui G et al. Aliment Pharmacol Ther 2016; 44: 411–421
3. Mohammed SS et al. J Acquir Immune Defic Syndr 2007;45:432–438
4. Price JC et al. Hepatology. 2017;65:853-863
5. Kardashian A et al. AIDS. 2017 Jan 28;31(3):365-373

Less Steatosis in HIV?

Price JC et al. Hepatology. 2017;65:853-863

Significant difference in :

- Heavy alcohol use (23% Neg vs 7% HIV pos)
- BMI (29 vs 26)
- WC (99 vs 93)

Kardashian A et al. AIDS. 2017;31(3):365-373

Significant difference (Women) in

- Heavy alcohol use (17% Neg vs 5.2% HIV pos)
- BMI (32 vs 27)

Is HIV-AFLD different from NAFLD ?

NAFLD characteristics (HIV pos vs HIV neg)

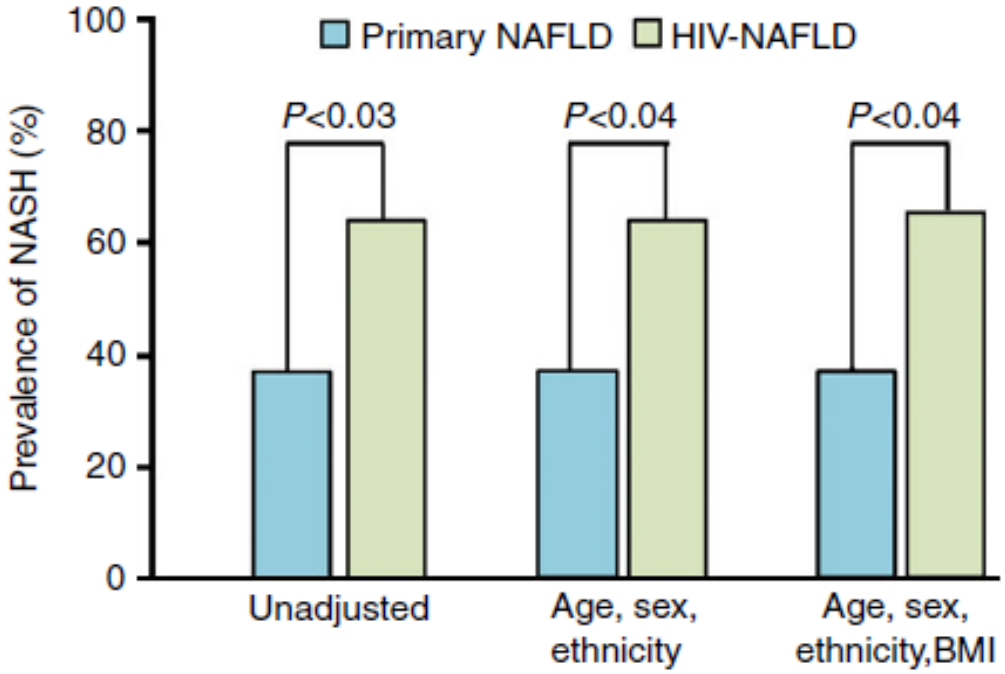
AP&T Alimentary Pharmacology and Therapeutics

Clinical, biochemical and histological differences between HIV-associated NAFLD and primary NAFLD: a case–control study

I. Vodkin*, M. A. Valasek†, R. Bettencourt‡, E. Cachay§ & R. Loomba*,‡,¶

Aliment Pharmacol Ther 2015; 41: 368–378

HIV-NAFLD vs Primary NAFLD



What is the prevalence of steatosis in HIV?

Hepatic steatosis in HIV (Imaging Studies)

- Prevalence

17-55%

Risk factors

- TRG
- Tot Chol
- HOMA-IR
- ALT/AST ratio
- BMI, WC
- NRTI exposure (D4T, DDI, DDC)

THERAPY?

Therapeutic options

- **Lifestyle interventions (Diet and exercise)**
- **Vitamina E**
- Pioglitazone
- Cenicriviroc
- Liraglutide (GLP-1), Elafibranor (PPAR$^{\delta}$), Obeticholic acid, Pentossifilline, Aramchol

Conclusions

- HIV-associated fatty liver disease prevalence is high in patients with abnormal liver tests. Higher or at least similar to HIV neg. More prevalent in patient with longer exposure to NRTI (D4T, DDI, ddc).
- Evolution in NASH has been found more often in HIV population.

Therapy

- Dietary intervention/Exercise
- Role of specific farmacological treatment should be considered in proven NASH/fibrosis especially in patients with Fibrosis staging ≥F2

Grazie!