Ottimizzazione della HAART nel paziente HIV positivo con epatopatia dismetabolica

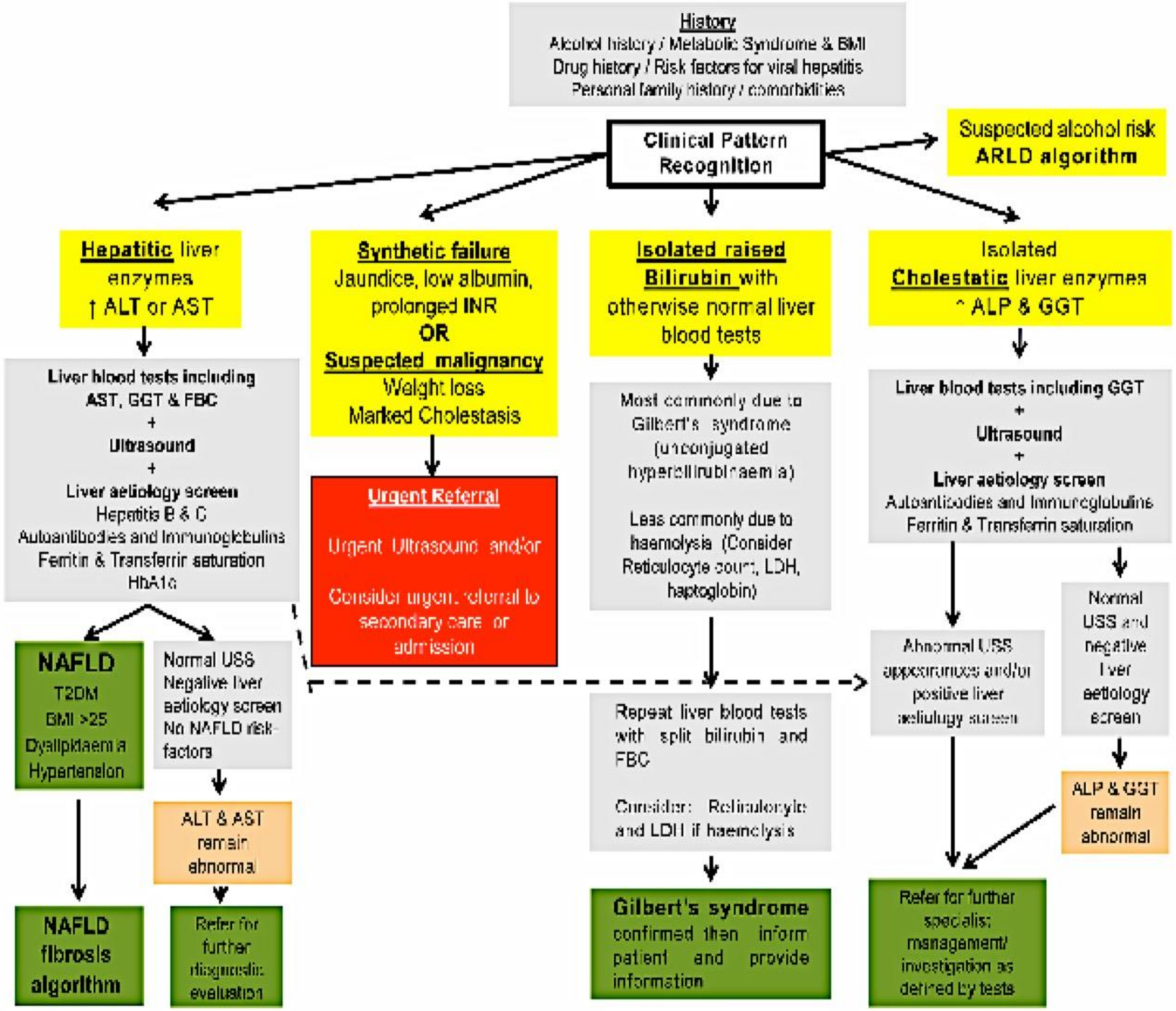
Carlo Torti

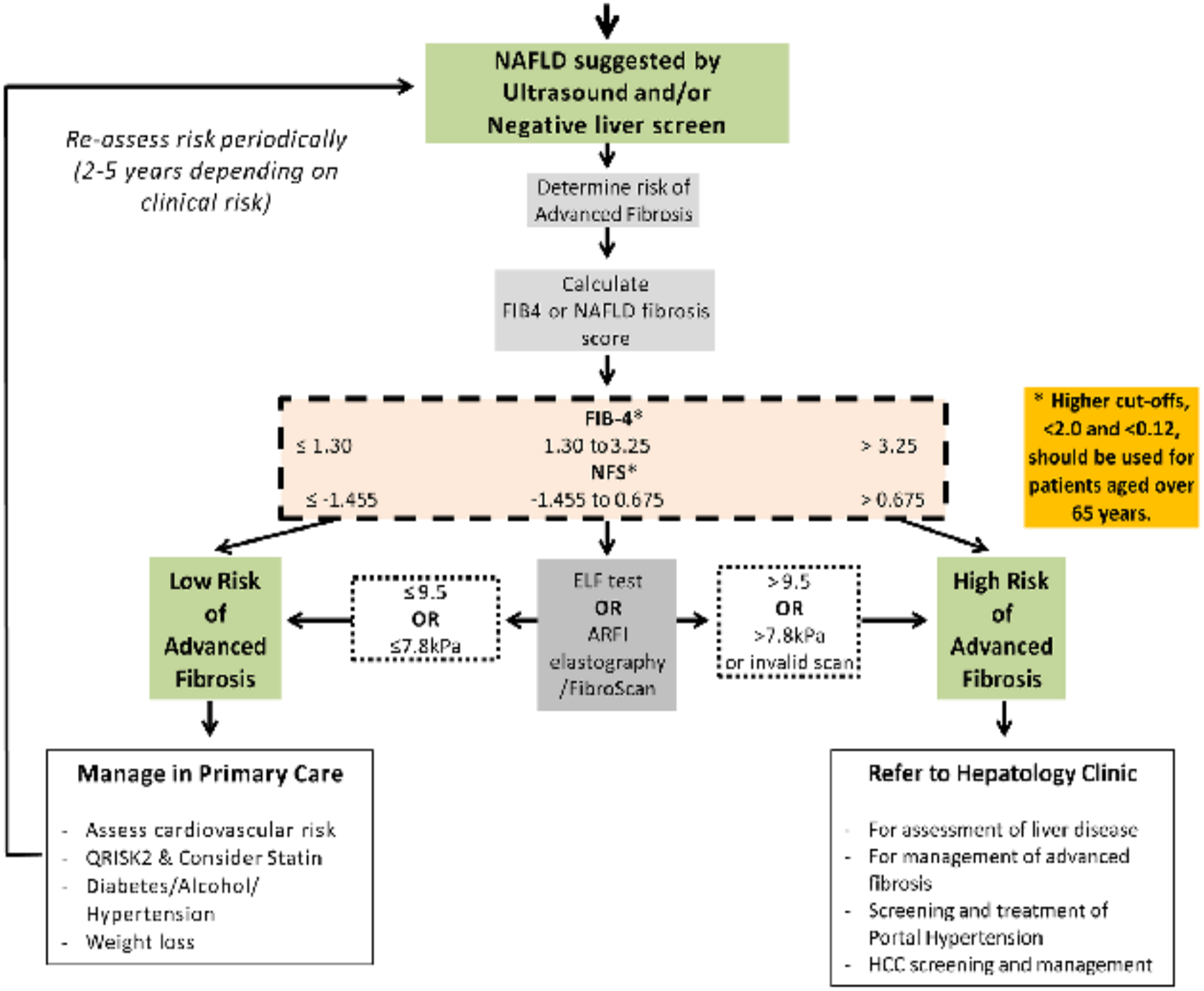
X Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica
TERAPIE INNOVATIVE
DELLE EPATITI CRONICHE VIRALI
Firenze, 13-14 gennaio 2020
Centro Congressi Hotel Londra

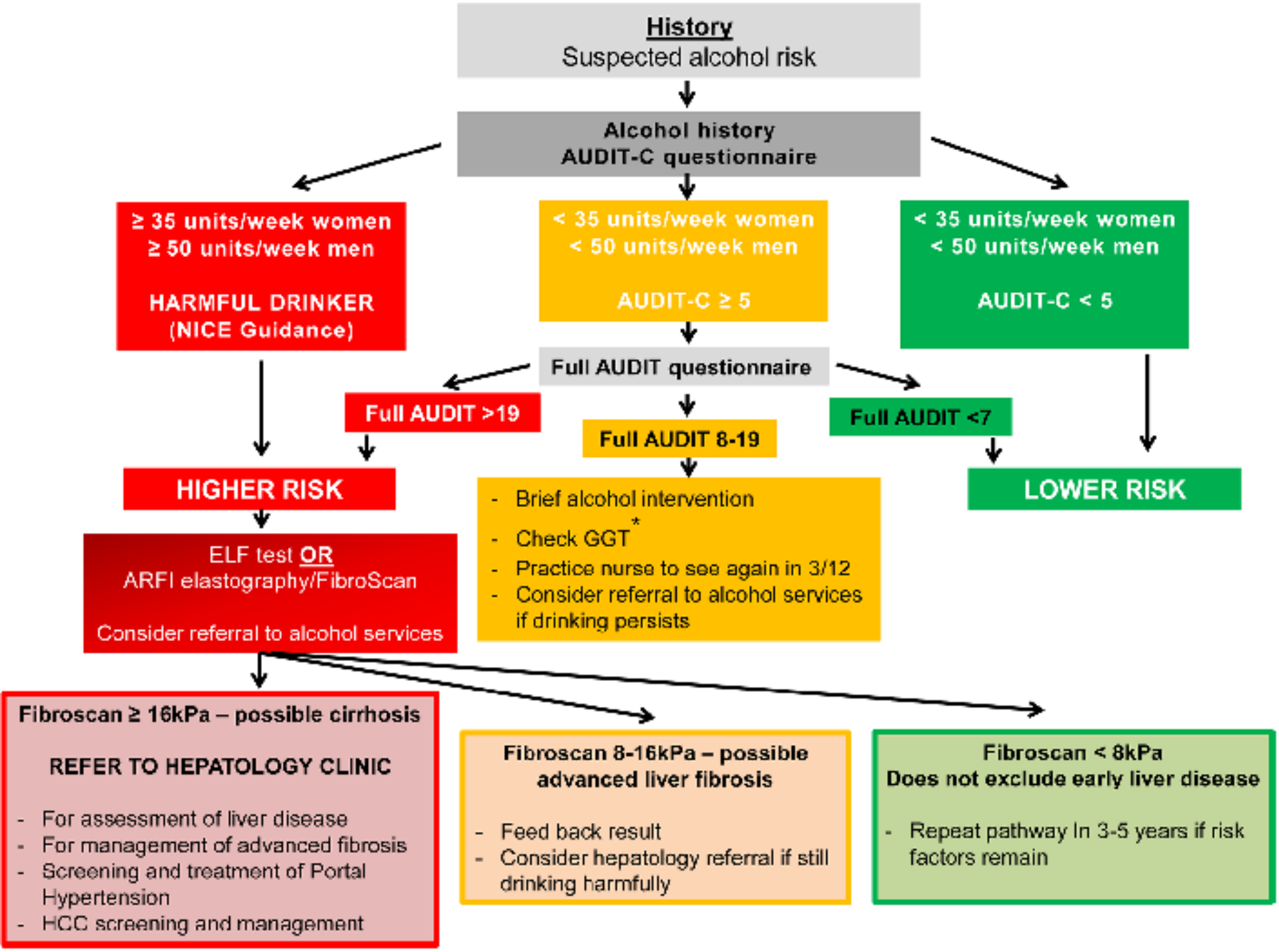
HIV patients - Don’t exclude similarities!

Guidelines on the management of abnormal liver blood tests

Philip N Newsome,[1,2] Rob Cramb,[1] Suzanne M Davison,[3] John F Dillon,[4] Mark Foulerton,[5] Edmund M Godfrey,[6] Richard Hall,[7] Ulrike Harrower,[8] Mark Hudson,[9,10] Andrew Langford,[11] Anne Mackie,[8] Robert Mitchell-Thain,[12] Karen Sennett,[13,14] Nicholas C Sheron,[15] Julia Verne,[8] Martine Walmsley,[16] Andrew Yeoman[17]


History
Alcohol history / Metabolic Syndrome & BMI
Drug history / Risk factors for viral hepatitis
Personal family history / comorbidities
Clinical Pattern Recognition
Suspected alcohol risk
ARLD algorithm
Hepatitic liver enzymes
↑ ALT or AST
Synthetic failure
Jaundice, low albumin, prolonged INR
OR
Suspected malignancy
Weight loss
Marked Cholestasis
Isolated raised Bilirubin with otherwise normal liver blood tests
Isolated Cholestatic liver enzymes
^ ALP & GGT
Liver blood tests including AST, GGT & FBC
+
Ultrasound
+
Liver aetiology screen
Hepatitis B & C
Autoantibodies and Immunoglobulins
Ferritin & Transferrin saturation
HbA1c
Urgent Referral
Urgent Ultrasound and/or
Consider urgent referral to secondary care or admission
Most commonly due to Gilbert's syndrome (unconjugated hyperbilirubinaemia)
Less commonly due to haemolysis (Consider Reticulocyte count, LDH, haptoglobin)
Liver blood tests including GGT
+
Ultrasound
+
Liver aetiology screen
Autoantibodies and Immunoglobulins
Ferritin & Transferrin saturation
NAFLD
T2DM
BMI >25
Dyslipidaemia
Hypertension
Normal USS
Negative liver aetiology screen
No NAFLD risk factors
ALT & AST remain abnormal
Repeat liver blood tests with split bilirubin and FBC
Consider: Reticulocyte and LDH if haemolysis
Abnormal USS appearances and/or positive liver aetiology screen
Normal USS and negative liver aetiology screen
ALP & GGT remain abnormal
NAFLD fibrosis algorithm
Refer for further diagnostic evaluation
Gilbert's syndrome
confirmed then inform patient and provide information
Refer for further specialist management/ investigation as dermed by tests


NAFLD suggested by Ultrasound and/or Negative liver screen
Re-assess risk periodically (2-5 years depending on clinical risk)
Determine risk of Advanced Fibrosis
Calculate FIB4 or NAFLD fibrosis score
FIB-4*
≤ 1.30
1.30 to3.25
> 3.25
NFS*
≤ -1.455
-1.455 to 0.675
> 0.675
* Higher cut-offs, <2.0 and <0.12, should be used for patients aged over 65 years.
Low Risk of Advanced Fibrosis
≤9.5 OR ≤7.8kPa
ELF test OR ARFI elastography /FibroScan
>9.5 OR >7.8kPa or invalid scan
High Risk of Advanced Fibrosis
Manage in Primary Care
- Assess cardiovascular risk
- QRISK2 & Consider Statin
- Diabetes/Alcohol/ Hypertension
- Weight loss
Refer to Hepatology Clinic
- For assessment of liver disease
- For management of advanced fibrosis
- Screening and treatment of Portal Hypertension
- HCC screening and management


History
Suspected alcohol risk
Alcohol history
AUDIT-C questionnaire
≥ 35 units/week women
≥ 50 units/week men
HARMFUL DRINKER
(NICE Guidance)
< 35 units/week women
< 50 units/week men
AUDIT-C ≥ 5
< 35 units/week women
< 50 units/week men
AUDIT-C < 5
Full AUDIT questionnaire
Full AUDIT >19
Full AUDIT 8-19
Full AUDIT <7
HIGHER RISK
LOWER RISK
- Brief alcohol intervention
- Check GGT*
- Practice nurse to see again in 3/12
- Consider referral to alcohol services if drinking persists
ELF test OR
ARFI elastography/FibroScan
Consider referral to alcohol services
Fibroscan ≥ 16kPa – possible cirrhosis
REFER TO HEPATOLOGY CLINIC
- For assessment of liver disease
- For management of advanced fibrosis
- Screening and treatment of Portal Hypertension
- HCC screening and management
Fibroscan 8-16kPa – possible advanced liver fibrosis
- Feed back result
- Consider hepatology referral if still drinking harmfully
Fibroscan < 8kPa
Does not exclude early liver disease
- Repeat pathway In 3-5 years if risk factors remain

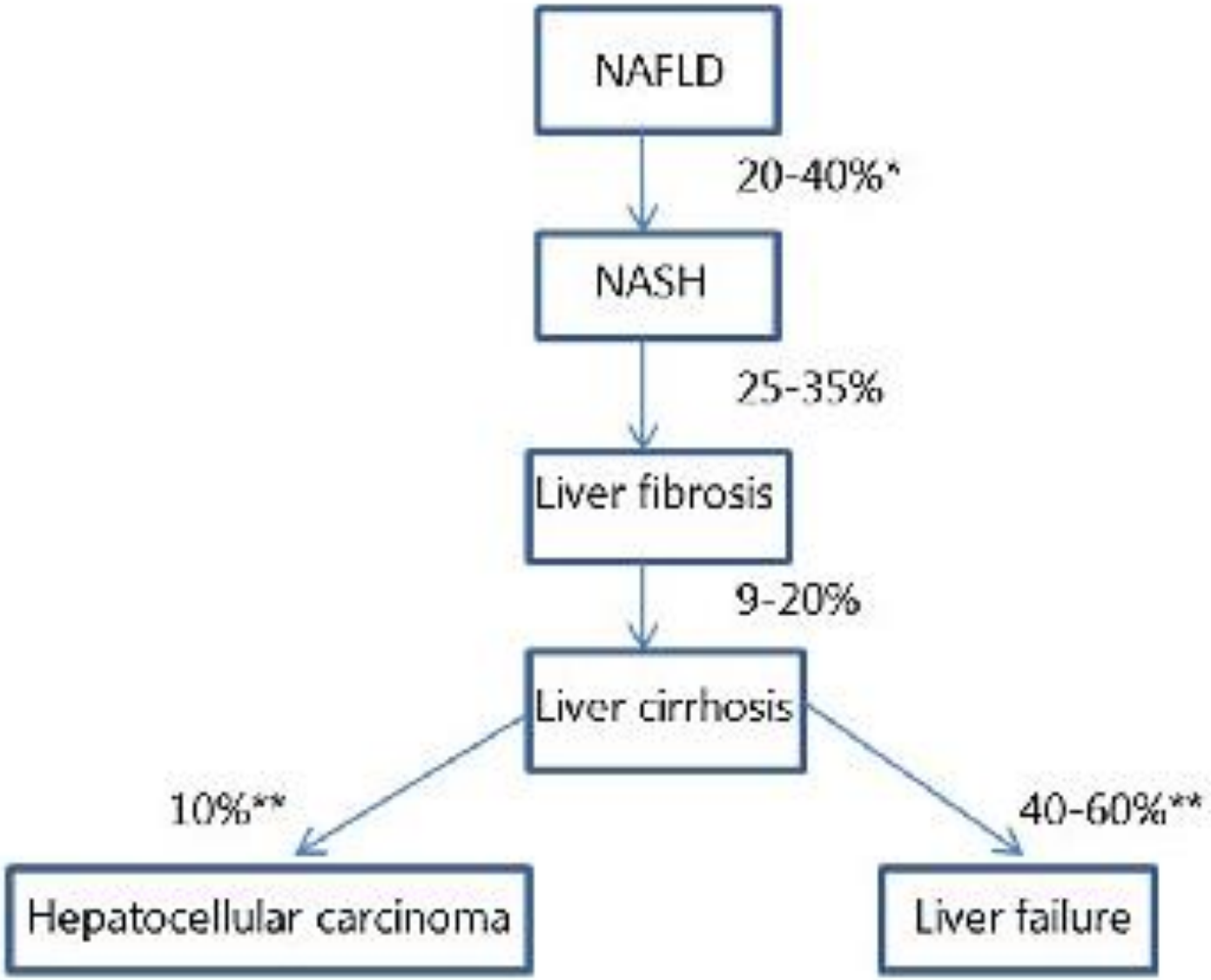
HIV patients - Are they different?

Infect Dis Ther (2019) 8:33–50
https://doi.org/10.1007/s40121-018-0229-7

REVIEW

A Review of Non-Alcoholic Fatty Liver Disease in HIV-Infected Patients: The Next Big Thing?

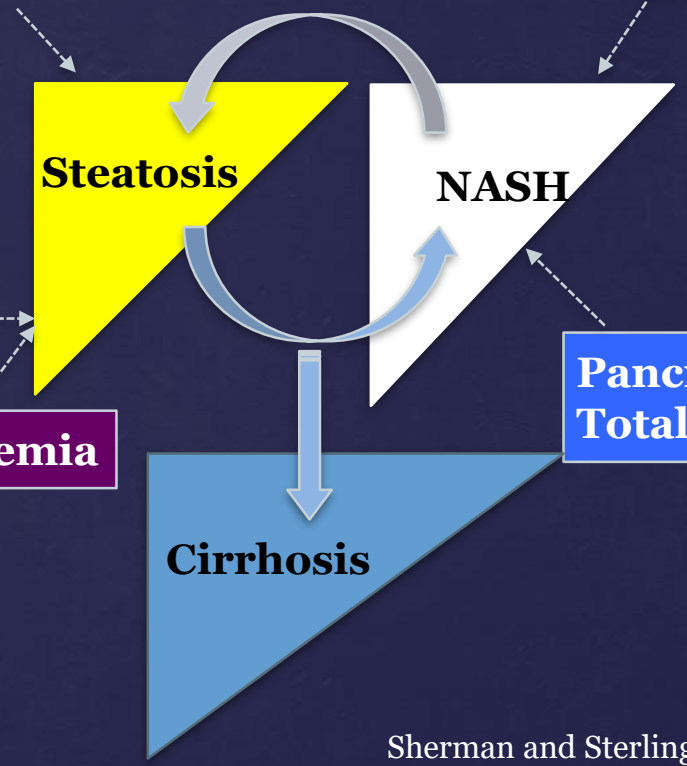
Berend J. van Welzen · Tania Mudrikova · Ayman El Idrissi · Andy I. M. Hoepelman · Joop E. Arends


NAFLD
20-40%*
NASH
25-35%
Liver fibrosis
9-20%
Liver cirrhosis
10%**
40-60%**
Hepatocellular carcinoma
Liver failure

Risk Factors for NALFD and NASH in those with HIV

Metabolic syndrome
- **Obesity**
- **Visceral and ectopic obesity**
- **Hypertension**
- **Diabetes**
- **Dyslipidemia**

Hormonal disturbances
- Hypothyroidism
- Hypopituitarism
- Hypogonadism
- PCOS



HIV Medications

Hyperuricemia

Pancreatico-biliary diversion
Total parenteral nutrition

Sherman and Sterling *in* Zakim and Boyer, HEPATOLOGY 2017

BMJ Open Gastroenterology

Mechanisms of liver disease in patients infected with HIV

Matthew B Kaspar,[1] Richard K Sterling[1,2,3]

Table 1 Mechanisms of hepatic injury/fibrosis and corresponding disease states

	Alcoholic liver disease	NAFLD	HBV	HCV	Drug effects	HIV-specific effects	Autoimmune disease	Senescence
Oxidative stress	+	++	+++	+++	+	++		
Mitochondrial injury	++	+			++	++		
Lipotoxicity		+++			+			
Immune mediated			+	+		++	+++	
Cytotoxic						+		
Accumulation of toxic metabolite	+++				+++			
Gut microbial translocation	+	+				+++		
Systemic inflammation		++	++	++		+++		
Senescence								+++
Nodular regenerative hyperplasia					+	+++		

+, mild contribution; ++, moderate contribution; +++, significant contribution.
HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.

Citation: Dold L, Luda C, Schwarze-Zander C, Boesecke C, Hansel C, Nischalke H-D, et al. (2017) Genetic polymorphisms associated with fatty liver disease and fibrosis in HIV positive patients receiving combined antiretroviral therapy (cART). PLoS ONE 12(6): e0178685. https://doi.org/10.1371/journal.pone.0178685

RESEARCH ARTICLE

Genetic polymorphisms associated with fatty liver disease and fibrosis in HIV positive patients receiving combined antiretroviral therapy (cART)

Leona Dold[1,2]*, Carolin Luda[1,2], Carolynne Schwarze-Zander[1,2], Christoph Boesecke[1,2], Cordula Hansel[3], Hans-Dieter Nischalke[1,2], Philipp Lutz[1,2], Raphael Mohr[1,2], Jan-Christian Wasmuth[1,2], Christian P. Strassburg[1,2], Jonel Trebicka[1], Jürgen Kurt Rockstroh[1,2], Ulrich Spengler[1,2]

Table 4. Parameters entering the final regression models.

A) Steatosis (CAP ≥300 dB/m):			
Parameter	Level of significance	Hazard ratio	95% Confidence Interval
Triglycerides (mg/dl)	p = 0.006	1.006	(1.002–1.009)
Bilirubin (mg/dl)	p = 0.021	2.568	(1.155–5.710)
BMI (Kg/m^2)	p = 0.068	1.103	(0.993–1.227)
B) Fibrosis (Stiffness ≥7.1 kPa)			
Parameter	Level of significance	Hazard ratio	95% Confidence Interval
AST (IU/ml)	p = 0.006	1.087	(1.027–1.151)

https://doi.org/10.1371/journal.pone.0178685.t004

Cohort studies (excluding: HBV/HCV, excess alcohol use)

Study	N.	% F	Prevalence
Crum-Cianflone, 2009	216	5.6	31% **NAFLD**
Guaraldi, 2008	255	24.3	37% **NAFLD**
Ingilinz, 2009	30	3	60% **steatosis** (89% of these w/ NASH)
Kardashian, 2017	229	35	F: 17% **steatosis** M: 41% **steatosis**
Lemoine, 2006	33	14.3	57% **NASH**
Lombardi, 2016	125	8	55% **steatosis**
Lui, 2016	240	7	29% **FL**
Mohammed, 2007	51	0	35% **steatosis** 65% **NASH**
Morse, 2015	62	6	73% **NAFLD** 55% **NASH**
Nishijima, 2014	435	7	31% **NAFLD**
Sebastiani, 2015	796	16	24% **steatosis** (6.8 x 100 PY)
Sterling, 2013	14	29	65% **steatosis** 26% **NASH**
Vodkin, 2015	66	21.2	64% **NASH**
Vuille-Lessard, 2016	300	23.3	48% **NAFLD**

Cohort studies (excluding: HBV/HCV, excess alcohol use)

Study	Associations
Crum-Cianflone	**NAFLD**: WC, TG, HDL; **ART: not significant**
Guaraldi	**NAFLD**: ALT/AST, WC, M, **longer NRTI exposure**
Ingilinz	**NASH** (univariate): fasting G, fasting I, HOMA; **ART: not significant**
Kardashian	**Liver fatty fraction**: VAT, HOMA-IR; **HIV factors: not significant**
Lemoine	**Stetosis**: **expression of SREBP-1**
Lombardi	**Steatosis**: M, age, HOMA index, GGT; **ART: not significant**
Lui	**FL**: TG; HIV factors: **not significant**
Mohammed	-
Morse	**NASH**: IR, obesity, **PNPLA3 gene SNPs**; **HIV factors: not significant**
Nishijima	**NAFLD**: BMI, dyslipidaemia, ALT/AST; **HIV factors: not significant**
Sebastiani	**Steatosis**: black ethnicity, albumin
Sterling	**Steatosis:** GGT **NASH**: HOMA-IR
Vodkin	**NAFLD**: APRI, FIB-4 **NASH**: **duration of HIV**
Vuille-Lessard	**NAFLD**: BMI, ALT

HIV patients - Still an impact of cART?

- **NRTIs**
  - **Mitochondrial dysfunction** (peripheral, liver)
    - Insulin resistance, dyslipidemia
  - Nowadays less than a problem
  - TDF vs. TAF?
- **PIs**
  - **Isoform specific inhibition of the transport function of the GLUT4-receptor**
  - **Inhibition of insulin secretion**
    - Hyperglycemia, hyperinsulinemia
  - **Apolipoprotein B increase**
  - **Inhibition of triglyceride clearance** (RTV, mice)
    - Dyslipidemia
  - Nowadays less than a problem
- **NNRTIs**
  - Less than a problem (especially nowadays)
- **INSTIs**
  - Body weight effect?
  - Pro-adipogenic and pro-fibrotic effects?

Canadian Journal of Cardiology 35 (2019) 249–259

Review

Lipid Abnormalities in Persons Living With HIV Infection

David D. Waters, MD, and Priscilla Y. Hsue, MD

Division of Cardiology, Zuckerberg San Francisco General Hospital, and Department of Medicine, University of California, San Francisco, California, USA

Table 3. Effects of selected new ART drugs on lipid and related parameters

	Maraviroc	Raltegravir	Atazanavir
Type of drug	Entry inhibitor	Integrase inhibitor	Protease inhibitor
Effect on lipids	Improved TC and LDL-C	Improved TC, LDL-C, TGs vs most regimens	Improved TC, LDL-C, TGs
Metabolic effects	Increased BMI, more new-onset diabetes	Increased BMI, truncal fat, less lipoatrophy	Increased truncal fat vs same regimens
Flow-mediated dilatation	Improved	No change	No change; decreased cIMT

The findings listed in the table are usually from studies comparing these drugs with other commonly used ART drugs, or with placebo against a background of ART.

ART, antiretroviral therapy; BMI, body mass index; cIMT, carotid intima-media thickness; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

Canadian Journal of Cardiology 35 (2019) 249–259

Review

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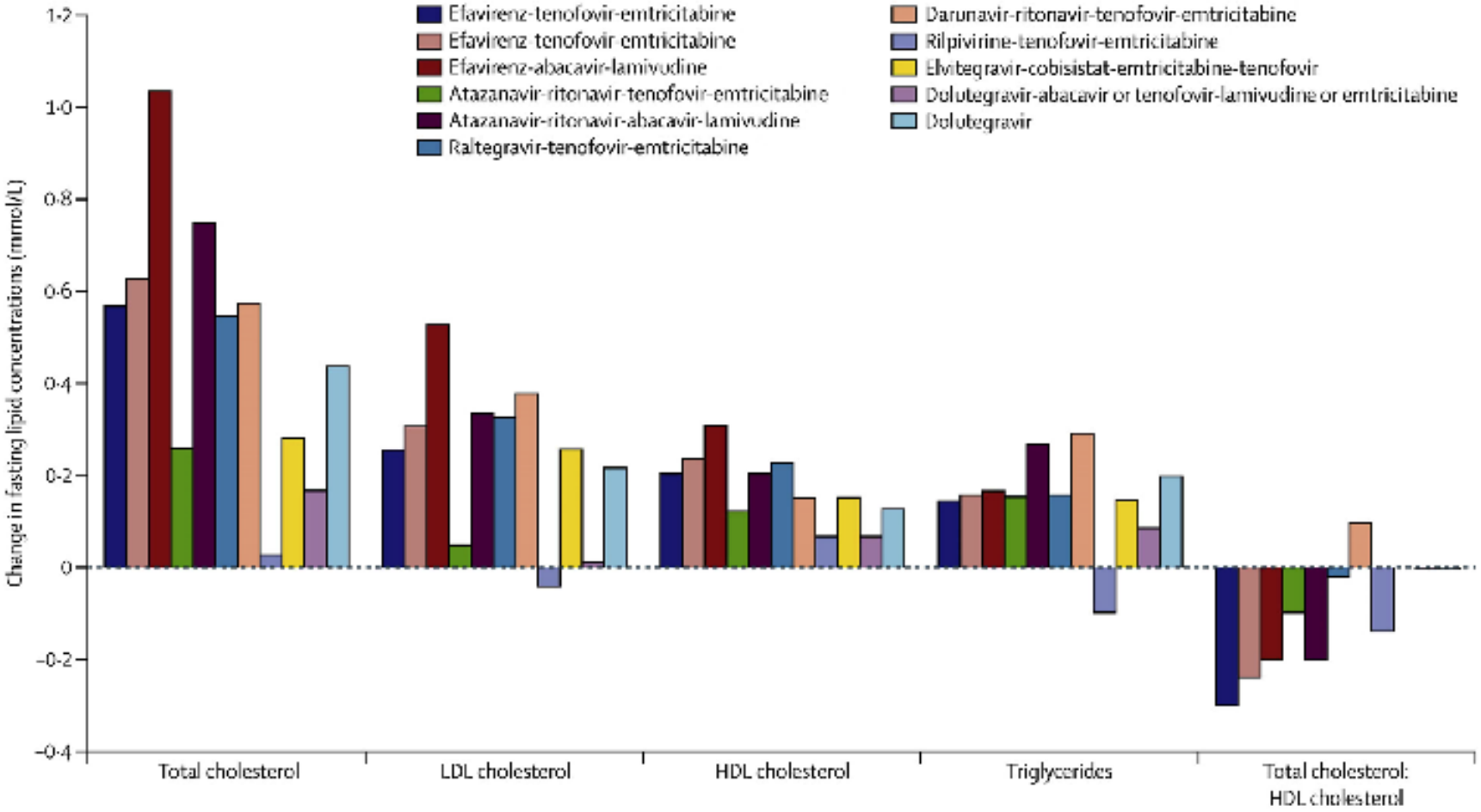

Figure 2. Effects of common combinations of antiretroviral therapy on lipid levels. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

BMJ Open Diabetes Research & Care

Incidence of diabetes mellitus and factors associated with its development in HIV-positive patients over the age of 50

Faizal Samad,[1] Marianne Harris,[2,3] Cathy M Puskas,[4] Monica Ye,[5] Jason Chia,[5] Sarah Chacko,[6] Gregory P Bondy,[7] Viviane D Lima,[5,8] Julio SG Montaner,[2,8] Silvia A Guillemi[3,4]

To cite: Samad F, Harris M, Puskas CM, *et al*. Incidence of diabetes mellitus and factors associated with its development in HIV-positive patients over the age of 50. *BMJ Open Diab Res Care* 2017;**5**:e000457. doi:10.1136/bmjdrc-2017-000457

Objective We sought to determine the incidence and factors associated with development of diabetes mellitus (DM) in older HIV-infected individuals.

Research design and methods We analyzed data from people living with HIV (PLWH) ≥50 years of age enrolled in a large urban HIV outpatient clinic in Vancouver, British Columbia. Patients were categorized as having DM if they had random blood sugar ≥11.1 mmol/L, fasting blood sugar ≥7 mmol/L, HbA1C ≥6.5%, antidiabetic medication use during the follow-up period, or medical chart review confirming diagnosis of DM. We estimated the probability of developing DM, adjusting for demographic and clinical factors, using a logistic regression model.

Results Among 1065 PLWH followed for a median of 13 years (25th and 75th percentile (Q1–Q3): 9-18), the incidence of DM was 1.61/100 person-years follow-up. In the analysis of factors associated with new-onset DM (n=703), 88% were male, 38% had a history of injection drug use, 43% were hepatitis C coinfected, and median body mass index was 24 kg/m^2 (Q1–Q3: 21–27). Median age at antiretroviral therapy (ART) initiation was 48 years (Q1–Q3: 43–53) and at DM diagnosis was 55 years (Q1–Q3: 50–61). Patients who started ART in 1997–1999 and had a longer exposure to older ART were at the highest risk of developing DM.

Conclusions Among PLWH aged ≥50 years, the incidence of DM was 1.39 times higher than men in the general Canadian population of similar age. ART initiated in the early years of the epidemic and exposure to older ART appeared to be the main drivers of the development of DM.

BMJ Open Diabetes Research & Care

Incidence of diabetes mellitus and factors associated with its development in HIV-positive patients over the age of 50

Faizal Samad,[1] Marianne Harris,[2,3] Cathy M Puskas,[4] Monica Ye,[5] Jason Chia,[5] Sarah Chacko,[6] Gregory P Bondy,[7] Viviane D Lima,[5,8] Julio SG Montaner,[2,8] Silvia A Guillemi[3,4]

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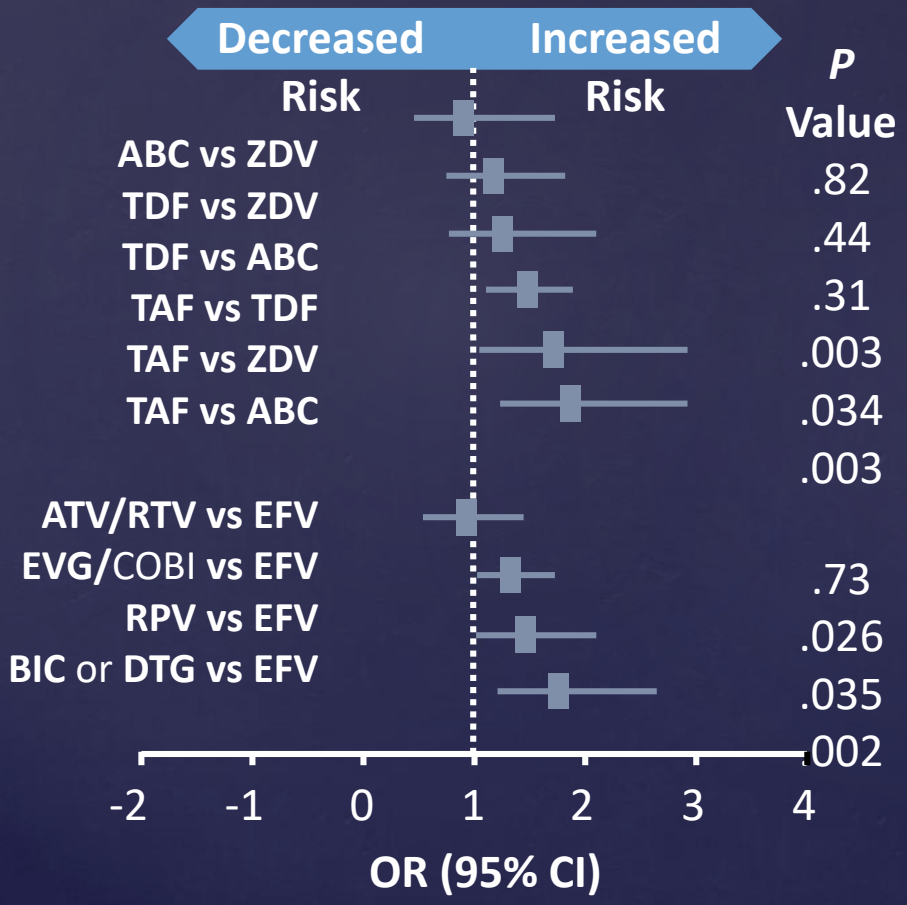
Table 4 Proportion of time (%) on antiretroviral agents during follow-up (n=703)

Antiretroviral agents	Proportion of follow-up time (%); no diabetes (n=571) Mean (SD)	Proportion of follow-up time (%); with diabetes (n=132) Mean (SD)	P value
Nucleoside reverse transcriptase inhibitors			
Stavudine	7.2 (14.6)	21.1 (26.4)	<0.001
Zidovudine	5.0 (14.5)	10.9 (22.8)	0.011
Didanosine	3.6 (11.0)	11.5 (21.7)	<0.001
Lamivudine or emtricitabine	82.5 (23.1)	78.8 (23.2)	0.027
Abacavir	23.1 (32.7)	16.3 (26.6)	0.084
Tenofovir disoproxil fumarate	51.5 (38.1)	38.4 (33.4)	<0.001
Protease inhibitors			
Indinavir	2.1 (7.5)	6.4 (15.0)	<0.001
Saquinavir	1.3 (6.5)	2.3 (9.6)	0.079
Nelfinavir	0.6 (3.5)	2.8 (11.4)	0.033
Lopinavir	9.3 (21.1)	21.1 (29.2)	<0.001
Atazanavir	38.1 (39.0)	28.4 (33.5)	0.021
Darunavir	3.5 (13.2)	1.6 (9.1)	0.007

INSTIs and TAF Associated With Greater Weight Gain vs Other ARVs

Risk of Weight Gain ≥ 10%[1]

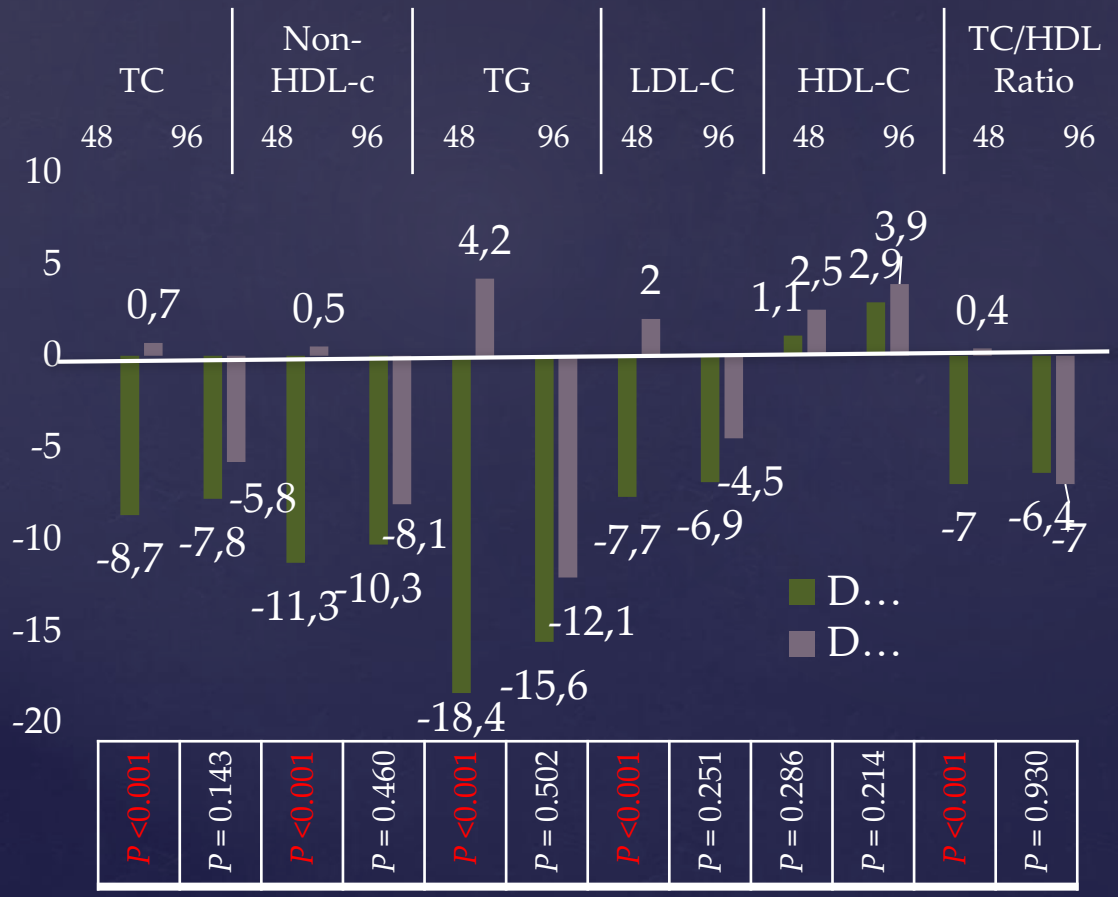


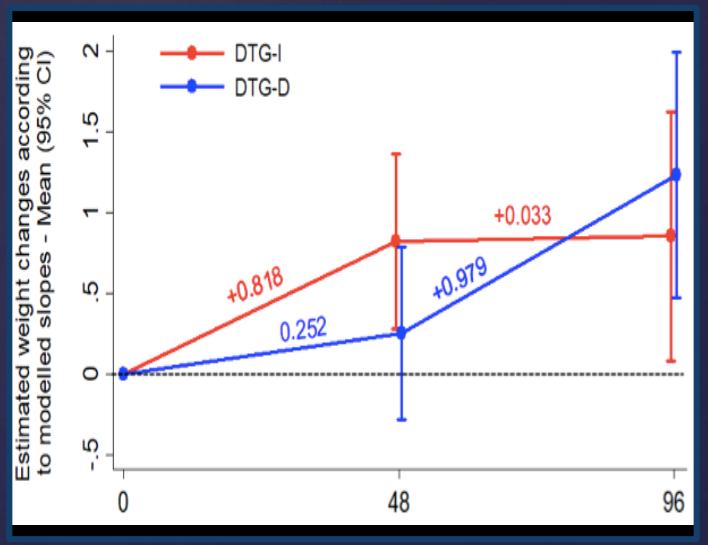
- In separate retrospective observational study, 6-12 mos after suppressed patients switched from TDF to TAF (N = 110)[2,3]:
  - 0.45 BMI increase (P < .01)
  - 13% increase in ASCVD 10-yr risk score (P < .01)
    - Shifted 50.7% of patients to ASCVD scores indicating use of a statin

1. Sax. Clin Infect Dis. 2019;[Epub]. 2. Schafer. IDWeek 2019. Abstr 979. 3. Schafer. Open Forum Infect Dis. 2019;[Epub].

NEAT 022: Switch from PI/r to DTG improved lipids, led to increased weight

Lipid Profile (percentage variation)





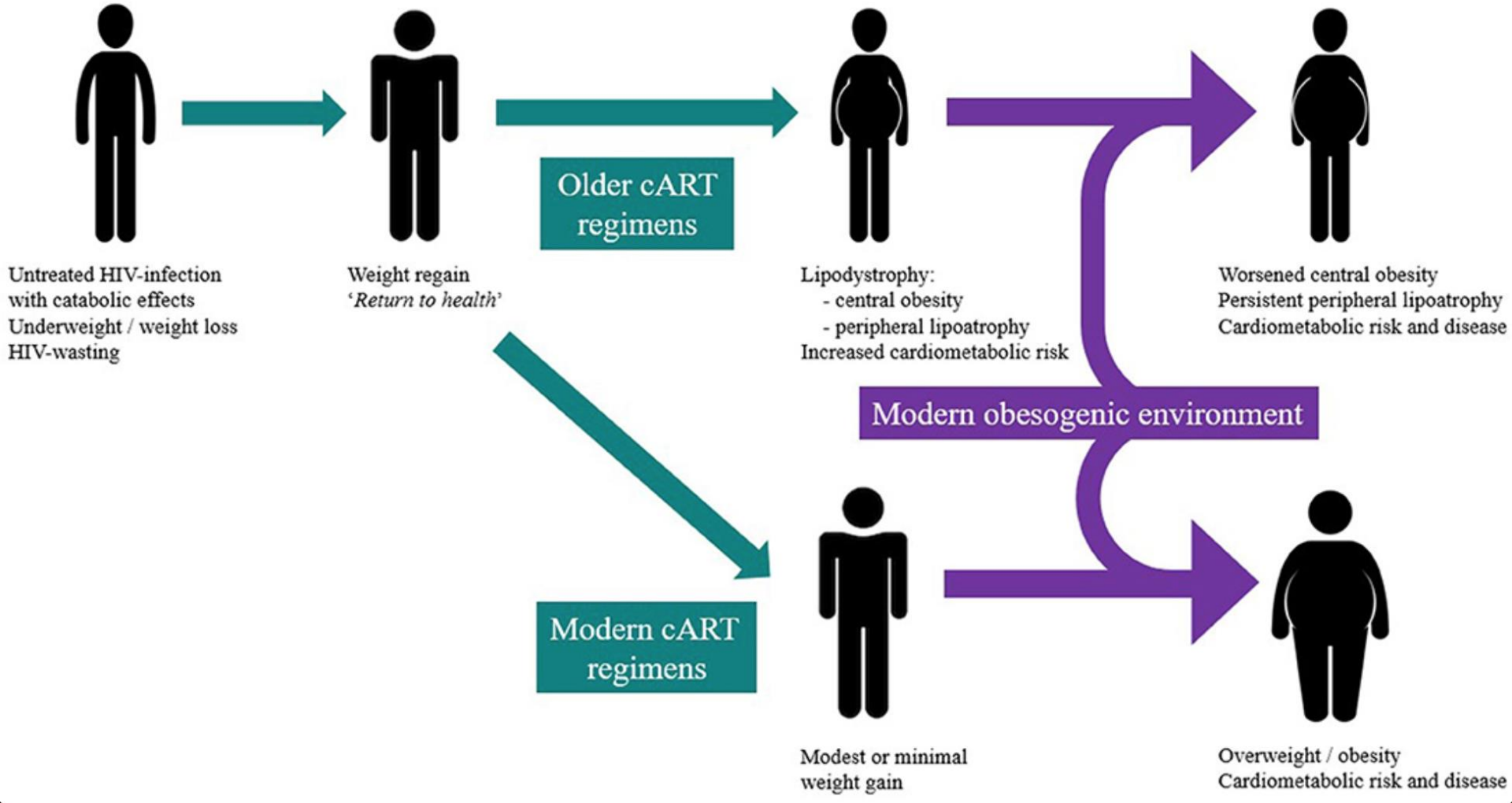
DTG-I = Immediate Switch Arm; DTG-D = Delayed Switch Arm

Gatell JM, et al. *Clin Infect Dis*. 2019;68(4):597–606.

REVIEW ARTICLE
Front. Endocrinol., 27 November 2018 | https://doi.org/10.3389/fendo.2018.00705 (https://doi.org/10.3389/fendo.2018.00705)

The Impact of Weight Gain During HIV Treatment on Risk of Pre-diabetes, Diabetes Mellitus, Cardiovascular Disease, and Mortality

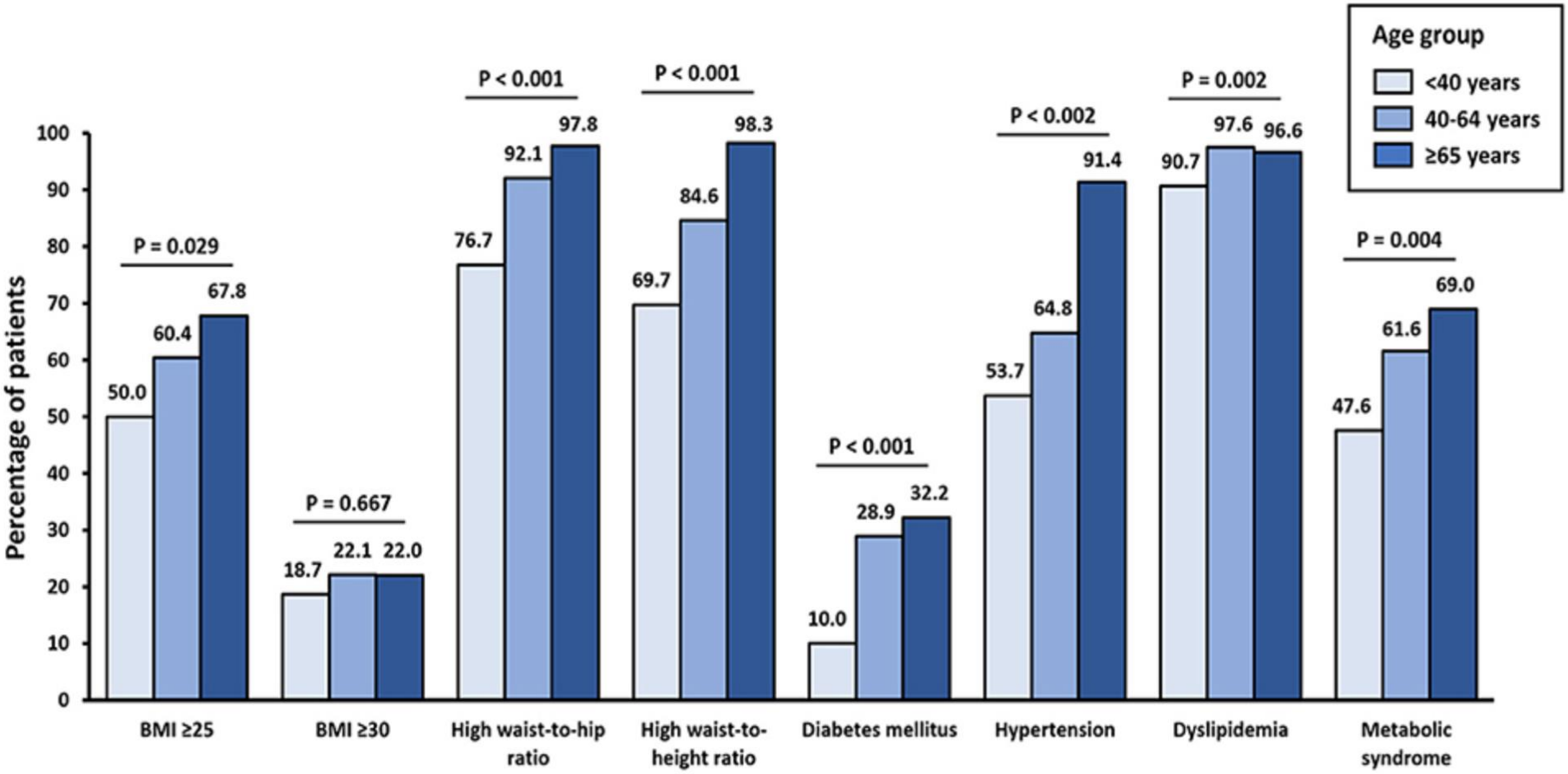
Shejil Kumar (http://www.frontiersin.org/people/u/568649)[1*] and Katherine Samaras (http://www.frontiersin.org/people/u/351098)[2,3,4]



ORIGINAL RESEARCH ARTICLE
Front. Endocrinol., 16 November 2018 | https://doi.org/10.3389/fendo.2018.00681 (https://doi.org/10.3389/fendo.2018.00681)

Metabolically Healthy or Metabolically Unhealthy Obese HIV-Infected Patients: Mostly a Matter of Age?

João Sérgio Neves (http://www.frontiersin.org/people/u/283481)[1,2*], Vanessa Guerreiro[1], Davide Carvalho (http://www.frontiersin.org/people/u/568711)[1,3], Rosário Serrão[3,4], António Sarmento[4] and Paula Freitas[1,3]



Exploring the Prevalence and Characteristics Associated with Weight Gain and Metabolic Changes in PLWH who are Virologically Suppressed on Antiretroviral Therapy and Switch to Integrase Inhibitor Containing Regimens

Matty Zimmerman[1], PharmD Student, Joseph DeSimone Jr.[2], MD, Jason J. Schafer[1], PharmD, MPH, BCPS-AQ ID, BCIDP, AAHIVP
Jefferson College of Pharmacy[1] and Sydney Kimmel Medical College[2], Thomas Jefferson University, Philadelphia, PA[1]

- Observational, retrospective chart review of PLWH at a single academic medical center from May 2015 to December 2017
- Eligible patients had been virally suppressed on a non-INSTI-containing ART regimen for at least 1 year before switching to INSTI-containing ART
- Body weight, cholesterol and A1C values were collected for the year prior to and 18 months following the switch
- Pre and post-switch median values of each parameter were calculated and compared using the Wilcoxon signed-rank test
- Predictors of weight gain were determined with simple linear regression

Conclusions

- Patient weight increased by a median of 1.7 kg after switching and 26% of patients gained ≥ 4.5 kg
- Despite changes in weight, patients did not experience significant changes in cholesterol or A1C values
- Weight gain appeared to be more substantial in individuals switching from NNRTIs and to DTG/TAF in unadjusted analyses
- In the regression model, sex, race, pre-switch BMI, and pre- and post-switch ART were not predictors for weight gain
- Increased age was protective against weight gain in the model

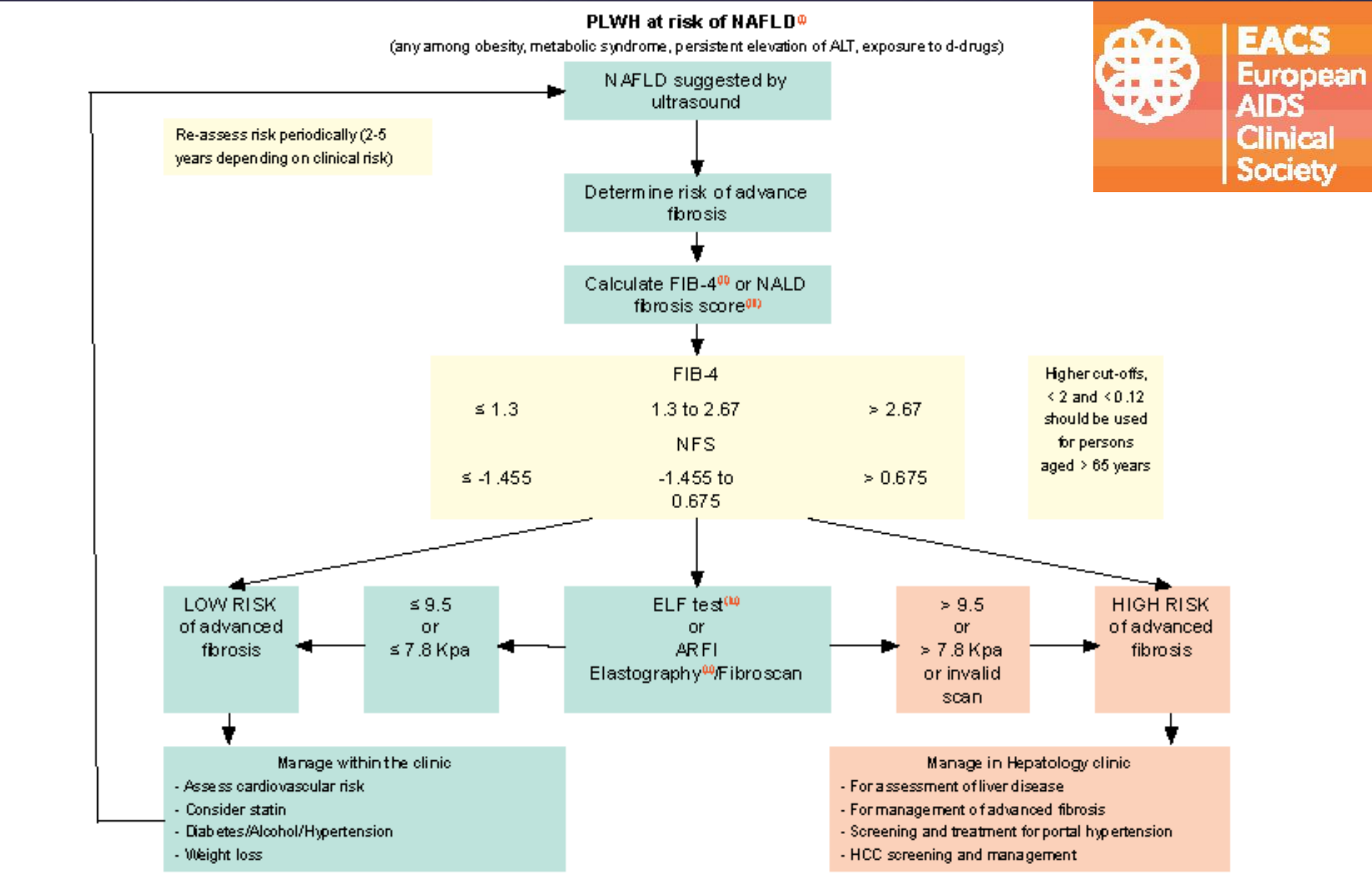
Characteristic	All (n = 90)
Mean Age - Years (range)	49.5 (28-75)
Male Sex, n (%)	75 (83)
Race, n (%)	
African American	49 (54)
Caucasian	30 (33)
Mean Years since HIV diagnosis (range)	12.9 (2-30)
Mean Number of Previous Regimens (range)	1.7 (1-7)
Mean Years on Previous Regimen (range)	7.0 (1-21)
Pre-switch BMI category, n (%)	
Underweight	2 (2)
Normal Weight	27 (30)
Overweight	38 (42)
Obese	23 (26)
Pre-switch ART, n (%)	
PI-based	47 (52)
NNRTI-based	40 (44)
Post-switch integrase inhibitor, n (%)	
Elvitegravir	57 (63)
Dolutegravir	33 (37)

Characteristic	Pre Switch	Post Switch	Change*
Total Cholesterol (n=79)	185.0 (51.0)	185.0 (46.5)	-1.0 (47.2)
HDL Cholesterol (n=79)	48.0 (18.5)	48.0 (19.7)	1.0 (12.0)
LDL Cholesterol (n=78)	107.5 (39.5)	104.0 (37.8)	1.3 (35.0)
Triglycerides (n=79)	147.8 (135.7)	140.0 (121.0)	5.0 (68.3)
Hemoglobin A1C (n=24)	5.8 (1)	5.6 (1.4)	-0.1 (0)
ASCVD Risk Score (n=67)	6.8 (12)	7.2 (11)	0.6 (3.1)

Data displayed as medians and IQR
*All p-values >0.05

Effect	Parameter Estimate	95% Confidence Interval	p value
Intercept	7.182	3.413, 10.952	
Age	-0.101	-0.176, -0.027	0.008

HIV patients – What to do?



These recommendations are largely inspired by the EASL–EASD–EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease: European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity [18]

i NAFLD, Non-alcoholic fatty liver disease

ii FIB-4 = Age ([years] x AST [U/L]) / ([platelet [10^9/L]) x ALT [U/L])

iii NFS, Non-alcoholic fatty liver disease Fibrosis Score = -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x impaired fasting glucose/diabetes mellitus[N] (yes=1/no=0) + 0.99 x AST/ALT ratio-0.013 x platelet (x10^9)-0.66 x albumin(g/dL)

iv ELF™ test, Enhanced Liver Fibrosis Test is a blood test that provides an estimate of liver fibrosis severity by measuring Hyaluronic Acid (HA), Amino-terminal propeptide of type III procollagen (PIIINP), Tissue inhibitor of metalloproteinase 1 (TIMP-1)

v ARFI elastography, Acoustic Radiation Force Impulse

DOI: 10.1111/hiv.12799
HIV Medicine (2019)

ORIGINAL RESEARCH

Application of guidelines for the management of nonalcoholic fatty liver disease in three prospective cohorts of HIV-monoinfected patients*

G Sebastiani,[1,2] S Cocciolillo,[1] G Mazzola,[3] A Malagoli,[4] J Falutz,[2] A Cervo,[3] S Petta,[5] T Pembroke,[1,6] P Ghali,[1] G Besutti,[7,8] I Franconi,[4] J Milic,[4,8] A Cascio[3] and G Guaraldi[4,9]

A total of 1534 HIV-infected adults without significant alcohol intake or viral hepatitis coinfection were included in the study. Of these, 313 (20.4%) patients had the metabolic comorbidities (obesity and/or diabetes) required for entry in the diagnostic algorithm. Among these patients, 123 (39.3%) required specialist referral to hepatology, according to guidelines. A total of 1062 patients with extended metabolic comorbidities (any among obesity, diabetes, hypertension and dyslipidaemia) represented most of the cases of NAFLD (79%), elevated ALT (75.9%) and medium/high-risk fibrosis category (75.4%). When the algorithm was extended to these patients, it was found that 341 (32.1%) would require specialist referral to hepatology.

Conclusions

According to current guidelines, one in five HIV-monoinfected patients should undergo detailed assessment for NAFLD and disease severity. Moreover, one in ten should be referred to hepatology. Expansion of the algorithm to patients with any metabolic comorbidities may be considered.

Obesity/Diabetes

Any metabolic comorbidities

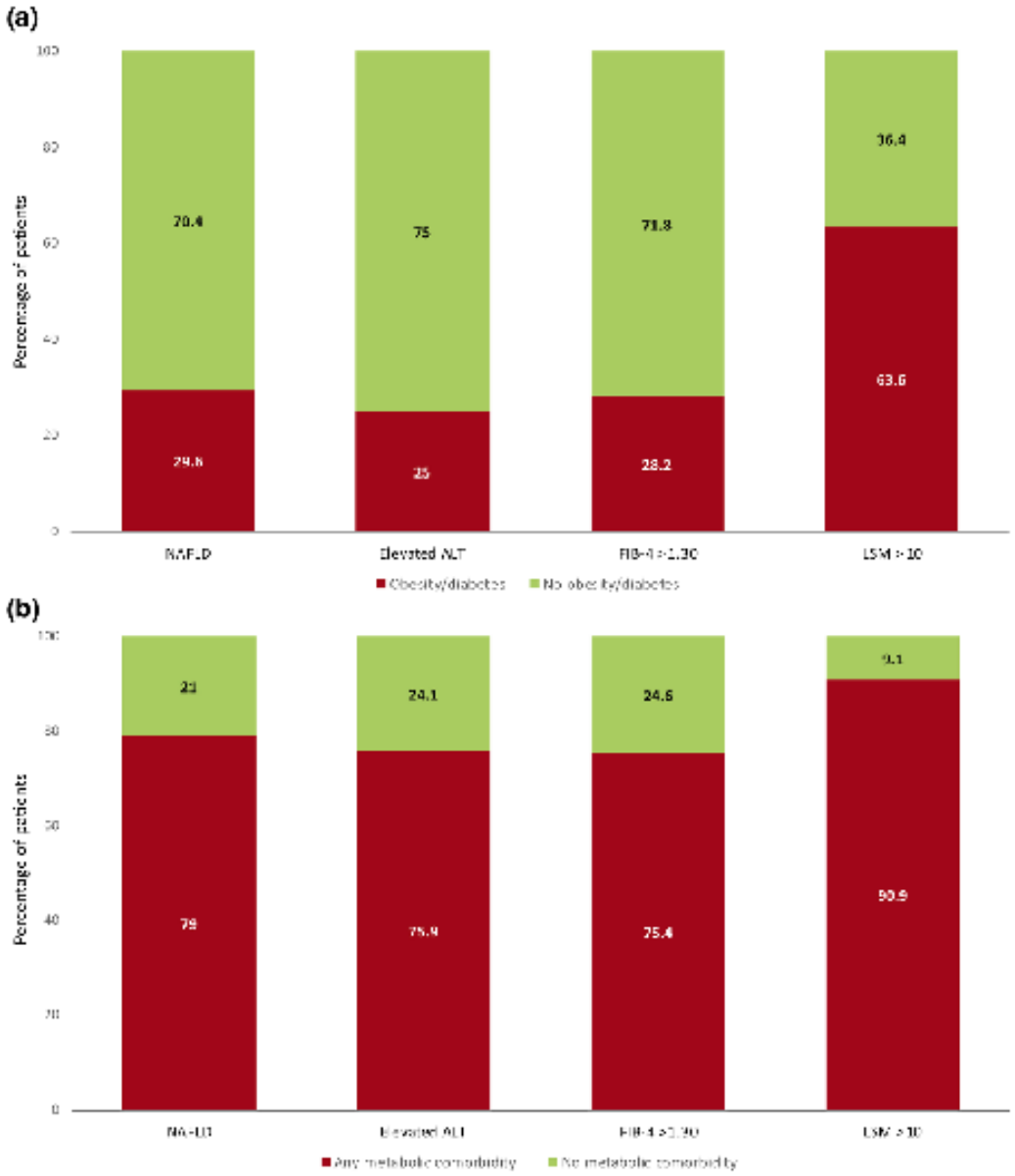


Fig. 2 (a) Proportion of patients with and without obesity/diabetes in those with nonalcoholic fatty liver disease (NAFLD), elevated alanine aminotransferase (ALT), fibrosis 4 (FIB 4) > 1.30 and liver stiffness measurement (LSM) > 10 kPa; (b) proportion of patients with and without any metabolic comorbidities in those with NAFLD, elevated ALT, FIB 4 > 1.30 and LSM > 10 kPa. LSM was available in the Liver Disease in HIV (LIVEHIV) and Liver Pathologies in HIV in Palermo (LivHIVPa) cohorts only.

Table 3 Multivariable analysis of factors associated with the need for specialist referral to hepatology in patients with obesity and/or diabetes (n = 313) and in patients with any metabolic comorbidities (n = 1062)

Variable	OR (95% CI)	aOR (95% CI)
Obesity and/or diabetes		
Age (per 10 years)	1.35 (1.06 1.72)	0.97 (0.68 1.40)
Male sex (yes versus no)	2.71 (1.55 4.72)	1.92 (0.91 4.04)
Black ethnicity (yes versus no)	0.15 (0.06 0.34)	0.24 (0.08 0.71)
Hypertension (yes versus no)	1.81 (1.14 2.87)	1.32 (0.68 2.55)
IDU (yes versus no)	2.73 (1.41 5.28)	3.14 (1.33 7.39)
Undetectable HIV viral load (yes versus no)	1.36 (0.74 2.49)	0.49 (0.21 1.15)
NNRTI exposure (yes versus no)	0.60 (0.36 0.99)	0.79 (0.43 1.47)
Triglycerides (per mmol/L)	1.22 (1.01 1.48)	1.14 (0.89 1.46)
Any metabolic comorbidities		
Age (per 10 years)	1.27 (1.10 1.47)	0.97 (0.78 1.21)
Male sex (yes versus no)	2.37 (1.67 3.36)	2.34 (1.51 3.62)
Black ethnicity (yes versus no)	0.23 (0.12 0.45)	0.24 (0.11 0.56)
Diabetes (yes versus no)	1.77 (1.30 2.41)	1.78 (1.21 2.61)
Hypertension (yes versus no)	1.89 (1.46 2.46)	1.44 (1.02 2.04)
IDU (yes versus no)	2.76 (2.01 3.80)	2.57 (1.75 3.79)
Undetectable HIV viral load (yes versus no)	1.12 (0.75 1.66)	0.63 (0.38 1.04)
NNRTI exposure (yes versus no)	0.88 (0.66 1.18)	1.09 (0.78 1.52)

aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; IDU, injecting drug use; MSM, men who have sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor.
Odds ratios and 95% confidence interval are presented for each variable in the unadjusted and adjusted analysis.

Non-Alcoholic Fatty Liver Disease is a significant predictor of cardiovascular risk in HIV-infected patients

17th EUROPEAN AIDS CONFERENCE November 6 - 9, 2019 Basel, Switzerland

G. Mazzola, A. Cervo, G. Sebastiani, G. Guaraldi, S. Mazzola, T. Krahn, J. Milovic, C. Gioé, P.Colletti, A. De Luca, S. Petta, A. Cascio

Conclusion

- NAFLD is a strong predictor of cardiovascular disease in people living with HIV.
- Early recognition of NAFLD may allow to implement life-style modification and treatment to prevent cardiovascular disease.

Table 2. Multivariable analysis of predictors of higher cardiovascular risk in the study population (n =982)

	aOR	95 % CIs	p - value
NAFLD (CAP ≥ 288 dB/m)	**1.50**	**1.05 – 2.14**	**0.03**
Liver Fibrosis (TE > 7 kPa)	1.19	0.82 – 1.74	0.35
BMI > 25 kg/m²	**1.85**	**1.38 - 2.49**	**< 0.001**
Nadir CD4 < 200/mmc	1.28	0.97 – 1.69	0.07
Active IVDU	0.99	0.65 – 1.53	0.99
Duration of HIV infection	**1.05**	**1.03 – 1.06**	**< 0.001**

Adjusted odds ratio (aOR) and 95% confidence intervals (CIs) are shown for each variable analysed in multivariate logistic regression model. P-value is considered significant when less than 0.05.

Components of a lifestyle approach to NAFLD

Energy restriction
- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake
- Avoid fructose-containing food and drink

Coffee consumption
- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake
- Strictly below 30 g men and 20 g women

Macronutrient composition
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Treatment: pharmacotherapy

- Treatment should be indicated in:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necroinflammatory activity
- Treatment should reduce NASH-related mortality and progression to cirrhos
  - Resc dpoint
- Safety
  - Exte acy and increased likelihood of DDIs

No drugs are approved for NASH
No specific therapy can be recommended
Any drug treatment is off label

Recommendations	Grade of evidence	Grade of recommendation
Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression could also be candidates for treatment	B	1

*Age > 50 years, diabetes, MetS, increased ALT

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Treatment: pharmacotherapy

- Insulin sensitizers
  - Little evidence of histological efficacy with metformin
  - PPARγ agonist pioglitazone better than placebo
    - Improved all histological features except fibrosis
    - Achieved resolution of NASH more often
- Antioxidants
  - Vitamin E may improve steatosis, inflammation and ballooning and resolve NASH in some patients
    - Concerns about long-term safety exist

Recommendations	Grade of evidence	Grade of recommendation
While no firm recommendations can be made, pioglitazone* or vitamin E† or their combination could be used for NASH	B	2
The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy‡	C	2

*Most efficacy data, but off-label outside T2DM; †Better safety and tolerability than pioglitazone in the short-term; ‡No recommendations can be made in patients with normal baseline ALT

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Treatment: pharmacotherapy

- Lipid-lowering agents
  - Statins have not been adequately tested in NASH

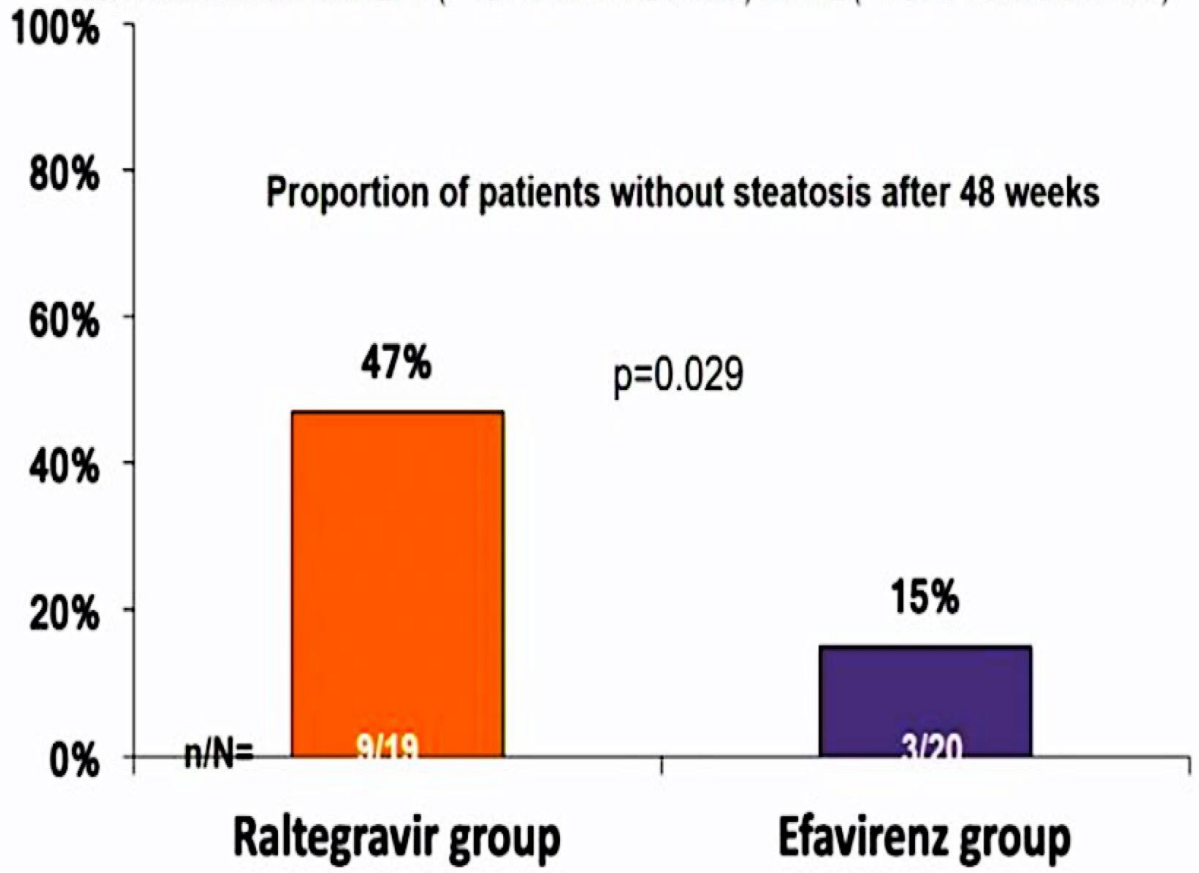
Recommendations	Grade of evidence	Grade of recommendation
Statins may be confidently used to reduce LDL cholesterol and prevent cardiovascular risk, with no benefits or harm to liver disease. Similarly, n-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH	B	1

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Changes in liver steatosis after switching efavirenz to raltegravir: the STERAL trial

N=39 HIV/HCV co-infected patients with steatosis diagnosed with CAP>238

Intervention: switch from EFV (+ TDF/FCT or ABC/3TC) to RAL (+ TDF/FTC or ABC/FCT)



Macias, Cilinical Infectious Diseases 2017


LESS IS
MORE

Patients characteristics at baseline

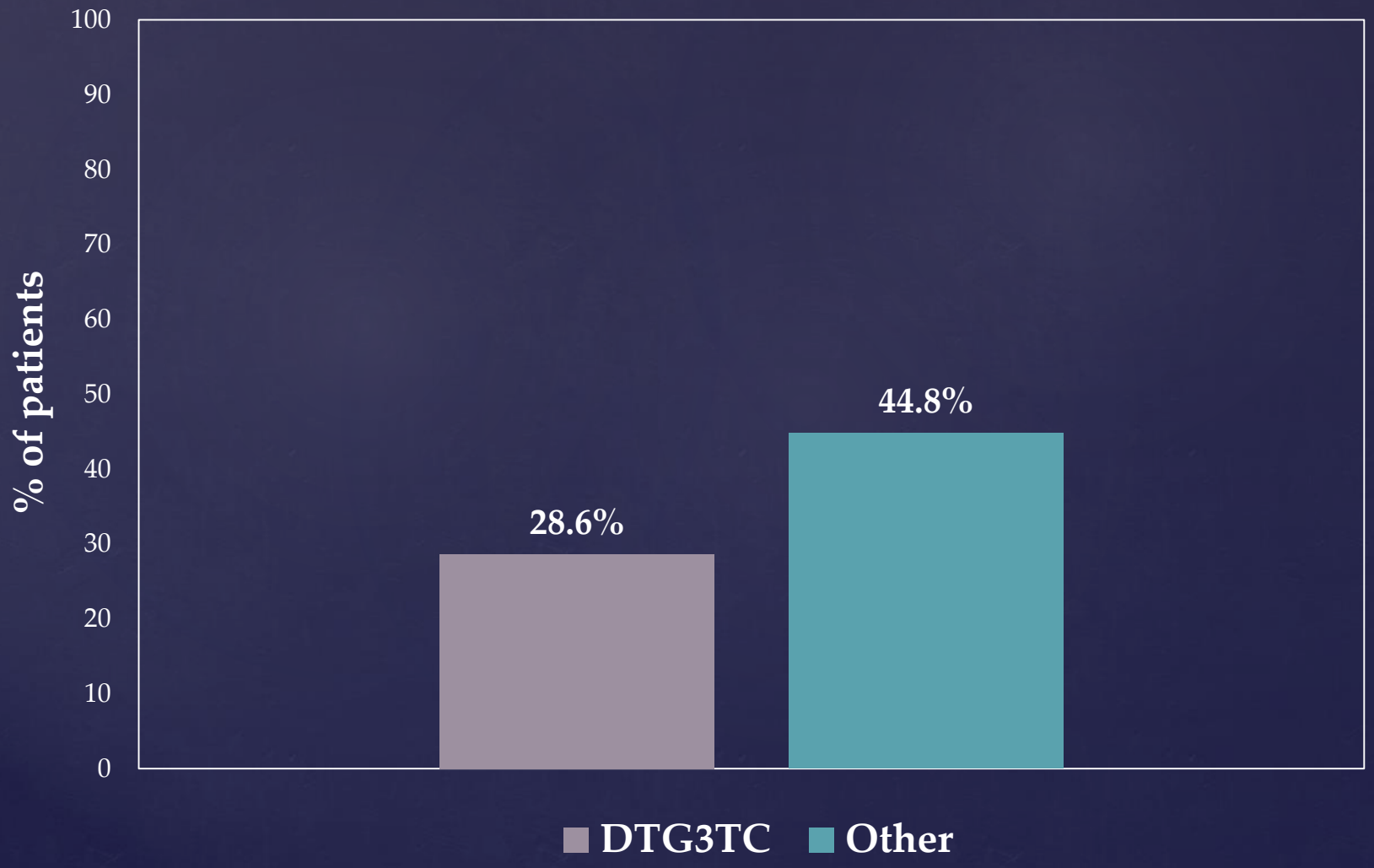
	Overall (n=72)
Male sex, n (%)	51 (70.8)
Age (Years), median (IQR)	47.9 (41.4-55.0)
HIV risk factor, n (%):	
- MSM	40 (55.6)
- Heterosexual	31 (43.1)
- IDU	1 (1.3)
Years from HIV diagnosis, median (IQR)	10.2 (3.9-17.7)
Years on ARV, median (IQR)	8.0 (3.8-13.7)
Previous AIDS event, n (%)	23 (31.9)
Months of virological suppression, median (IQR)	60.2 (26.3-111.9)
Peak HIV-RNA (log10 copies/mL), median (IQR)	5.01 (4.15-5.70)
Nadir CD4+ cell count (cell/mm3), median (IQR)	167 (30-271)
Previous virological failure, n (%)	25 (34.7)
ARV regimen at baseline, n (%):	
- 2NRTI + INI	32 (44.4)
- 2NRTI + NNRTI	9 (12.5)
- 2NRTI + PI	4 (5.6)
- 3TC+bPI	9 (12.5)
- 3TC+DTG	16 (22.2)
- Other	2 (2.8)
Diagnosis of steatosis, n (%)	30 (41.7)
Right hepatic lobe diameter (cm), median (IQR)	14.8 (13.1-16.1)
Spleen diameter (cm), median (IQR)	10.5 (9.6-12.0)
Spleen surface (cm2), median (IQR)	36.5 (32.1-49.5)

Courtesy Dr Simona Di Giambenedetto, UCSC, Rome

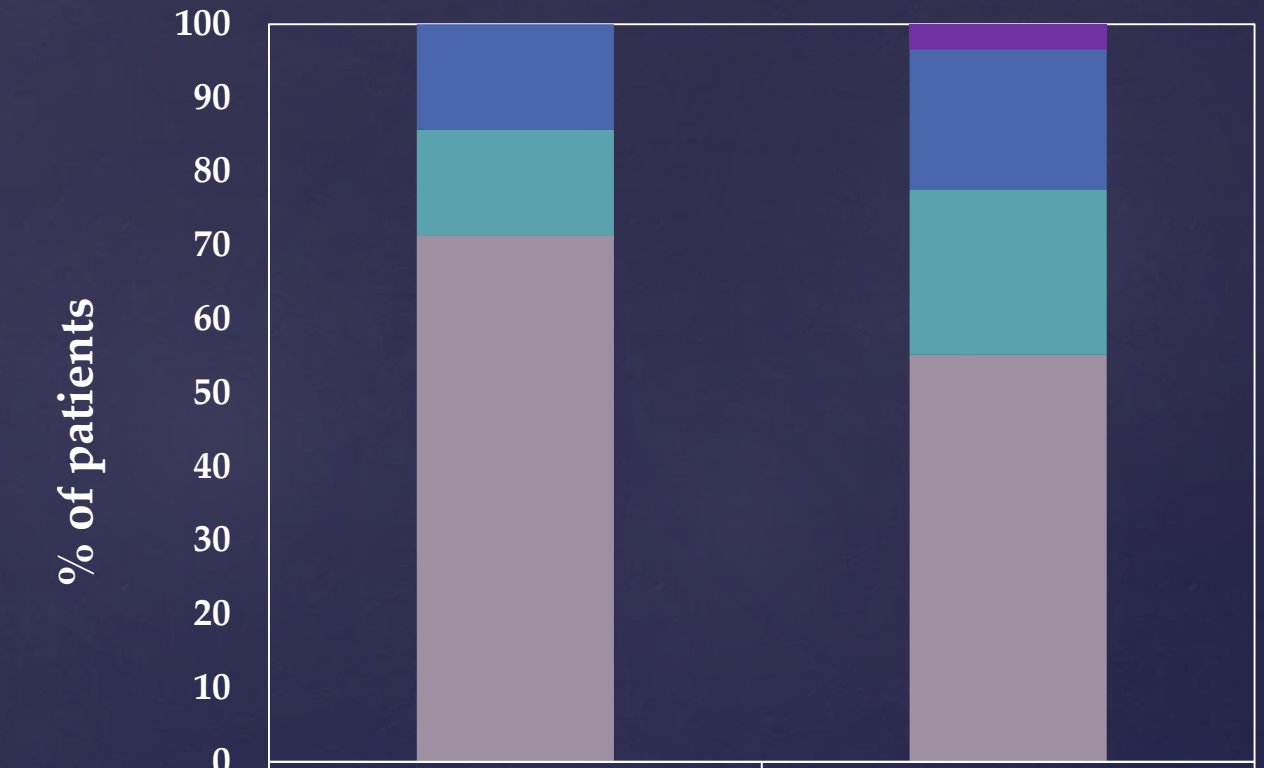
Results

- Thirty patients (41.7%) presented a radiologic pattern of steatosis: 15 presented with mild steatosis, 13 moderate and 2 with severe steatosis.
- In our cohort, in a multivariate analysis, we found that:
  - the condition of steatosis was predicted by a previous baseline AIDS event (aHR 13.1, 95%CI 1.9-90.0, p=0.009) and a higher baseline GPT value (aHR 1.05, 95%CI 1.01-1.10, p=0.029)
  - being on a dual regimen with 3TC+DTG (aHR 0.03, 95%CI 0.01-1.08, p=0.05) was inversely associated with hepatic steatosis, after adjusting for age, sex and HIV risk factor.

Proportion of patients presenting hepatic steatosis



Grade of steatosis in our population



	DTG3TC	Other
Severe	0	3,4
Moderate	14,3	19
Mild	14,3	22,4
No steatosis	71,4	55,2

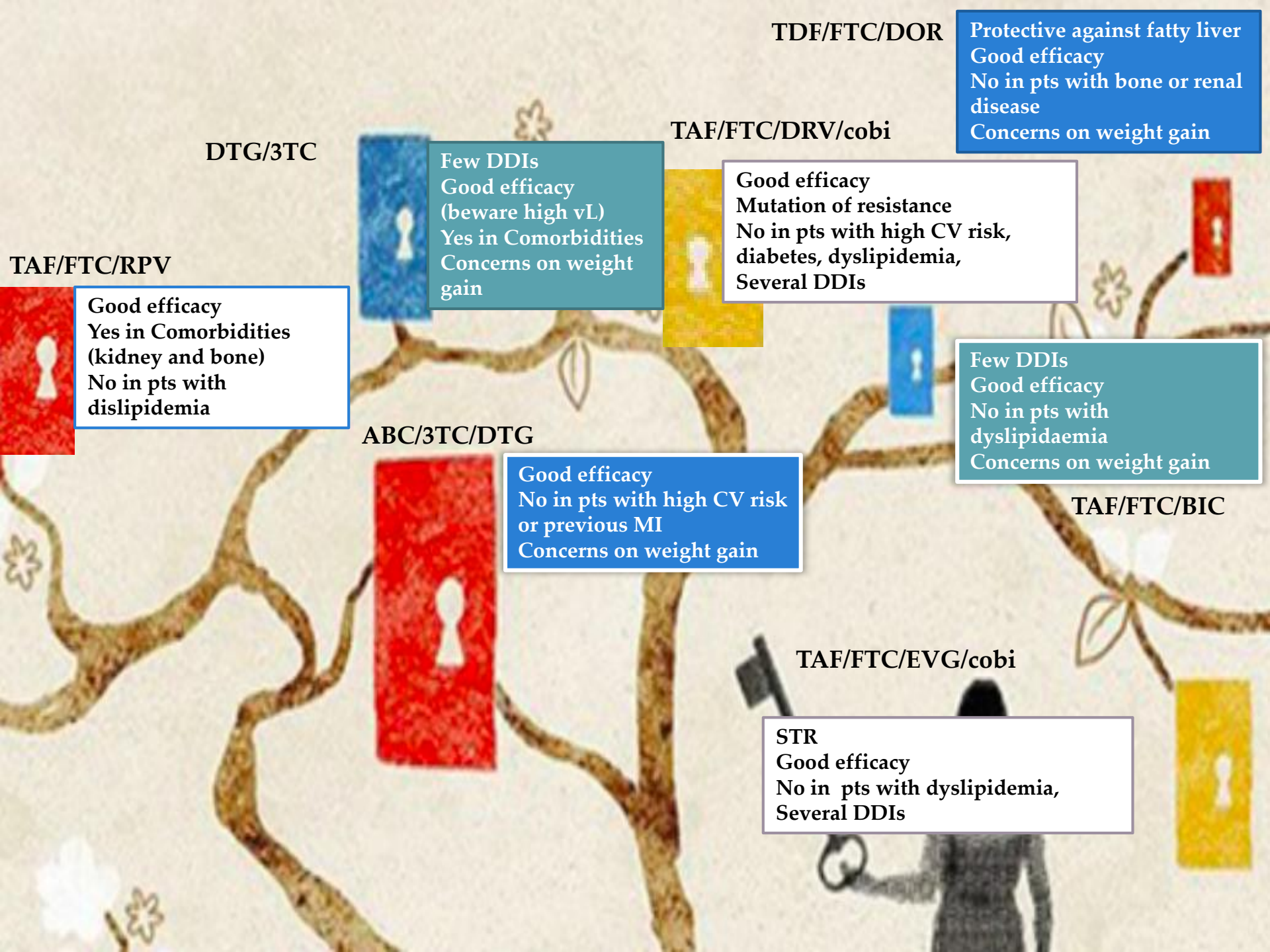
No steatosis Mild Moderate Severe

AIDSinfo

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A
Dyslipidemia	**ZDV > ABC:** ↑ TG and ↑ LDL **TAF:** ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	**EFV:** ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-Boosted PIs:** ↑ TG, ↑ LDL, ↑ HDL **LPV/r > DRV/r and ATV/r:** ↑ TG	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF, and greater with DOR than EFV.			INSTI > other ARV drug classes	N/A

AIDSinfo

Adverse Event	ARV Agent(s) or Drug Class		Comments
	Switch from	Switch to	
Dyslipidemia Hypertriglyceridemia (with or without elevated LDL level)	RTV- or COBI-boosted EFV-based regimens	BIC, DTG, RAL, DOR, or RPV	Elevated TG and LDL levels are more common with LPV/r and FPV/r than with other RTV-boosted PIs. Improvements in TG and LDL levels have been observed with switch from LPV/r to ATV or ATV/r.[c]
Insulin Resistance	LPV/r	INSTI, NNRTI	Results of switch studies have been inconsistent. Studies in HIV-negative patients suggest a direct causal effect of LPV/r on insulin resistance. However, traditional risk factors for insulin resistance may be stronger risk factors than the use of any PI.


TDF/FTC/DOR
Protective against fatty liver
Good efficacy
No in pts with bone or renal disease
Concerns on weight gain
DTG/3TC
Few DDIs
Good efficacy
(beware high vL)
Yes in Comorbidities
Concerns on weight gain
TAF/FTC/DRV/cobi
Good efficacy
Mutation of resistance
No in pts with high CV risk, diabetes, dyslipidemia,
Several DDIs
TAF/FTC/RPV
Good efficacy
Yes in Comorbidities (kidney and bone)
No in pts with dislipidemia
Few DDIs
Good efficacy
No in pts with dyslipidaemia
Concerns on weight gain
TAF/FTC/BIC
ABC/3TC/DTG
Good efficacy
No in pts with high CV risk or previous MI
Concerns on weight gain
TAF/FTC/EVG/cobi
STR
Good efficacy
No in pts with dyslipidemia,
Several DDIs

Integrase inhibitors dolutegravir and raltegravir exert proadipogenic and profibrotic effects and induce insulin resistance in adipose tissue and adipocytes

Jennifer Gorwood

Christine Bourgeois, Valérie Pourcher, Guillaume Pourcher, Matthieu Mantecon, Cindy Rose, Romain Morichon, Frédéric Charlotte, Roger Le Grand, Christine Katlama, Bruno Fève, Olivier Lambotte, Jacqueline Capeau, Véronique Béréziat* & Claire Lagathu*

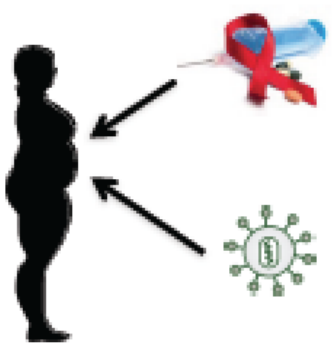
UMRS_938 Saint-Antoine Research Centre
Team "Lipodystrophies, hormonal and metabolic adaptations, and aging "

ObeVIH study: ART-controlled HIV-infected obese patients

Undergoing bariatric surgery

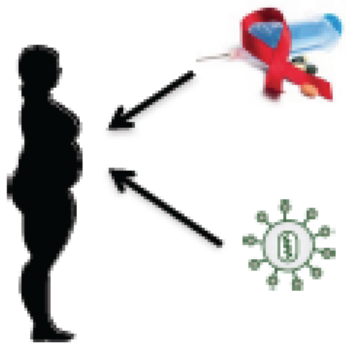
Age: 46.9±2.0 years
BMI: 41.5±1.3kg/m²
Known duration of HIV infection: 16.3±1.7 years
14 women, 4 men

without INSTIs
(n=5)



Non-INSTI ART

with INSTIs
(n=14)



INSTIs

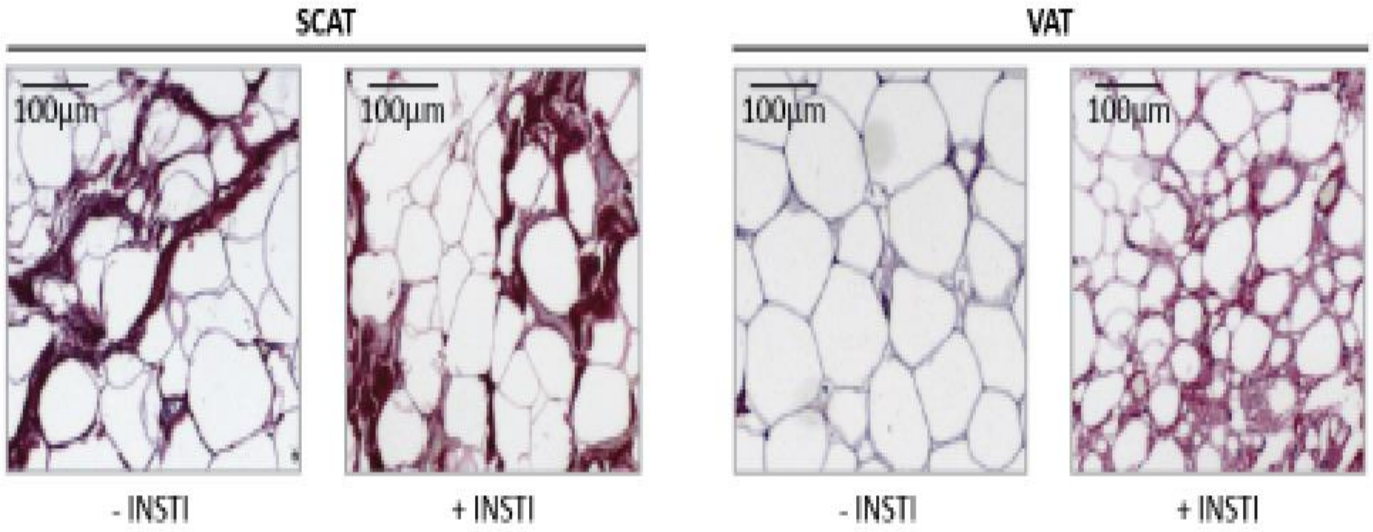
DTG n=10
RAL n=2
EVG n=2

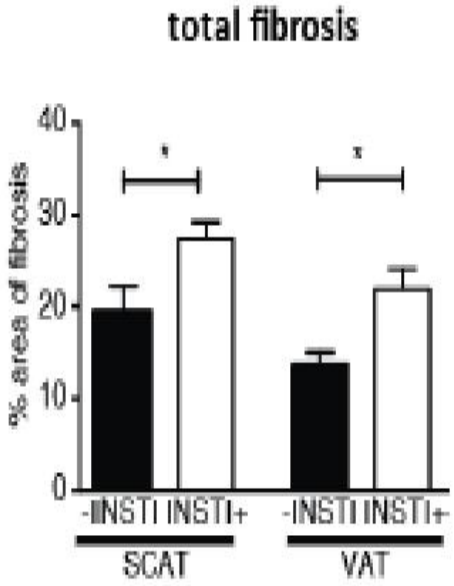
Subcutaneous and visceral adipose tissues
Surgical samples

Mean±SEM

Results

Increased fibrosis in SCAT & VAT of INSTIs-treated patients



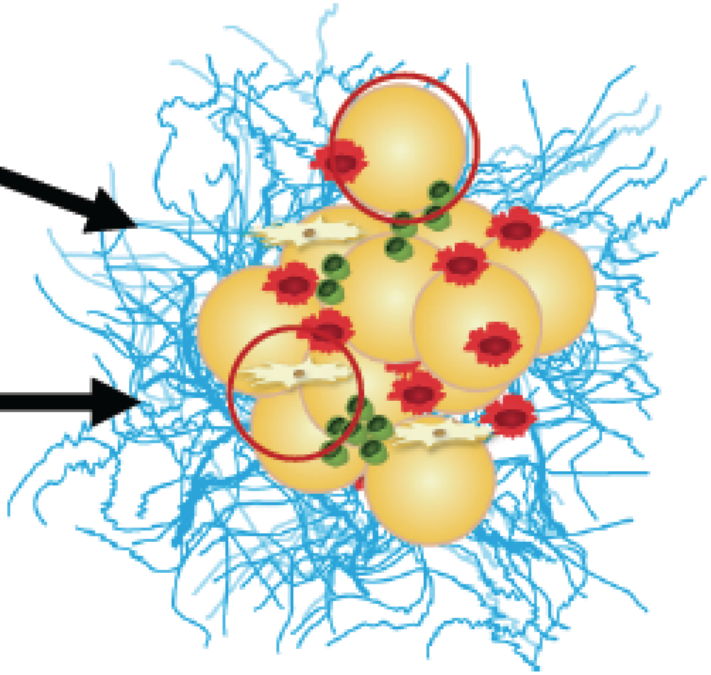


Sirius red staining

Impact of INSTIs on Adipose tissue

HIV

DTG RAL



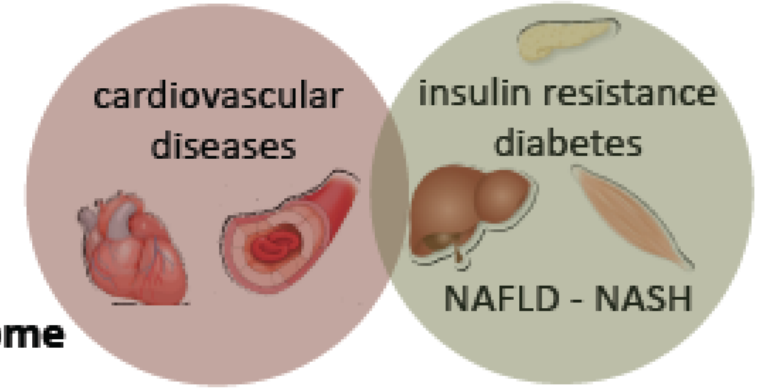
ASC and adipocytes
↑ Adipogenesis
↑ ECM production
↓ Adiponectin
↑ Insulin-resistance

Adipose tissue fibrosis and dysfunction

?

Weight gain

Cardiometabolic outcome



Gorwood J et al 2019

Gorwood J et al submitted

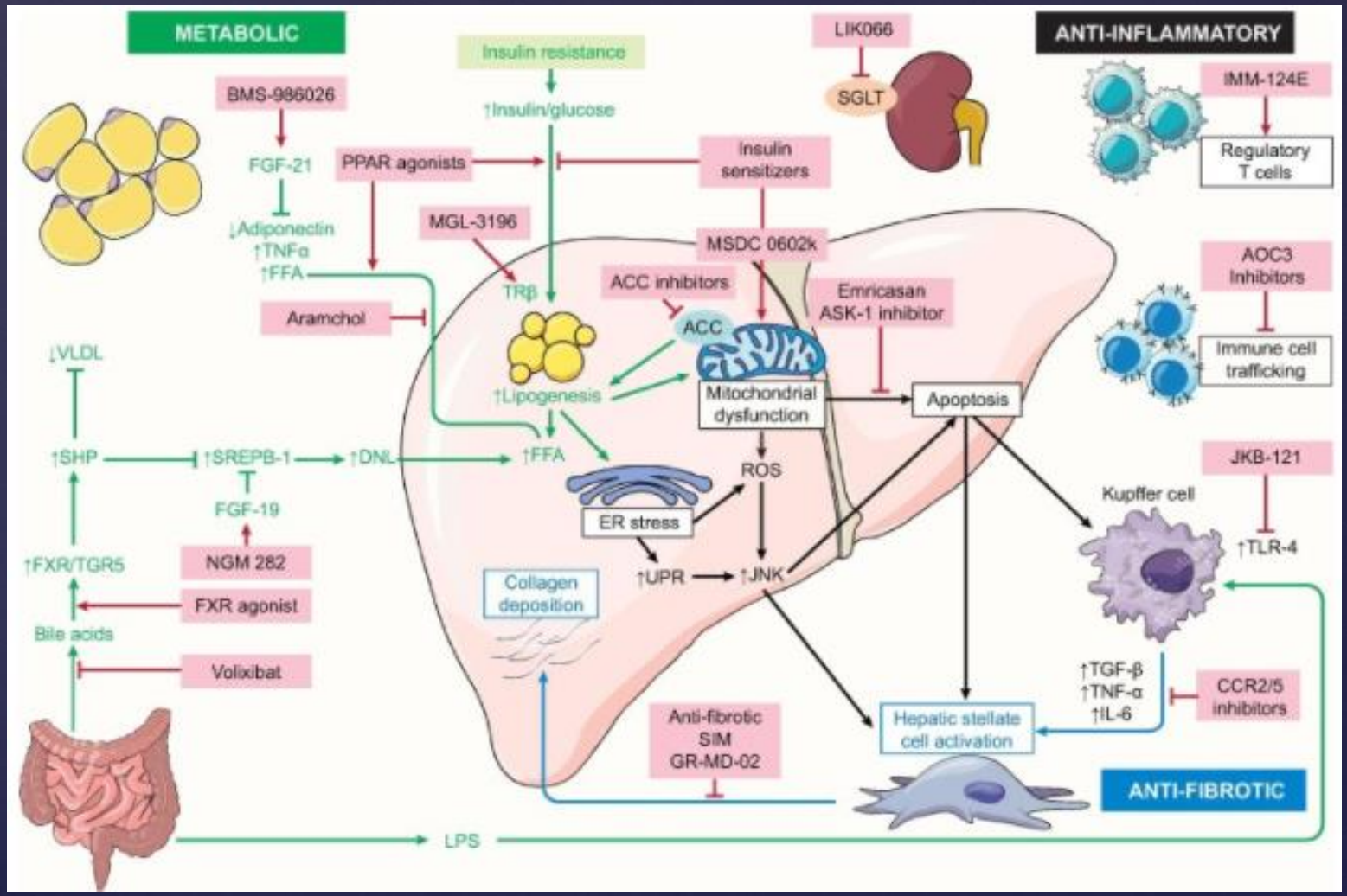
HIV patients – What we can do in the future?

What we can do in the future?

- Multidimensional pathways of care
  - HIV specialist
  - Hepatologist
  - Dietitian

- Validation of new and reliable NI markers of disease

MOA of pharmacological treatments for NAFLD



Konerman MA, et al. J Hepatol 2018;68:362–75

New pharmacological perspectives

THE LANCET

COMMENT | VOLUME 394, ISSUE 10215, P2131-2133, DECEMBER 14, 2019

Obeticholic acid: towards first approval for NASH

Mohammed Eslam • Rino Alvani • Gamal Shiha

Published: December 05, 2019 • DOI: https://doi.org/10.1016/S0140-6736(19)32963-0 •

Could it be an option in PLWH?

Adding MAraViroc &/or METformin for Hepatic Steatosis in People Living With HIV (MAVMET)

ClinicalTrials.gov Identifier: NCT03129113

Recruitment Status : Recruiting
First Posted : April 26, 2017
Last Update Posted : January 25, 2019

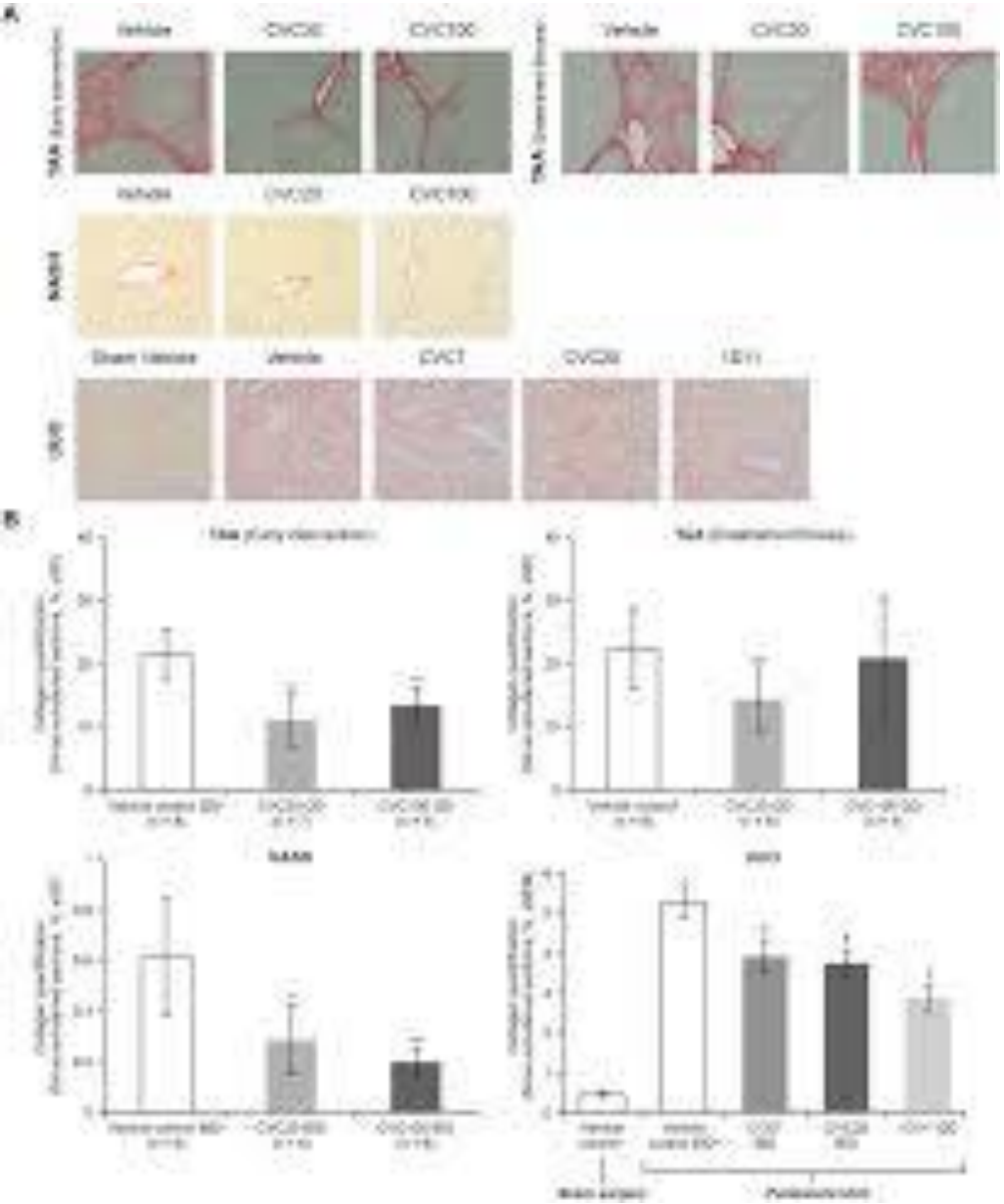
See Contacts and Locations

Other ongoing trials

- **MASH trial**
  - Maraviroc Add-on Therapt for Statohepatitis in HIV (liver biopsy confirmed)

- **HEPMARC**
  - A phase IV open-label pilot study investigating non invasive markers of hepatic fibrosis in people living with HIV-1 and non-alcoholic fatty liver disease randomised to receveing optimised background therapy (OBT) plus maraviroc or OBT

PLOS ONE



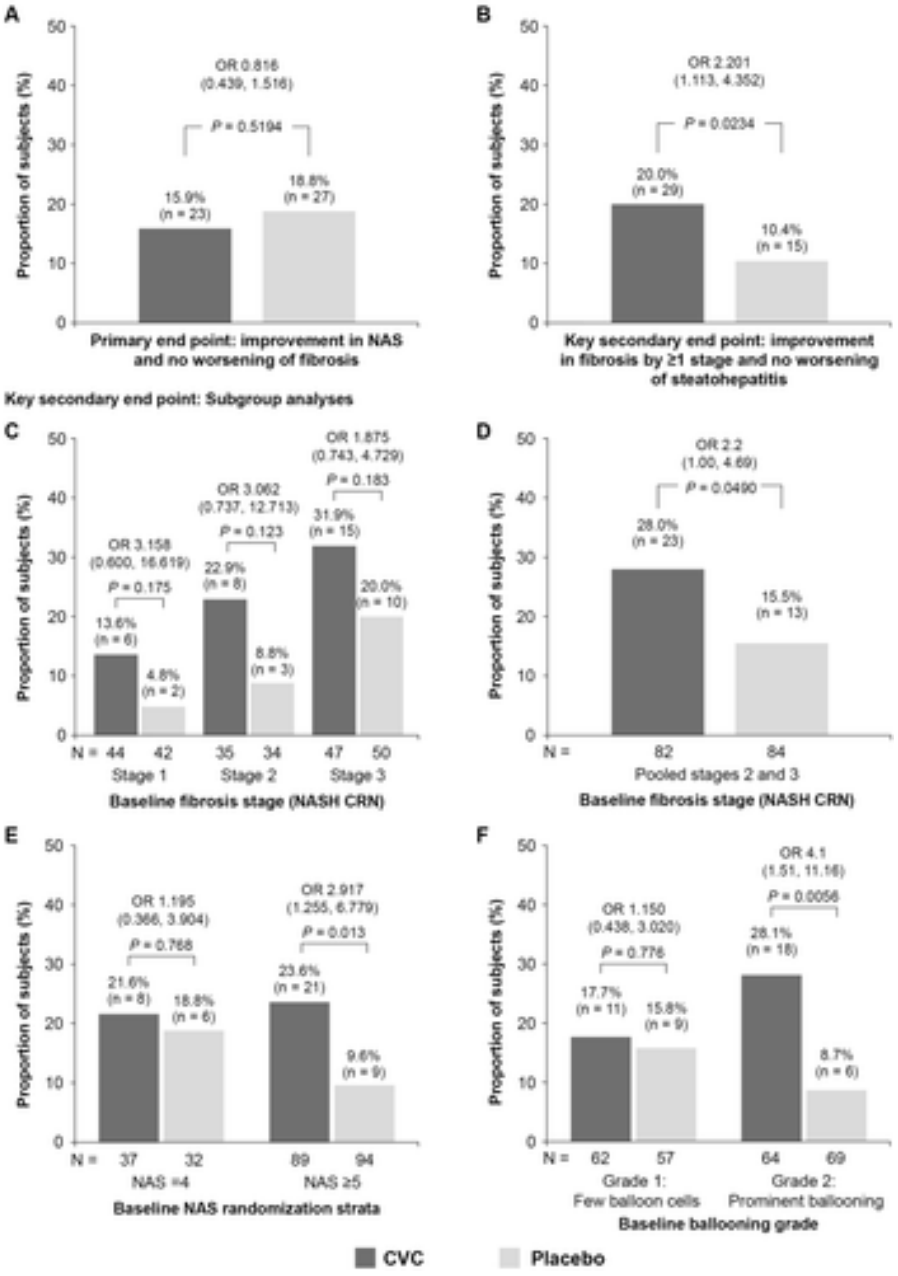
RESEARCH ARTICLE

Antifibrotic Effects of the Dual CCR2/CCR5 Antagonist Cenicriviroc in Animal Models of Liver and Kidney Fibrosis

Eric Lefebvre[1], Graeme Moyle[2], Ran Reshef[3], Lee P. Richman[4], Melanie Thompson[5], Feng Hong[6], Hsin-I Chou[6], Taishi Hashiguchi[7], Craig Plato[8], Dominic Poulin[9], Toni Richards[8], Hiroyuki Yoneyama[7], Helen Jenkins[1], Grushenka Wolfgang[10], Scott L. Friedman[6]*

Citation: Lefebvre E, Moyle G, Reshef R, Richman LP, Thompson M, Hong F, et al. (2016) Antifibrotic Effects of the Dual CCR2/CCR5 Antagonist Cenicriviroc in Animal Models of Liver and Kidney Fibrosis. PLoS ONE 11(6): e0158156. doi:10.1371/journal.pone.0158156

Editor: Silvia C. Sookoian, Institute of Medical Research A Lanari-IDIM, University of Buenos Aires-National Council of Scientific and Technological Research (CONICET), ARGENTINA



Original Article | Open Access

A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis

Scott L. Friedman, Vlad Ratziu, Stephen A. Harrison, Manal F. Abdelmalek, Guruprasad P. Aithal, Juan Caballeria, Sven Francque, Geoffrey Farrell, Kris V. Kowdley, Antonio Craxi, Krzysztof Simon, Laurent Fischer, Liza Melchor-Khan, Jeffrey Vest, Brian L. Wiens, Pamela Vig, Star Seyedkazemi, Zachary Goodman, Vincent Wai-Sun Wong, Rohit Loomba, Frank Tacke, Arun Sanyal, Eric Lefebvre ... See fewer authors

First published: 17 August 2017 | https://doi.org/10.1002/hep.29477 | Citations: 157

grazie per l'attenzione

BACKUP

Author and country	Population characteristics	Diagnostic test	NAFLD prevalance
Studies describing the prevalence of NAFLD in a general HIV-positive population			
Guaraldi et al. [15], Italy	*n* = 225. Mean BMI: 23.8 Consecutive patients evaluated in metabolic clinic	CT-scan	36.9%
Crum-Cianflone et al. [14], USA	*n* = 216. Mean BMI: 26.0 Consecutive patients in American military clinic	Ultrasound	31.0%
Macias et al. [13], Spain	*n* = 505. Median BMI: 23.2 Consecutive patients under follow-up in 5 different clinics	CAP	40.0%
Nishijima et al. [17], Japan	*n* = 435. Mean BMI: 22.8 All HIV-infected patients that underwent ultrasound between 2004-2013. HBV&HCV co-infection excluded	Ultrasound	31.0%
Lui et al. [16], China	*n* = 80. Mean BMI: 23.6 Consecutive patients under follow-up in ID clinic	MRS	28.8%
Vuille-Lessard et al. [18], Canada	*n* = 300. Mean BMI: 26.6 Consecutive patients under follow-up in ID clinic	CAP	48.0%
Studies describing the prevalence of NAFLD in HIV-patients with persistent liver enzyme elevations			
Lemoine et al. [23], France	*n* = 14. Mean BMI: 23.0 HIV-mono infection with ALT levels > 2 × ULN over 3 months	Liver biopsy	57.1%
Ingiliz et al. [20], France	*n* = 60. Mean BMI: 23.0 ALT or AST > 2× ULN on two occasions in previous 6 months	Liver biopsy	60.0%
Sterling et al. [22], USA	*n* = 14. Mean BMI: 29.9 AST or ALT 1.25–5× ULN over > 6 months	Liver biopsy	64.3%
Morse et al. [21], USA	*n* = 62. Mean BMI: 28.0 ALT or AST > ULN on three occasions in previous 6 months	Liver biopsy	72.6%
Lombardi et al. [24], UK	*n* = 66. Mean BMI: Not available Retrospective cohort analysis of patients with ALT or AST > ULN on two occasions in 6 months	Ultrasound	71.0%

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BMI* body-mass index, *CAP* controlled attenuation parameter, *ID* infectious diseases, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *MRS* magnetic resonance spectroscopy, *NAFLD* non-alcoholic fatty liver disease, *UK* United Kingdom, *ULN* upper limit of normal, *USA* United States of America