2020 Ryan White HIV/AIDS Program
CLINICAL CONFERENCE

Liver Disease and HIV Infection

Marion G. Peters, MD
Professor of Medicine
Northwestern University
Chicago, Illinois

Financial Relationships With Commercial Entities

Dr Peters has served as an advisor to Abbott, Antios, Aligos, and Atea. Her spouse is employed by Hoffman-La Roche. (Updated 7/30/20)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe most common causes of liver disease in people living with HIV (PLWH)
- Determine how to evaluate abnormal liver tests in PLWH
- Discuss new issues with HBV, HCV and fatty liver disease in PLWH

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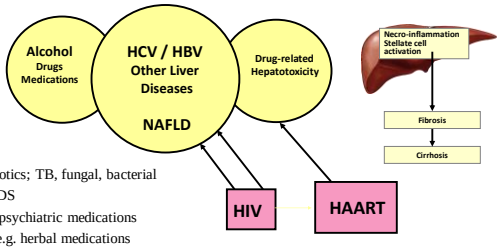
Liver Disease in PLWH



–Antibiotics; TB, fungal, bacterial
–NSAIDS
–Neuropsychiatric medications
–OTC e.g. herbal medications

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Evaluation of Abnormal LFTs in PLWH

- **Liver Tests**:
  - -Function: Albumin, bilirubin, INR
  - -Cholestasis: Alk Phos, bilirubin
  - -Inflammation: AST, ALT
  - -portal HTN: platelets, WBC
- **Common liver diseases**:
  - HBV: HBsAg, anti-HBs, anti-HBc
  - HCV: HCV Ab, HCV RNA
  - NAFLD: Fasting glucose, TG, cholesterol, Hgb A1c
  - -alcohol
  - -drug toxicity
- **Less common**
  - Metabolic: Iron, Tsat, ferritin (hemochromatosis), Ceruloplasmin (Wilson Disease)
  - Autoimmune diseases: AMA, IgM (for PBC), ASMA, ANA, IgG (for AIH)
  - A1AT phenotype
- Hepatotoxicity
- Vaccination status for HAV (IgG) and HBV
- Liver imaging and fibrosis assessment

Fibrosis: APRI: AST/Platelet ratio;
FIB-4 (AST, ALT, plt, age);
Fibroscan, ARFI (ultrasound)
Liver biopsy
Imaging –only if PHTN

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Worse outcomes with HBV-HIV coinfection

HIV HBV vs HBV

- higher % HBeAg positivity
- Lower loss of HBsAg after acute infection (79% vs >95%)
- higher HBV DNA levels
- longer duration of viremia
- lower aminotransferase levels
- more rapid progression to cirrhosis

HIV HBV vs HIV

- 14-fold higher liver-related mortality
- higher risk of progressing to AIDS or death

Thio, 2002; Konopnicki 2005; Hoffmann 2009; Chun 2012

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HBV-HIV still a problem in this decade

- Analysis of 72,584 HBV; 133,880 HIV; and 8,155 HBV/HIV

Compared to HIV monoinfection

- Higher liver related admissions: HBV/HIV patients (48%) vs HIV (28%, P<0.001)

Compared to HBV monoinfection

- HBV/HIV higher liver-related mortality (OR 1.73, 95% CI 1.20-2.48)
- HBV/HIV higher all cause mortality (OR 1.50, 95% CI 1.10-2.04)
- Longer length of stay HBV/HIV (+1.41 days, 95% CI 0.84-1.99)

2011 US Nationwide Inpatient Sample 214,621 HBV+ patients: Rajbhandari JVH 2018

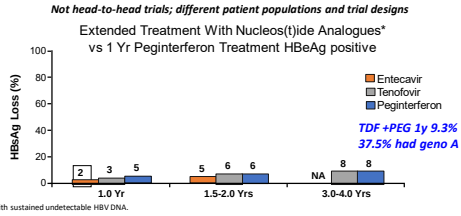
Treatment of HBV HIV

- ART including agents with activity against HIV and HBV is recommended for **all** patients co-infected with HIV and HBV, regardless of CD4 cell count or need for HBV treatment
- ART must include **two drugs active against HBV**, preferably tenofovir and emtricitabine, regardless of the level of HBV DNA. Such a regimen will
  - reduce the likelihood of immune reconstitution inflammatory syndrome (IRIS) against HBV
  - reduce risk of resistance which could occur with newer regimens without HBV active drugs or with 3TC or FTC alone

DHHS Guidelines 2017

With current therapies
HBsAg loss in HBV monoinfection is a high bar…

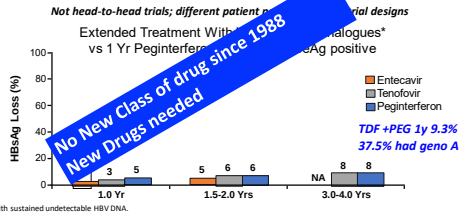
Not head-to-head trials; different patient populations and trial designs



*With sustained undetectable HBV DNA.

Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129; Marcellin Gastro 2016

With current therapies HBsAg loss is a high bar…



Not head-to-head trials; different patient p… …rial designs

Extended Treatment With… …alogues*
vs 1 Yr Peginterfer… …sAg positive

TDF +PEG 1y 9.3%
37.5% had geno A

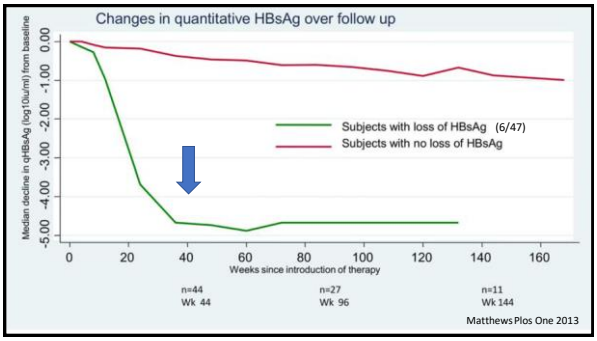
*With sustained undetectable HBV DNA.

Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129; Marcellin Gastro 2010

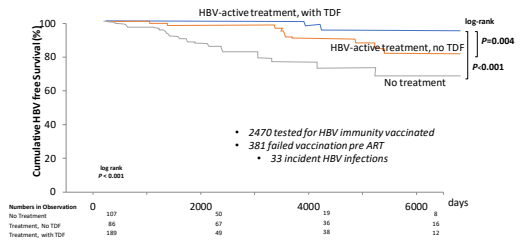
Loss of HBsAg in HIV/HBV with ART therapy

Country	N	% HBsAg loss	Predictor	Reference
Zambia	284	10.2 % at 2 years	BL CD4 < 350 OR 4.94 (1.02-23.8)	Chihota et al JID 2020
Germany	359	18% median 4 yrs	Less robust CD4 response associated with non-seroconversion	Boesecke et al CROI 2019

CROI 2019: not clear if adult acquired (20% chronic) HBV or perinatal (95% chronic)
Increase in clearance with ART- Matthews



ART as HBV PrEP: HBV-Free Survival in MSM



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Heuft and Brinkman K, AIDS 2014

HBV in PLWH Summary

- HIV increases HBV chronicity after acute HBV infection
- HBV increases antiretroviral-related hepatotoxicity
- HIV/HBV coinfection increases the risk of end stage liver disease compared to HBV alone
- Tenofovir based therapy can be HBV PrEP
- ART can lead to loss of HBsAg especially in first 1-2y
- Screen all HBV patients for HCC not just those with severe fibrosis
- There are new drugs on the horizon
  (Virologic failures may indicates poor adherence)
  (Reactivation of HBV can occur with immune suppression)

Thio CL, et al. Lancet. 2002: Koziel NEJM 2007; Rajbhandari J Viral Hepat 2016

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HCV in PLWH

- DAA are highly effective in HIV/HCV co-infection
- Treatment of HCV is same regardless of HIV but
  - Drug-drug interactions greater, esp with NS3 PI containing regimens
  - TDF regimens appears safe with LDV/SOF, SOF/VEL
- Switch of ARVs prior to DAA therapy - likely safe and effective- ☑☐ stable
- Early treatment of acute HCV is successful
- Reinfection can occur
- HCV cure improves survival (liver, AIDS, all cause), renal dz and diabetes

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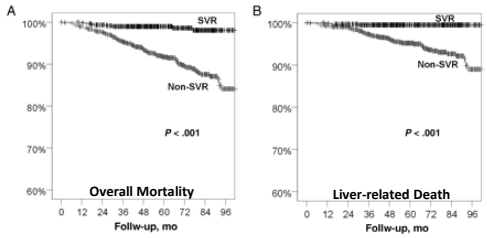
HCVguidelines.org

Lower Mortality after SVR in HIV HCV



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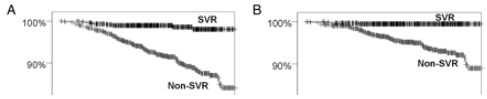
Gesida cohort Berenguer CID 2012

Lower Mortality after SVR in HIV HCV



Lower AIDS-defining conditions: P = .003

Lower non-liver-related deaths: P = .002

Lower non-liver-related, non-AIDS-related deaths: P = .002

5 y follow up: SVR associated with

Significant decrease in diabetes mellitus
(sHR 0.57[95% CI, 0.35 - 0.93] P = .024)

Decline in chronic renal failure
(sHR 0.43 [95% CI, 0.17 - 1.09], P =.075

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Gesida cohort Berenguer CID 2012; Hepatology 2017

Predictors of HCC post HCV SVR

33,005 VA patients; 10,827 SVR — 100 new HCC cases

Incidence rate of

- No SVR — 1.32% per year
- SVR to IFN-based Rx — 0.33% per year

	OR (CI)	P value
Cirrhosis at SVR	**6.69 (4.3-10.4)**	**<0.0001**
Age >65	**4.51 (2.0-10.4)**	**0.004**
Age 55-64 y	2.04 (1.3-3.2)	0.002
Hispanic vs Cauc	2.3 (1.1-4.8)	0.03
DM	1.80 (1.2-2.9)	0.005
Alcohol	1.68 (1.08-2.60)	0.02

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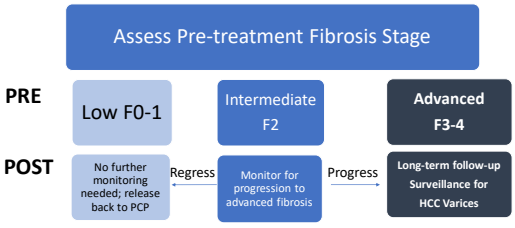
El-Serag. Hepatology. 2016

Post-HCV cure follow-up depend on pre Rx Fibrosis Stage



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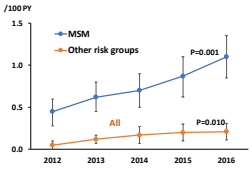
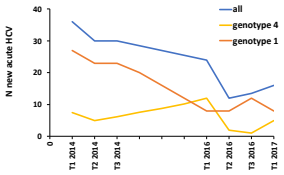
HCV: Incident Infection



HCV incidence is still increasing in French HIV-infected MSM. *Cotte Liver International 2018*

Treatment as prevention



Declining HCV incidence in Dutch HIV+ MSM after unrestricted access to HCV therapy. *Boerekamps et al. Clin Inf Dis, 2018*

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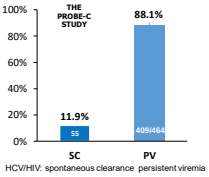
HCV: Reinfection and spontaneous clearance

- HCV Ab is not protective
- Reinfection can occur
  - Germany: GECCO 9
    - 9.02/100py in MSM; 1.14/100py in PWIDS
  - Madrid: 5.93 per 100 patient-years in MSM
  - Canada: 3.1 per 100 patient- years active PWID
- Spontaneous clearance after acute HCV is lower in PLWH



SVR: 75.6% (245/324);
Reinfections: 17% (51/300)

Inglitz CID 2019; Berenguer AIDS 2019; Rossi JHEP 2018: Boesecke et al. CROI 2018

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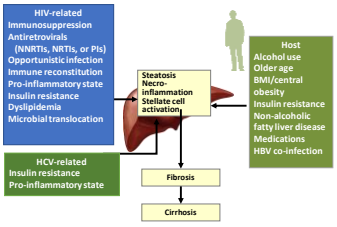
Concomitant Liver Disease

Prospective Longitudinal cohort

- N=275, HIV/HCV and HCV
- >95% with liver bx prior to treatment
- After SVR abnormal LE in ~12% overall
  20% in PLWH
- Risk factors for LE elevation
  - HIV (ARV toxicity)
  - Steatosis
  - ETOH
  - Statin use
  - Severe fibrosis/cirrhosis



Hadigan et al, 18th Int Workshop on Comorbidities and Adverse Drug Reactions in HIV, Sep 2016, New York. Abstract O024; Naggie & Sulkowski, Gastro 2012

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HCV Summary in PLWH

- Many benefits of HCV cure: liver and non-liver- systemic inflammation
- Those with F3/4 pre-treatment need HCC monitoring post-SVR
  - Imaging and alfa fetoprotein q 6months
- Need to stage fibrosis **pre**-treatment to optimally monitor post- cure
- Concurrent alcohol or fatty liver places patients at risk for future cirrhosis
  - Monitor for fibrosis progression in these patients
- Counsel healthy liver practices for all- alcohol, drugs, diet, lifestyle, MS
- Monitor for reinfection in at-risk patients
  - Discuss reinfection risk with patient

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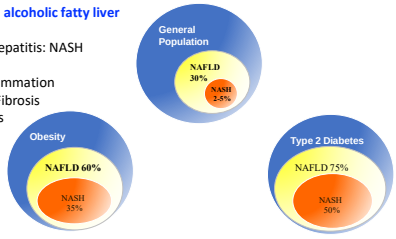
NAFLD in the general population and high risk groups

NAFL: non alcoholic fatty liver

- Fat
- Steatohepatitis: NASH
  - Fat
  - Inflammation
  - +/- Fibrosis
- Cirrhosis
- HCC



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Risk Factors

Metabolic Syndrome
- Obesity/central adiposity
- Insulin resistance
- Hypertriglyceridemia
- Hypertension

NAFLD is the hepatic manifestation of the metabolic syndrome

Emerging associations:
- Hispanic ethnicity
- Hereditary/genetic (*PNPLA3)*
- Polycystic ovary syndrome (PCOS)
- HIV
- Sleep apnea
- Hypothyroidism

Bedogni, Hepatology, 2005.
Chalassani, Hepatology 2012.

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Primary NAFLD vs HIV-associated NAFLD

	Primary NAFLD	HIV-associated NAFLD
NAFLD Prevalence	~30%, varies by study	35%, 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 "lean NASH" 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	1 stage 5y (1 study 30 pts)*
Long-term outcomes	Increased CVD risk Increased liver-related and all-cause morality	Emerging evidence of independent a/w CVD, scant data on long-term outcomes

Determine liver fibrosis: FIB-4 (AST, ALT, plt, age); Nash Fibrosis score (age, BMI, hyperglycemia, plt, alb, AST/ALT
Determine inflammation: liver biopsy; abnormal ALT (47% had NASH, Lemoine JAIDS 2019) *Stanley Lancet HIV 2019

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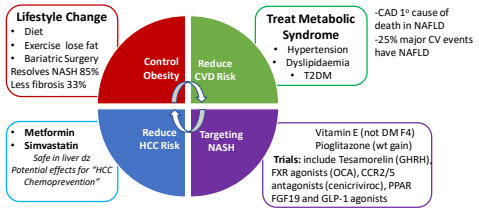
Management options



Promrat et al, 2010; Thoma et al, 2012; Vilar-Gomez et at, 2015; Lassailly et al, 2015; Ratziu et al, 2010; Musso et al, 2010; Sanyal et al, 2010; Lavine et al, 2011; Cusi et al, 2016; Armstrong et al, 2012; Zhang et al 2012; Chen et al 2013; El-Serg et al, 2009; Singh et al 2013; Stanley Lancet HIV 2019

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Summary of NAFLD in PLWH

- NAFLD is an umbrella term that includes NAFL and steatohepatitis (NASH)
  - NAFLD is common in PLWH
- NASH (inflammation +/- fibrosis)–higher progression to cirrhosis
  - Biopsy is needed to diagnose NASH
  - NASH is higher in PLWH
  - Steatogenic and fibrotic effects of HIV/ART likely impact the natural history
  - PLWH at higher risk for "lean" NAFLD (45% in one series)
- NAFLD Prevalence is likely to increase with aging HIV+ population
- Main risk factors are metabolic, genetic/hereditary
- Leading cause of death in NAFLD: CAD
- NAFLD is an important contributor to HCC incidence and need for liver transplant
- Management hinges on weight loss, exercise, avoiding added carbohydrates, metabolic syndrome control

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Hepatocellular carcinoma in PLWH

- Increasing prevalence of HCC with longer life span
  - Viral hepatitis, ETOH and NAFLD most common cause of cirrhosis
- Treatment of viral hepatitis decreases fibrosis/cirrhosis and risk of HCC
  - **But** HCC can occur after HCV cure
- HCC occurs in younger PLWH with likely worse survival
- Essential to diagnose cirrhosis- Fibroscan, APRI, FIB-4, imaging if PHTN
- Screen all HBV patients (HCC can occur without F3-4) and all cirrhotics
- Screening and early diagnosis critical for optimal therapy
- Access to therapies includes locoregional therapy and liver transplant

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Liver Disease in PLWH

- There is a lot of liver disease in HIV persons
  - HCV can be treated and can recur
  - HBV: new drugs in pipeline
  - NALFD major new disease requiring diagnosis and management of metabolic syndrome
- While viral hepatitis, alcohol and NAFLD are most common, abnormal LFTs should be evaluated as in HIV negative persons
- Less hepatotoxicity with newer ART
- With longer life span
  - Increasing morbidity and mortality from liver disease
  - Increased HCC- so need to determine amount of fibrosis

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Thank you

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Question-and-Answer Session