Non-Viral Liver Disease in HIV

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Discuss common etiologies for non-viral liver disease in patients with HIV
• Outline important clinical tools for the diagnosis and staging of liver disease in patients with HIV
• Review the epidemiology, diagnosis, and management of non-alcoholic fatty liver disease in patients with HIV

Faculty and Planning Committee Disclosures
Please consult your program book or the Conference App.

Off-Label Disclosure
There will be no discussion of off-label/investigational uses of approved agents.
Liver disease common cause of non-AIDS death

- D:A:D multicohort study 1999-2011
  - 11 cohort studies, 212 clinics
  - N= 49,731 participants → 3909 deaths
- Trends in causes of death in HIV
  - Overall vs. time trends (1999-2000 vs. 2010-2011)
    - AIDS related death: 29% ↓ (34 to 22)
    - Non-AIDS defining cancers: 15% ↑ (9 to 23)
    - Liver disease: 13% ↓ (16 to 10)
    - Cardiovascular disease: 11% ↓
Liver disease in patients with HIV is multifactorial

Liver disease in patients with HIV is multifactorial. Various factors contribute to liver disease in HIV patients, including opportunistic diseases, hepatitis viruses, immune reconstitution, pre-existing diseases, alcohol abuse/IVDU, co-morbidity treatment, HIV treatment (NNRTIs, PIs, NRTIs, INSTIs), and entry inhibitors. Sulkowski M, et al. Ann Intern Med 2003; 138:197-207.

Diagnostic investigation of liver disease in HIV

- Definitions of abnormal LFTs
- Initial investigation of abnormal LFTs
- Assessment of liver fibrosis
What Is an Elevated ALT Level?

- Reference ranges for ALT vary widely with upper limits ranging from 55-60 U/L (men) and 40-50 U/L (women)
- Previous AASLD and US treatment algorithms recommended lower upper limit of normal levels for ALT based on Prati criteria
  - 30 U/L (men) and 19 U/L (women)
- ACG 2017 LFT Guidelines provide normal range
  - 29-33 U/mL (men) and 19-25 U/L (women)
- AASLD 2018 Guidelines provide updated normal range
  - 35 U/mL (men) and 25 U/mL (women)


ACG 2017 LFT Guideline: individualized approach to evaluation

- Careful history and exam – risk factors for liver disease, medications, supplements, alcohol, stigmata of liver disease
- Step-wise rather than shotgun approach to diagnostic evaluation
- Mild ALT elevation (<5x ULN): viral hepatitis, iron panel, ultrasound
- Moderate ALT elevation (5-15x ULN): + autoimmune, Wilsons, A1AT deficiency
- Severe ALT elevation (>15x ULN): urine tox/drug panel, EBV/HSV/CMV, doppler
- Individualized testing: celiac sprue, tick-borne, thyroid, muscle, genetic/rare
- Assess for liver failure (PT/INR, encephalopathy) → refer to transplant center
- Selective use of liver biopsy if diagnostic evaluation is negative

Differential diagnosis of liver disease in HIV

- Hepatic parenchymal disease
  - Infection
    - Viral hepatitis: HCV, HBV, HAV, HEV, CMV, EBV, HSV, VZV, HHV-6
    - Mycobacterium avium complex
    - Cryptococcus neoformans
    - Microsporidia
    - Pneumocystis jiroveci
    - Bacillary peliosis hepatitis
    - Histoplasma capsulatum
  - NAFLD
  - Medication toxicity
  - Alcoholic liver disease
  - Recreational drugs
    - Cocaine
    - Methyleneoxyxymethamphetamine (Ecstasy)
  - Neoplasm
    - Lymphoma
    - KS
    - HCC
    - NRH
  - Autoimmune hepatitis
  - Hemochromatosis
  - Wilson’s disease
  - Alpha-1 antitrypsin deficiency

- Biliary disease
  - AIDS cholangiopathy
  - Cryptosporidium
  - CMV
  - Microsporidia
  - C. difficile colitis
  - Mycobacterium avium intracellulare
  - Histoplasma capsulatum
  - Acute cholecystitis
  - Cholangiocarcinoma
  - CMV
  - Isospora
  - Microsporidia
  - Neoplasm
    - Lymphoma
    - KS
  - Primary sclerosing cholangitis
  - Primary biliary cirrhosis

Prevalence of abnormal LFTs in patients with HIV

- N=299 HIV-positive patients seen in academic HIV clinic
- 80/299 (27%) had abnormal LFTs during 6-month study period
- Most common diagnoses:
  - NAFLD (30%)
  - Alcoholic liver disease (13%)
  - Viral hepatitis: HBV (9%), HCV (5%)
  - Other diagnosis: hemochromatosis (2%), autoimmune hepatitis (2%)
- No definitive etiology was identified in 51% of patients
Abnormal LFTs in HBV(-)/HCV(-) patients with HIV

- Retrospective cohort analysis (UK)
  - N=3872 HIV+ patients (2005-2012)
  - Persistently abnormal LFTs (ALT> ULN on 2 occasions over 6 months) and negative HBV/HCV serologies in 1047 patients (27.0%)
- LFT evaluation uncommonly performed
  - Diagnostic evaluation in 243/1047 patients (23.2%)
  - Chronic liver disease identified in 147 patients (66.2%) → fatty liver (47.3%)
  - Liver biopsy (n=42): F3-F4 in 21.4% patients


Abnormal LFTs post-SVR in DAA-treated HCV

- Prospective observational cohort
  - 4 centers in Spain
- N=1112 patients (38.8% F4, 56.8% HIV)
- Assessment of ALT at SVR12 and SVR24
- Persistent +LFT in 130 patients (11.7%)
  - HCV vs. HCV-HIV (9.4% vs. 13.5%, p<0.05)
  - Predictors of +LFT on multivariate analysis:
    - cirrhosis (OR 2.12)
    - Etiologies for +LFT: NAFLD (36.2%), alcohol (23.1%), drugs (14.6%)

Viral hepatitis common etiology for liver disease in HIV


Evolving epidemiology of liver disease in HIV

Evolving epidemiology of liver disease in HIV

Evolving epidemiology of liver disease in HIV

Differential diagnosis of liver disease in HIV

Hepatic parenchymal disease
- Infection
  - Viral hepatitis: HCV, HBV, HDV, HAV, HEV, CMV, EBV, HSV, VZV, HIV-6
  - Mycobacterium avium complex
  - Cryptococcus neoformans
  - Micoplasma
  - Pneumocystis jiroveci
  - Bacterial/peliosis hepatitis
  - Hepatitis C virus
  - Hepatitis D virus
  - NAFLD
  - Medication toxicity
  - Alcoholic liver disease
- Recreational drugs
  - Cocaine
  - Metylenedioxymethamphetamine (Ecstasy)
- Neoplasia
  - Lymphoma
  - KS
  - HCC
  - NRH
- Autoimmune hepatitis
- Hemochromatosis
- Wilson’s disease
- Alpha-1 antitrypsin deficiency

Biliary disease
- AIDS cholangiopathy
- Cryptosporidium
- CMV
- Microsporidia
- Cyclospora cayetanensis
- Mycobacterium avium intracellulare
- Histoplasma capsulatum
- Acute cholecystitis
- Cryptosporidium
- CMV
- Isospora
- Microsporidia
- Neoplasm
- Lymphoma
- KS
- Primary sclerosing cholangitis
- Primary biliary cirrhosis

**Differential diagnosis of liver disease in HIV**

- Hepatic parenchymal disease
  - Infection
    - Viral hepatitis: HCV, HBV, HDV, HAV, HEV, CMV, EBV, HSV, YZV
    - Mycobacterium avium complex
    - Cryptococcus neoformans
    - Microsporidia
    - Pneumocystis jiroveci
    - Bacillary peliosis hepatis
    - Herpesvirus salivarius
  - NAFLD
    - Medication toxicity
  - Alcoholic liver disease
  - Recreational drugs
    - Cocaine
    - Methyleneoxydymethanamine (Ecstasy)
  - Neoplasms
    - Lymphoma
    - KS
    - HCC
  - NRH
  - Autoimmune hepatitis
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  - Histoplasma capsulatum
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  - KS
  - Primary sclerosing cholangitis
  - Primary biliary cirrhosis


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**DILI in patients with HIV: Role of ART**

- DILI is common in patients with HIV
  - Likely under-reported as 50% asymptomatic in context of +LFTs
  - Grading system per ACTG – “severe” defined by grade 3 or 4
  - Incidence of severe ART-DILI 8.5-23%
- Five common patterns:
  - hypersensitivity, idiosyncratic, mitochondrial, immune reconstitution, hepatic steatosis
- Risk factors:
  - advanced fibrosis, low platelet count, HBV/HCV

ART-DILI in patients with HIV

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic host-mediated</td>
<td>NNRTIs and PIs</td>
</tr>
<tr>
<td>(intrinsic and idiosyncratic)</td>
<td>Usually 2-12 months after initiation</td>
</tr>
<tr>
<td></td>
<td>Occurrence can vary by agent</td>
</tr>
<tr>
<td></td>
<td>Dose-dependence for intrinsic damage</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>NVP=ABC-3cAPV</td>
</tr>
<tr>
<td></td>
<td>Early, usually within 2-12 weeks</td>
</tr>
<tr>
<td></td>
<td>Often associated with rash</td>
</tr>
<tr>
<td></td>
<td>HLA-linked</td>
</tr>
<tr>
<td>Mitochondrial toxicity</td>
<td>d4T=AZT=ABC=TDF=FTC/3TC</td>
</tr>
<tr>
<td>Immune reconstitution</td>
<td>Chronic Hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Chronic HCV?</td>
</tr>
<tr>
<td></td>
<td>Within first few months</td>
</tr>
<tr>
<td></td>
<td>More common if low CD4 count/large rise</td>
</tr>
</tbody>
</table>


ART hepatotoxicity

Non-ART drug-induced hepatotoxicity

- Both ART and non-ART DILI contribute to liver injury in patients with HIV
- Careful assessment of both prescribed and non-prescribed medications, supplements, and herbal remedies should be performed
- Utilize pharmacy databases or online resources for drug-induced liver injury resources: livertox.nih.gov

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pattern of liver injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antifungals</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole, fluconazole, amphotericin B</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Azithromycin, dapsone</td>
<td>Cholestatic injury</td>
</tr>
<tr>
<td>Trimethoprimer-sulfamethoxazole</td>
<td>Mixed hepatocellular-cholestatic injury</td>
</tr>
<tr>
<td>Tuberculosis treatment</td>
<td></td>
</tr>
<tr>
<td>Isoniazid, rifampin, pyrazinamide</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Cholestatic injury</td>
</tr>
<tr>
<td>Antivirals</td>
<td></td>
</tr>
<tr>
<td>Ganciclovir, acyclovir</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>Anabolic/androgenic steroids</td>
<td></td>
</tr>
<tr>
<td>Testosterone, nandrolone, oxandrolone</td>
<td>Cholestatic injury, liver tumors, peliosis hepatitis</td>
</tr>
</tbody>
</table>


Differential diagnosis of liver disease in HIV

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    - Cryptococcus neoformans
    - Microsporidia
    - Pneumocystis jiroveci
    - Bacillary peliosis hepatitis
    - Herpesvirus saimiri
    - NAFLD
  - Medication toxicity
    - Alcoholic liver disease
  - Recreational drugs
    - Cocaine
    - Methyleneđimethylanethaline (Ecstasy)
  - Neoplasms
    - Lymphoma
    - KS
    - HCC
    - NHL
  - Autoimmune hepatitis
  - Hemochromatosis
  - Wilson’s disease
  - Alpha 1 antitrypsin deficiency

- Biliary disease
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  - Primary sclerosing cholangitis
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Alcoholic liver disease in HIV

- Alcohol use common in patients with HIV
  - 67% report alcohol use
  - 35% abuse/dependence
  - 23% hazardous

- cross-sectional analysis (VACS)
- n= 3565 patients
  - 701 HCV+/HIV+
  - 1410 HCV-/HIV+
  - 296 HCV+/HIV-
  - 1158 HCV-/HIV-

- Assessment of relationship between alcohol use and prevalence of advanced fibrosis
- For each alcohol category, advanced fibrosis more common among HIV+ than HIV-

Differential diagnosis of liver disease in HIV

Hepatic parenchymal disease
- Infection
  - Viral hepatitis: HCV, HBV, HDV, HAV, HEV, CMV, EBV, HSV, VZV, HIV-6
  - Mycobacterium avium complex
  - Cryptococcus neoformans
  - Microsporidia
  - Pneumocystis jiroveci
  - Bacillary peliosis hepatis
  - Histoplasma capsulatum

- NASH
  - Medication toxicity
  - Alcoholic liver disease
  - Recreational drugs
  - Cocaine
  - Methylenedioxymethamphetamine (Ecstasy)
  - Neoplasms
  - Lymphoma
  - KS
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  - Isospora
  - Microsporidia
  - Neoplasms
  - Lymphoma
  - KS
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  - Primary biliary cirrhosis

NAFLD in patients with HIV

- NAFLD is most common chronic liver disease in the U.S. (25%)
- NAFLD/NASH will soon represent #1 cause of cirrhosis and indication for liver transplantation in the U.S.
- As HCV coinfection declines as source of liver disease in DAA era, NAFLD is expected to rise in prevalence among patients with HIV
- Pre-ART era: NAFLD 85% → malnutrition/opportunistic infections
- Early-ART era: NAFLD 60% → DILI/mitochondrial injury/microsteatosis
- Modern ART era: NAFLD 13-55% → obesity/diabetes


What is NAFLD?

- **NAFLD**: Nonalcoholic Fatty Liver Disease
  - Includes a spectrum of pathology with steatosis
    - Simple steatosis → steatohepatitis → fibrosis → cirrhosis
    - Seen in individuals without significant alcohol consumption (21 drinks per week in men, 14 drinks per week in women)
  
- **NASH**: Nonalcoholic Steatohepatitis
  - A more severe form of NAFLD
  - Steatosis + ballooning degeneration + alcoholic hepatitis-like lesions (sinusoidal fibrosis and PMN infiltrates ± Mallory’s hyaline)

What is the Burden of NAFLD?

- NAFLD is common – **global prevalence of 25.2%**
  - Middle East (31.8%)
  - South America (30.5%)
  - Asia (27.4%)
  - North America (24.1%) – estimated 64 million in US
  - Europe (23.7%) – estimated 52 million in EU
  - Africa (13.5%)
- Metabolic comorbidities are common: obesity (51.3%), type 2 diabetes mellitus (22.5%), hyperlipidemia (69.2%), hypertension (39.3%), metabolic syndrome (42.5%)
- Emerging cause of liver cirrhosis and liver failure
- Will be leading indication for liver transplantation in U.S. by 2020
- Associated with increase in liver-related and all-cause mortality
- Associated with substantial cost: $103 billion (US), €35 billion (EU)


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What is the natural history of NAFLD?

**Histological Subtypes**[1,2]

- **NAFLD**
  - Isolated steatosis
  - Steatosis with mild inflammation
- **NASH**
- **Cirrhosis**
- **Fibrosis**

**Change in Fibrosis**[3,4]

- Regression: 18%-22%
- Stable: 40%-43%
- Progression: 34-42%

*N = 108 pts with NAFLD/NASH and median 6.6 yrs follow-up (data from serial biopsies).

What is the natural history of NAFLD?

- Leading cause of death is **cardiovascular disease**
- Key predictor of death or liver transplantation is **liver fibrosis** (retrospective cohort study of 619 patients 1975-2005, median follow-up 12.6 years):
  - Stage 1 (HR 1.88, 95% CI 1.28-2.77)
  - Stage 2 (HR 2.89, 95% CI 1.93-4.33)
  - Stage 3 (HR 3.76, 95% CI 2.40-5.89)
  - Stage 4 (HR 10.9, 95% CI 6.06-19.62)


How can I diagnose NAFLD?

- Abdominal ultrasound often first diagnostic study to signal presence of fatty liver
- Radiologic features: increased echogenicity, bright liver, vascular blurring
- Advantages: widely available, inexpensive
- Limitations: low sensitivity (requires 30% steatosis), does not distinguish NAFLD from ALD
- Alternatives: CT scan-Liver/Spleen, MRI-PDIFF, MRS, Fibroscan-CAP
How can I diagnose NAFLD?

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIVER ENZYMES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>45%</td>
<td>85%</td>
<td>60% with advanced disease can have normal ALT</td>
</tr>
<tr>
<td>GG12</td>
<td>53%</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>IMAGING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound Overall</td>
<td>85%</td>
<td>94%</td>
<td>None can distinguish NASH from IHS</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>93%</td>
<td></td>
<td>• Cheap, accessible</td>
</tr>
<tr>
<td>&lt;20-30%</td>
<td>20-30%</td>
<td></td>
<td>• Fibrosis and steatosis have similar features</td>
</tr>
<tr>
<td>CT w/o contrast &gt;30%</td>
<td>70%</td>
<td>97%</td>
<td>• Better in morbid obesity</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td>• Affected by iron, fibrosis</td>
</tr>
<tr>
<td>Overall POF, &gt;6.4%</td>
<td>86%</td>
<td>83%</td>
<td>• Less accurate with less steatosis</td>
</tr>
<tr>
<td>Spectroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HISTOLOGY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Biopsy</td>
<td>95%-100%</td>
<td>100%</td>
<td>GOLD standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sampling Error, Invasive</td>
</tr>
</tbody>
</table>


How can I diagnose NASH among patients with NAFLD?

- Non-alcoholic steatohepatitis (NASH) is a histologic diagnosis
- Liver biopsy not feasible for all patients with NAFLD
- Identify established risk factors and predictors of NASH
- No non-invasive tools currently available in clinical practice to reliably distinguish NASH from steatosis alone – research need for biomarkers
- CK-18 best established biomarker although limited to use in clinical trials
Established Risk Factors for NASH

Risk Factors
- Obesity (central)
- Hypertension
- Dyslipidemia
- Type 2 diabetes
- Metabolic syndrome

Adult Treatment Panel III Definition of the Metabolic Syndrome
Patient must have 3 or more of the following:
- Waist circumference of greater than 102 cm in men and greater than 88 cm in women
- Level of triglycerides of 150 mg/dL or greater
- High-density lipoprotein cholesterol level of less than 40 mg/dL in men and less than 50 mg/dL in women
- Systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 85 mm Hg
- Fasting plasma glucose level of 110 mg/dl or greater

How can I diagnose NASH fibrosis?

- **Liver biopsy remains gold standard** although is not feasible for all patients with NAFLD
- Non-invasive tools are clinically available to identify patients who are likely to have advanced fibrosis/cirrhosis:
  - Serum indices (APRI, FIB-4, NAFLD fibrosis score)
  - Serum assays (NASH FibroSure, ELF, Hepascore)
  - Imaging (ultrasound, CT, MRI)
  - Elastography (VCTE-Fibroscan, MR elastography, 2D-Shearwave, ARFI)
How can I diagnose NASH fibrosis?

- **NAFLD Fibrosis Score (NFS)** is a commonly used serum-based tool to identify patients with advanced liver fibrosis/cirrhosis among patients with NAFLD
- May be combined with liver imaging and/or elastography to guide staging and management

### NAFLD Fibrosis Score

<table>
<thead>
<tr>
<th>Impaired Fasting Glucose/Diabetes</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
</tr>
</tbody>
</table>

**Formula:**

\[
-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m2)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \frac{\text{AST/ALT ratio}}{0.013} \times \text{platelet (x 10^9)} - 0.68 \times \text{albumin (g/dL)}
\]

How can I diagnose NASH fibrosis?

- Vibration-controlled transient elastography (VCTE-Fibroscan) and magnetic resonance elastography (MRE) represent increasingly common tools to identify patients with advanced fibrosis/cirrhosis
- Liver biopsy continues to be indicated to clarify fibrosis stage if other markers are indeterminate, and to exclude alternative etiologies
**Transient Elastography: Fibroscan**

- Fibroscan: vibration-controlled transient elastography (VCTE)
- Approved by FDA in 2013
- Primary measure: liver stiffness measurement (LSM) in kPa units (2.5-75 kPa) range
- Secondary measure: controlled attenuation parameter (CAP) for measurement of liver fat (dB/m)
- Non-invasive, point-of-care
- Limitations: BMI, central obesity, ascites, cholestasis, acute hepatitis, alcohol, operator experience
- Technical failure in 3-27%
- AASLD (2017): VCTE and MRE are “clinically useful” tools
- AGA (2017): no recommendation regarding role of VCTE for assessment of cirrhosis in NAFLD; MRE suggested over VCTE for assessment of cirrhosis in NAFLD


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**Pathogenesis of NAFLD in HIV**

**Prevalence of NAFLD fibrosis in patients with HIV**

- Systematic review/meta-analysis
- N=10 studies (1256 patients)
- NAFLD prevalence 35.3% (28.8-42.5)
  - Predictors: BMI, DM, HTN, high CD4
- NASH prevalence 41.7% (22.3-64.0)
  - Predictors: none identified
- Fibrosis prevalence 21.7% (13.1-33.7)
  - Predictors: BMI, glucose, AST


**Noninvasive assessment of NAFLD in HIV**

- UCL/Royal Free Hospital (UK)
  - N=97 liver biopsies in HIV+ patients (negative HBV/HCV) with +LFTs between 2010-2017
- Assessment of steatosis (28%)
- Assessment of fibrosis (≥F2) (18%)
  - FIB-4 (>1.3): Sp 82%, NPV 95% (exclude advanced fibrosis)
  - Fibroscan (≥7.5 kPa): Sp 77%, NPV 94% (exclude advanced fibrosis)

Diagnostic strategy for patient with suspected NAFLD

- Exclude other etiologies for abnormal LFTs
- Identify other causes of fatty liver: alcohol, medications
- Assess for significant liver fibrosis –
  - start with noninvasive test
  - consider two tests to increase confidence
  - Interpret in context of full clinical data
- Consider liver biopsy in patients in whom significant fibrosis is predicted


Initial Management of NAFLD

- Lifestyle Changes
  - Medical weight loss (hypocaloric diet)
  - Exercise (aerobic/resistance)
  - Stop alcohol and potential offending drugs
    - methotrexate, amiodarone
  - Correct nutritional deficiencies if present
    - Consider choline in TPN
  - Treat co-existing metabolic syndrome
    - hyperlipidemia, diabetes, HTN
What are the key approaches to NAFLD treatment?

**Genetic predisposition**
- PNPLA3
- ApoC3
- CPT1-CHUK

**Insulin resistance**
- Accumulation of fat in the liver
- Oxidative stress?

**Central obesity**
- Exercise
- Weight loss
- Pioglitazone
- Endoscopic or surgical weight loss

**Chronic hepatocellular injury, inflammation**
- Fibrosis, cirrhosis

**Weight Loss Remains First Line Treatment for NAFLD/NASH**

- Weight loss ≥ 10%
- Fibrosis regression (45% of pts)
- Analysis of data from 4 randomized studies
- Weight loss ≥ 7%
- NASH resolution (64% to 90% of pts)*
- Weight loss ≥ 5%
- Ballooning/inflammation (41% to 100% of pts)*
- Weight loss ≥ 3%
- Steatosis (35% to 100% of pts)

Goals of NASH Therapy
- Patients with: 1) NAFLD; 2) NASH with F0 or F1 fibrosis
  → **Low Risk Group**: require **medical weight loss only**
- Patients with **NASH with F2-F4 fibrosis**
  → **High Risk Group**: requires **active intervention**
  - **Medical weight loss**: aim for 5-10% or more
  - **Pharmacologic weight loss**: lorcaserin, orlistat
  - **Endoscopic weight loss**: gastric balloon, sleeve gastrectomy
  - **Surgical weight loss**: gastric banding, Roux-en-Y gastric bypass
  - **NASH pharmacotherapy**: Vitamin E, pioglitazone
- **Investigational NASH-directed therapy**


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**Key NASH Therapies: Phase 3 Trials**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population</th>
<th>Trial</th>
<th>Primary Endpoint</th>
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</table>
| ELAFIBRANOR       | PPAR α/δ agonist    | NASH with F2-F3 fibrosis (plus high-risk F1) | RESOLVE-IT (n=2000, 72 wks) | 1) NASH resolution (w/o worsening fibrosis)  
2) Long-term composite of all-cause mortality, cirrhosis, and liver-related outcomes |
| OBETICHOLIC ACID (OCA) | FXR agonist         | NASH with F2-F3 fibrosis (plus high-risk F1) | REGENERATE (n=2065, 72 wks) | 1) NASH resolution (w/o worsening fibrosis)  
2) Fibrosis improvement (w/o worsening NASH) without NASH worsening  
3) Long-term: all-cause mortality and liver-related outcomes |
| SELONSERTIB       | ASK1 inhibitor      | NASH with F3  
NASH with F4 (compensated cirrhosis) | STELLAR 3 (n=408, 48 wks)  
STELLAR 4 (n=883, 48 wks) | 1) Fibrosis improvement (w/o without worsening NASH)  
2) Event-free survival (EFS) |
| CENICRIVIROC     | CCR2/5 antagonist   | NASH with F2-F3 fibrosis                 | AURORA (n=2000, 48 wks) | 1) Fibrosis improvement (w/o worsening NASH)  
2) Long-term composite of cirrhosis, liver-related outcomes, all-cause mortality |

Targets for NASH Drug Development


Role of Future NASH Pharmacotherapy

- Will **not** replace medical weight loss as 1st line
- Reserved for patients with biopsy-proven NASH and F2-F4 fibrosis
- None are “home runs” — limited efficacy and non-negligible safety/tolerability profiles
- May be complementary to other interventions
- Individualized approach – DM/non-DM, lean/obese, moderate fibrosis/F3-F4
- Adoption may be driven by evolution of non-invasive surrogates of NASH fibrosis
Conclusions

• Liver disease is common among patients living with HIV and is associated with substantial morbidity and mortality

• Differential diagnosis of liver disease is wide – most common etiologies include: viral hepatitis, alcoholic liver disease, DILI, and fatty liver disease

• Role of viral hepatitis in HIV remains significant but is expected to decline in response to effective antivirals

• NAFLD/NASH is emerging as major source of liver disease in patients with HIV

• Identifying patients with NASH with fibrosis represents critical step in management – biopsy gold standard

• Novel therapies offer hope for more effective liver-directed therapies for NASH in the future