HIV, AGING and the LIVER

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The HIV-Infected Population is Aging

- Increasing number of persons 50 years and older among new HIV infections \(^1\)
  - 4% in 1995 vs 6% in 2000 vs 15% in 2005
- Increasing number of persons 50 years and older living with HIV/AIDS in the US
  - From 2004 to 2007, the prevalence of persons living with HIV/AIDS increased the most in those aged 40-49 years old
- In 2005, persons 50 years and older accounted for 35% of all deaths of persons living with AIDS.

Persons Living with HIV/AIDS USA (33 states)
CDC Surveillance Program

![Graph showing increasing numbers of individuals aged 50 and older with HIV/AIDS over time.]

- 2001: 17.1%
- 2003: 19.7%
- 2006: 25.4%

It is expected that by 2015, 50% of the HIV population will be 50 and older.

CDC 2007. HIV/AIDS surveillance report 2005
Fauci AS. National HIV/AIDS and Aging Awareness Day

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection,
31 May – 2 June 2010, Tel Aviv, Israel
Complex Interactions between HIV and Aging Result in Accelerated Age-related Conditions

- Development of frailty, muscle wasting
- Insulin resistance, diabetes and cardiovascular disease
- Chronic kidney disease
- Bone disease
- Cognitive impairment and dementia
- HIV-related and unrelated malignancies

Liver disease and HCC

Consequences of HIV, Aging and the Liver

- Clinical manifestations of aging HIV and the liver
  - Chronic elevations of liver enzymes
  - Steatosis/steatohepatitis
  - Increased drug-related toxicity
  - More severe liver disease in aging patients with hepatitis B and C

- Mortality associated with liver disease is high among HIV-infected patients
Clinical case: Michelle

- 48 yo, AA woman
- Referred in 2002 for suspicion of cirrhosis
  - HIV diagnosed in 1989 (nadir CD4+ T-cell: 220)
  - No HBV/HCV co-infection
  - On didanosine + stavudine /PI, HIV RNA undetectable
  - BMI 20, severe lipoatrophy
  - Thrombocytopenia (plt=80) and CT-SCAN of the abdomen showed signs of portal hypertension
Complex interactions between aging, HIV, the immune system and the liver: role of microbial translocation
Aging, HIV and the Immune System: Interactions

- Early immune senescence in HIV disease¹
  - Aging and HIV seem to share common mechanisms by which they alter cellular immunity
  - Immune activation and inflammation are characteristic of both aging and HIV infection
  - In HIV infection, microbial translocation might contribute to premature aging by promoting immune activation
    - And may have direct effects on the liver²

Microbial Translocation in HIV

HIV -

HIV +

Early Immune Senescence in HIV Disease

Viral replication

Circulating antigen

Antigen

Loss of CD28 on T cells

Shortening of telomeres

Antigen

Inability to control mucosal dysregulation

Loss of Naïve T cells

Activation

Non-AIDS-defining co-morbidities

Inflammation

Premature aging

End-stage senescent T cells

Thymic dysfunctionality

Aging, HIV and the liver: interactions

- Aging and the liver\(^1,2\):
  - Decrease in liver volume
  - Impaired hepatic blood flow
  - Decreased amount of surface endoplasmic reticulum (SER)
  - Decline in regenerative response of hepatocytes following liver injury

- HIV and the liver\(^3,4,5,6\):
  - Several liver cell types can be productively infected with HIV
  - Replication of HIV in hepatic stellate cells by detection of p24 ag and HIV mRNA
    - Pro-fibrogenic (collagen I)
    - Pro-inflammatory (MCP-1)

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Clinical Manifestations of Aging Liver in HIV
Chronic Elevation of Liver Enzymes in HIV

- Abnormal liver enzymes are frequently seen in HIV infected patients (15-43%)\(^1,2,3,4\)

- Risk factors
  - Increased BMI, hypertension, ART exposure, severe alcohol use, HIV RNA level, low CD4 cell count, and age

- No studies have compared the prevalence of liver enzymes elevation in younger vs older HIV-infected patients

Chronic Elevation of Liver Enzymes in HIV

- Steatosis/steatohepatitis is an emerging cause of chronic liver enzymes elevations in HIV\(^1,2\)
  - 30 HIV-infected patients on ART with transaminase elevation (> 6 months) were biopsied\(^1\)
    - Mean age 46, duration of HIV infection 13 years
    - 18/30 had steatosis, 16/30 had steatohepatitis
    - Associated with insulin resistance
  - 24 HIV-infected patients were biopsied\(^2\)
    - Mean age 50, duration of HIV infection 17 years, mean duration of ART 12 years
    - 9/24 had steatohepatitis (37.5%)

Steatosis and Steatohepatitis

- 83/225 (37%) of HIV patients with NAFLD based on CT-scans
  - Mean age 48 years, 72% male, mean duration of HIV 13 years
- Factors associated with steatosis
  - Elevated ALT/AST, male sex, elevated waist circumference, and cumulative NRTI exposure
- 67/216 (31%) of HIV-infected patients with NAFLD based on US examination
  - Mean age 40 years, 94% male, mean duration of HIV 10 years, 65% on ART
- 165 patients with elevated liver enzymes and/or steatosis suggested at US
  - 55 underwent a liver biopsy
    - 20 of them (36%) had biopsy-proven steatosis and 6 also had steatohepatitis

The HIV aging liver: Steatosis

- Insulin Resistance, Diabetes, Obesity, Dyslipidemia
- EtOH Drugs
- Co-infection w/ Hepatitis C and B
- Fibrosis progression

ART (mitochondrial toxicity)
HIV (chronic inflam. state)
Drug-induced Toxicity

- In the post ART era, drug-induced toxicity has become a major problem in the management of HIV
  - Mitochondrial toxicity and microvesicular steatosis with NRTIs
  - Liver enzyme elevations with NNRTIs and PIs
- Aging increases susceptibility to drug toxicity
  - ↓ amount of SER + ↓ in P450 activity
    - Decline in phase I drug metabolism
- Increase pill burden in older HIV patients
  - Increased drug interactions and toxicity

Non Cirrhotic Portal Hypertension: Long-Term Liver Complication of ART

- Case-series of HIV mono-infected patients with cryptogenic liver disease\textsuperscript{1,2,3,4}
  - Signs and symptoms of portal hypertension
    - Thrombocytopenia
    - Hepatosplenomegaly
    - Esophageal varices (EV) / EV bleeding
    - Encephalopathy
  - Liver enzymes usually normal. INR, bilirubin and albumin normal
  - Prolonged exposure to ddI and median duration of HIV > 10 years

Non Cirrhotic Portal Hypertension: Long-Term Liver Complication of ART

- LIVER BIOPSY
  - Nodular Regenerative Hyperplasia (NRH) or
  - HepatoPortal Sclerosis (HPS),
    - Non cirrhotic portal hypertension
Non Cirrhotic Portal Hypertension: Long-Term Liver Complication of ART

In January of 2010, the United States Food and Drug Administration issued a statement that patients using Didanosine are at risk for a rare but potentially fatal liver disorder, non-cirrhotic portal hypertension.
HCV Co-Infected Patients Are Aging

- **1st cause of non-AIDS-related-deaths: LIVER**\(^1\)
  - Risk factors for liver deaths: lower CD4\(^+\) T cell count, IVDU, HCV, HBV and age (RR 1.3 per 5 years older)
- Patients with chronic HCV get older\(^2\)
  - A recent multiple cohort model of HCV prevalence and disease progression (in the US) estimated the burden of HCV and cirrhosis for the next decades


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The total number of patients with cirrhosis is expected to peak in 2020, but the proportion of patients with cirrhosis will climb up to 45% in 2030*

Davis GL et al. Gastroenterology 2010. Figure 2 and Figure 4.

The total number of cases of hepatic decompensation and HCC is also expected to peak in 2020*

* Not including treatment effect in model
Baseline Fibrosis Stage According to Age in HCV/HIV Coinfection


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Liver fibrosis is accelerated in HIV/HCV co-infected patients

- Why?
  - Decreased immunity
  - HIV replication in stellate cells
  - ART toxicity?
  - Steatosis/steatohepatitis
  - Liver disease progression may be associated with microbial translocation¹

HIV-related Microbial Translocation and Progression of Hepatitis C¹

- HIV-related CD4+ T-cell depletion associated with microbial translocation²
- Markers of microbial translocation were strongly associated with HCV-related liver disease progression
  - Levels of LPS were elevated prior to recognition of cirrhosis

HIV-related Gut CD4+ T cell Depletion and Microbial Translocation Contributes to HCV Progression

Balagopal A et al. Gastroenterology 2008

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Hepatic Stellate Cell Activation: A Central Event in Liver Fibrosis

Friedman SL and Arthur, Science and Medicine, 2002

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Role of Microbial translocation in liver fibrosis?

Following HIV infection: gut permeability

LPS level in portal/systemic circulation

Kupffer cells are a target of LPS

Hepatic stellate cells activation (TLR4 dependent)

Liver fibrogenesis

Clinical case: Michelle

Liver biopsy 2002: Hepatoportal sclerosis (HPS)

- No significant fibrosis, no cirrhosis. No significant steatosis.
- Dx: Non cirrhotic portal hypertension
- Upper endoscopy: grade 3 varices: banded.
- Trace ascites. No encephalopathy.
- ART modified: tenofovir DF + lamivudine + efavirenz
- 2 years later, ALT increases to 3X ULN
- She had gained about 20 pounds in 1 year
- Liver biopsy 2004
Liver biopsy 2004: Steatosis

Only 2 portal tracts, portal vein branches not assessed

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Since 2002

- Still on TDF + lamivudine + efavirenz
- Lost weight and ALT in the 30s
- Bi-annual upper EGD: varices grade 1-2 in 02/2010, no bleeding, no further banding necessary
Conclusion

- The liver is a major target of the aging process that occurs in HIV-infected patients
- The causes are multiple:
  - Chronic immune activation
  - Accelerated senescence
  - HIV effect on stellate cells and liver fibrosis
  - Microbial Translocation leading to progressive liver disease
  - Worsening of chronic hepatitis
- Recognize the clinical importance of the aging liver and tailor treatment accordingly
• 1st International Workshop on HIV & Aging 4-5 October 2010, Baltimore, MD, USA
  ▸ Abstract submission deadline August 7, 2010
Take care of your patients livers and they will all be smiling!