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Liver disease, HIV and aging

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Abstract

The life expectancy of HIV-infected patients has increased due to the efficacy of highly active antiretroviral therapy (HAART) in controlling HIV replication; thus, the population living with HIV infection is steadily aging. Liver-related morbidity and mortality has emerged as a leading problem in HIV-infected patients. Since aging, HIV infection and HAART all affect the liver, understanding the impact of the combination of these factors on liver disease is crucial for optimisation of care in the aging HIV-infected population. This review will focus on the current understanding of liver disease in older (>50 years old) HIV-negative individuals and in HIV-infected individuals. Areas for future research in the area of HIV, liver disease and aging will also be discussed.

Additional keywords

cirrhosis; hepatitis; highly active antiretroviral therapy

Introduction

The number of HIV-infected patients above the age of 50 is increasing as a result of increased longevity from highly active antiretroviral therapy (HAART) and an increase in the number of new infections in older people.[1] Aging, in the absence of HIV infection, is known to affect function of the major organs including the liver, with a decrease in liver volume, blood flow, drug metabolism and hepatic regenerative capacity.[2] HIV infection also affects the liver, primarily through acceleration of liver disease from chronic viral hepatitis. Liver disease is currently a major cause of morbidity and the second leading cause of mortality after AIDS in HIV-infected patients.[3,4] Since aging in the HIV-infected population is an emerging issue, the data on the combined effects of HIV infection and aging on the liver are limited. This review will focus on our current understanding of liver disease in older (>50 years old) HIV-negative individuals and in HIV-infected individuals. Areas for future research in the area of HIV, liver disease and aging will also be discussed.

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Conflicts of interest

None declared.

Aging and hepatitis C

Due to shared modes of transmission, ~20% of HIV-infected patients worldwide are also infected with the hepatitis C virus (HCV).[5] This proportion ranges from 8% in men who have sex with men (MSM)[6] to over 80% in haemophiliac patients and intravenous drug users.[7,8] Outbreaks of sexually transmitted HCV have also been reported among HIV-positive MSM and appear to be associated with permucosal traumatic sexual techniques and other sexually transmissible infections.[9–12] Older patients are increasingly engaging in behaviours that put them at risk for both HIV and HCV.

HIV negatively affects the outcome of an acute HCV infection, and this may be further exacerbated by older age. HIV infection reduces rates of spontaneous recovery from an acute HCV infection by ~three-fold.[13–17] It is plausible that these rates may be further reduced in older age since HIV-negative patients who acquire HCV at or above the age of 45 years are half as likely to spontaneously clear their HCV infection compared with patients younger than 45.[17] Studies are needed to determine whether HIV and aging effects are synergistic in reducing the rates of spontaneous recovery from an acute HCV infection.

Once chronic HCV is established, older age has been associated with a more rapid progression of liver disease.[18] Asahina *et al.* demonstrated a faster rate of biopsy-proven progression of hepatic fibrosis in HIV-negative patients acquiring HCV after the age of 40 years compared with before this age.[19] In addition, the time to development of hepatocellular carcinoma (HCC) was shorter in the patients >40 years of age compared with those <40 years of age (22 and 40.6 years, respectively). These data are also supported by a meta-analysis demonstrating that 24% of HCV monoinfected patients who were infected with HCV at a mean age of 42 years developed cirrhosis after 20 years compared with only 7% of patients who were infected at a mean age of 29 years.[20] In a study of patients with post-transfusion hepatitis, the mean time from transfusion to development of HCC was 14.7 years among persons infected at 50 years or older compared with 31.5 years among those infected below age 50.[21] The aetiology of increased progression of liver disease in HCV infection with aging remains unclear; however, several mechanisms have been proposed. These include a higher vulnerability to environmental factors including oxidative stress, a reduction in hepatic blood flow rates and reduced mitochondrial capacity.[22,23]

HIV infection similarly accelerates progression of liver disease.[13,24] One meta-analysis of four studies from Europe and North America found the 15-year risk of progression to histological cirrhosis among HIV–HCV co-infected individuals to be almost twice that of HCV monoinfected patients (relative risk (RR): 1.94; 95% confidence interval (CI): 0.92–4.07).[24] Progression of HCV-related liver disease in older HIV-infected individuals has not been extensively studied. Thus, the combined effects of aging and HIV infection are not known. These combined effects may, however, lead to worse liver disease progression outcomes in older HIV–HCV co-infected individuals.

HCV treatment response to the current standard of care, pegylated interferon-alfa and ribavirin, in older individuals and in HIV-infected individuals is decreased, but there are limited data on treatment response in patients that are both older and HIV-infected. Rates of

sustained virological response (SVR), defined as absence of serum HCV RNA 6 months after pegylated interferon-alfa plus ribavarin, in HIV seronegative patients is 54–63%,[25–27] but in the HIV co-infected population, SVR ranges from 27% to 40%.[28–30] In one study of HIV-infected subjects, being older than 40 years was associated with a poorer virological response as judged by a 40% reduction in rates of SVR in those with HCV genotypes 2, 3 or 5.[28] In the HCV monoinfected population, age is emerging as a strong independent predictor of non-SVR, with patients older than 65 years being 2.5 times less likely to achieve SVR compared with patients <35 years of age.[19] In one study, the risk of non-SVR increased 1.8-fold for each additional 10 years of age, with SVR rates of 59.3% for patients younger than 49 years, 50.5% for 50–59-year-olds, 27.3% for 60–65-year-olds and 25.2% for patients older than 65 years.[19] In another recent study of Genotype 1 patients who had an undetectable HCV RNA after 1 month of therapy, older age was identified as the main predictor of subsequent relapse.[31] Taken together, these studies support older age as being a risk factor for a decreased response to HCV therapy, which could exacerbate the poor response that is seen with HIV infection.

Older patients are also less likely to tolerate HCV treatment due to an increase in adverse events including anaemia, neutropaenia and thrombocytopaenia, which often require stopping treatment or dose reduction.[32,33] A recent meta-analysis of three randomised controlled trials of HCV treatment in HIV-infected individuals found that adverse events requiring treatment discontinuation or first dose modification were more common in older individuals, with each additional 10 years of age being associated with a 60% increase in the risk of the former and a 48% increase in the risk of the latter.[34]

Common medical conditions such as diabetes mellitus and cardiovascular disease (CVD) that are typically associated with aging are also increasingly being associated with HCV infection. HCV-infected individuals above the age of 40 are three times as likely as HCV uninfected individuals of the same age to have diabetes.[35] In the HIV-infected population, HAART appears to increase this risk,[36] probably related to HAART-induced metabolic syndrome. In a study of US veterans during the HAART era, HIV–HCV co-infected patients had a 39% increased risk of diabetes mellitus compared with HIV-negative veterans, and this risk increased by 45% for each additional 10 years of age. Of note, HCV infection did not increase the risk of diabetes in the pre-HAART era.[37] It is also interesting to note that although HIV–HCV coinfection is associated with lower rates of hypercholesterolaemia, one study found rates of acute myocardial infarction (AMI) and CVD to be significantly higher among HIV–HCV compared with HIV monoinfected patients[38] When analyses were adjusted for cardiovascular risk factors and duration of HAART, HIV–HCV co-infection remained associated with a 20% increase in risk of AMI compared with HIV monoinfected US veterans (hazard ratio: 1.20, $P = 0.013$).

Aging and hepatitis B

Hepatitis B virus (HBV) co-infection with HIV is relatively common since transmission of both viruses occurs through sexual and percutaneous transmission. Approximately 10% of HIV-infected patients have evidence of chronic HBV infection,[39,40] and data suggest that the HIV–HBV co-infected population is aging. The HIV Outpatient Study, a multisite

observational cohort study in the USA, found that from 1996 to 2007, the HBV prevalence in study subjects entering the cohort over the age of 45 increased from 5.5% in 1996 to 8.0% in 2007.[41] In contrast, prevalence rates remained relatively stable in younger age groups.

In HBV monoinfection, older age decreases the likelihood of recovery (development of HBV surface antibodies (anti-HBs)) from an acute HBV infection, possibly related to a senescence of the immune system.[42] This is supported by a poor antibody response to the HBV vaccine in older individuals, with 2.4 times the risk of non-response to the HBV vaccine in individuals older than 45 years compared with younger subjects.[43,44] Similarly, HIV infection decreases rates of recovery. In one study, 23% of HIV-infected individuals compared with 4% of HIV-negative individuals progressed to chronic HBV after an acute HBV infection.[45] In the study by Bodsworth *et al.*, lower CD4 counts were significantly associated with an increased risk of progression to chronic HBV. This finding is supported by a more recent study showing rates of progression to chronic HBV of 11%, 16% and 19% for CD4 count strata of ≥500, 200–499 and <200 respectively.[46] Encouragingly, those on HAART who became acutely infected with HBV were more likely to develop anti-HBs.[46] While there are no studies looking specifically at acute HBV infection outcomes in elderly HIV-infected patients, it is probable that they are at an even higher risk of progression to chronicity given the combined effects of age and HIV-related immune system dysfunction.

Once chronic HBV develops, HIV-infected patients have higher rates of HBV replication as measured by HBV DNA levels and by hepatitis B ‘e’ antigen (HBeAg) positivity.[45,47] Conversely, a recent single-centre cross-sectional analysis of 1400 HBV monoinfected patients in Hong Kong found decreasing rates of HBeAg positivity with increasing age. Among the HBeAg-positive patients, those older than 45 years had significantly lower HBV DNA levels than the younger patients. However, the older (>55 years) HBeAg negative patients had higher HBV DNA levels than younger patients,[48] and they also had higher alanine transaminase levels, suggesting more active disease. Thus, the effect of aging on HBV replication varies based on the stage of HBV infection, making it difficult to predict how both aging and HIV infection would affect HBV replication.

The impact of HIV on HBV-related liver disease in older patients is largely unknown; however, there is one study suggesting that liver disease is worse with older age. In that study, HIV–HBV co-infected patients older than 40 years had greater than twice the risk of liver-related mortality compared with patients less than 40 years (22.1 liver related deaths per 1000 person-years (PY) versus 10.0 liver related deaths per 1000 PY).[39]

Limited data suggest that treatment efficacy of HBV is not compromised in older patients or in HIV-infected patients. A single-centre retrospective analysis of HBV monoinfected patients matched on gender, HBV DNA level and HBeAg status found similar rates of transaminase normalisation, HBV DNA loss, and development of lamivudine resistance mutations in patients greater than 60 years of age compared with patients younger than 60.[49] Similarly, in studies of HIV infection, response rates to lamivudine in HIV-infected individuals are similar to those of HIV-negative patients;[50,51] however, rates of developing lamivudine resistance are greater in HIV-infected subjects.[52,53] Thus, although there are no studies looking at outcomes of HBV treatment in older HIV–HBV co-infected patients,

extrapolation of the available data suggest that the response to the current anti-HBV agents should be similar in the older HIV–HBV co-infected patient compared with the younger HBV monoinfected patient.

Effects of aging on medication toxicity

Physiological changes related to aging such as reduced activity of hepatic enzymes (e.g. cytochrome P450, superoxide dismutase), reduced hepatic blood flow and reductions in renal function, with an attendant increase in the half-life and bioavailability of drugs, contribute to the increased risk of drug-related hepatotoxicity in the elderly.[54] Since many of the HIV drugs are metabolised via the cytochrome P450 system and since HIV can compromise renal function, it is possible that the older HIV-infected patient is at a higher risk for antiretroviral (ART)-related toxicity, although this has not been well studied. ART-related hepatotoxicity occurs by one of the following primary mechanisms: direct drug toxicity or metabolic host mediated injury, mitochondrial toxicity or hypersensitivity reactions.[55]

Decreases in concentrations of cytochrome P450 have been noted on liver biopsy with aging.[56] This would suggest a potential for toxicity with use of non-nucleoside reverse transcriptase inhibitors and protease inhibitors (PI), which are both metabolised through the cytochrome P450 system. Although few studies on the metabolism of ART drugs in elderly patients have been published, and most ART trials have excluded older patients, one study of patients 20–66 years old found an 11% increase in risk of ART toxicity for each year of increasing age.[57]

The nucleoside reverse transcriptase inhibitors (NRTI) are associated with an infrequent but distinctive type of hepatotoxicity caused by mitochondrial toxicity. Mitochondrial toxicity may evolve to acute liver failure with hepatic steatosis and lactic acidosis weeks to months after NRTI initiation.[55] Studies suggest that the risk of mitochondrial toxicity is related to individual susceptibility, with a higher risk of clinical manifestations in patients with subclinical mitochondrial impairment.[58] Thus, since mitochondrial dysfunction occurs as part of the natural aging process, older HIV-infected patients may be at higher risk of hepatic steatosis or lactic acidosis due to NRTI-related mitochondrial toxicity. Supporting this hypothesis, a retrospective analysis of 110 HIV-infected patients from 19 centres in 10 countries found being aged over 40 years to be associated with an increased risk of lactic acidosis (odds ratio: 2.6, 95% CI: 1.08–6.29) compared with being less than 40 years old.[59]

Polypharmacy, which has been associated with an increased risk of drug-induced hepatotoxicity in the elderly population in general,[60] is emerging as an issue in the older HIV-infected population. A recent study from Canada found a higher total median number of prescribed medications in HIV-positive patients aged 60 and older compared with HIV-positive patients below the age of 60 (seven versus four medications).[61] This increased prevalence of polypharmacy among older HIV-positive patients has been linked to a higher number of comorbidities and is associated with the potential for an increase in drug–drug interactions.[62] Although data are limited, it is likely that there are differential rates of drug-induced hepatotoxicity of non-ART medications by age among HIV-infected patients. For

example, isoniazid, a cornerstone of anti-tuberculosis treatment, is frequently associated with elevations in aminotransferases. Patients older than 49 years have almost five times the risk of experiencing isoniazid-related hepatotoxicity compared with patients aged 25–34 years.[63] There is a need for more data on the pharmacokinetics of ART in patients at the extremes of age as well as tolerability, drug–drug interactions, toxicities and interactions with other non-HIV medications.

Aging and alcoholic liver disease

Alcohol use, which has significant effects on the liver, appears to be increasing in individuals over 65 years of age.[64] In addition, several studies suggest that alcohol use is a growing problem in HIV-infected subjects. In a USA-based cohort, 47.3% of 2864 HIV-infected adults above age 50 admitted to any alcohol use, with 14.4% classified as heavy drinkers.[65] This is in contrast to the general USA population, in which 31.2% of adults above the age of 50 consumed alcohol in the preceding year, of whom 9.5% met criteria for alcohol abuse or dependence based on unpublished data from the 2001–2002 National Epidemiologic Survey on Alcohol-Related Conditions (NESARC) (B. F. Grant, K. Kaplan, J. Shepard, T. Moore, unpubl. data). An analysis of insurance claims in the USA found that the prevalence of alcohol abuse was two-fold greater in HIV-infected patients >50 years old compared with age- and gender-matched HIV-negative controls. This analysis also found that among HIV-infected patients, there was a 13% higher prevalence of alcohol abuse in the older (>50-year-old) patients compared with those 18–49 years old.[66]

Because the activity of enzymes that metabolise alcohol, acetaldehyde dehydrogenase and cytochrome P4502E1 diminish with age, older patients are more susceptible to the toxic effects of alcohol.[67] The presence of other co-existing diseases such as non-alcoholic fatty liver disease (NAFLD), HBV and HCV may further potentiate these toxic effects of alcohol in the elderly.[68] There are no studies evaluating the prevalence or course of alcoholic liver disease in HIV-infected patients. However, in the general population, prognosis is directly related to age.[69] In a British study, mortality from cirrhosis in alcoholic liver disease was 34% and 54% at Years 1 and 3 of follow-up, respectively, in patients over 60 compared with 5% and 24%, respectively, at 1 and 3 years of follow-up in patients under 60 years.[70] One mechanism whereby alcohol can damage the liver is through increasing the risk of steatosis and steatohepatitis. Alcohol can also increase generation of reactive oxygen species and lipid peroxidation, thus inducing oxidative damage to mitochondrial elements.[71] Thus, ART-associated mitochondrial dysfunction and diminished mitochondrial antioxidant defences in the aging liver may further potentiate the impact of alcohol as an independent predictor of liver disease progression.

Aging and NAFLD

NAFLD refers to a spectrum of liver histology abnormalities characterised by excess liver fat in individuals who drink little or no alcohol. It ranges from simple fatty liver (steatosis) to associated inflammation and fibrosis, termed non-alcoholic steatohepatitis (NASH). Two recent cross-sectional studies have evaluated the prevalence of NAFLD among HIV-infected patients without viral hepatitis. Guaraldi *et al.* reported a 36.9% NAFLD prevalence

diagnosed by computed tomography among 225 patients (mean age: 48 years).[72] In a similar study by Crum-Cianflone *et al.* among 216 HIV-infected persons (mean age: 40 years) in the USA, a 31% prevalence rate of NAFLD was reported.[73] This study found an estimated NASH prevalence rate of 6–10%.[73,74] The prevalence of NAFLD in the general population ranges from 16% to 41%, depending on the study population and the imaging method used to diagnose NAFLD. These study design differences also make it difficult to compare prevalence rates to the HIV-infected population.[75–77]

The severity of liver disease from NAFLD appears to be associated with increasing age in the general population.[78] A single-centre study of 144 patients in a gastrointestinal clinic found age >45 years to be associated with severe fibrosis (F3–F4).[79] While this may simply be related to increased duration of steatohepatitis, the influence of aging on progression of hepatic fibrosis needs to be explored.

NAFLD appears to be most strongly associated with central obesity and insulin resistance states such as diabetes and metabolic syndrome. HAART therapy, especially with NRTI–PI combinations, is commonly associated with metabolic abnormalities such as insulin resistance, hypertriglyceridaemia and lipodystropy, a disorder of peripheral fat distribution resulting in lipoatrophy and visceral adiposity.[80] Steatosis and NASH can also be induced by NRTI use via inhibition of mitochondrial DNA replication, resulting in triglyceride accumulation in the liver.[55] Thus, it is possible that NAFLD is increased in HIV-infected patients on HAART. Given data suggesting an association between increased duration of NRTI use and an increased prevalence of NAFLD,[72] NAFLD prevalence rates may be even higher among older HIV-infected patients, if only as a function of duration of HAART use. Additionally, HCV, which has been associated with steatosis prevalence rates as high as 69%[81] among HIV-co-infected patients, may be another modulator of steatosis development in older HIV-infected patients. Although there are no studies looking at prevalence, risk factors and progression of NAFLD in older HIV-infected patients, it potentially may become a major problem, especially since 10–15% of patients with NAFLD in the general population progress to NASH, 15–20% of whom progress to cirrhosis.[55] Well-designed prospective studies are needed to improve our general understanding of the natural history of NAFLD in HIV infection. Further clarification of the association between cumulative NRTI exposure and NAFLD would be particularly relevant in the older HIV-infected population, which, by virtue of prolonged HIV infection, is likely to have longer duration of NRTI exposure.

Aging and hepatocellular cancer

Age above 60, HCV and HBV infection, excessive alcohol consumption, tobacco use and diabetes are all risk factors for HCC.[4] Among HIV-infected persons, HCC is most closely associated with viral hepatitis co-infection.[82] HCC occurs at an earlier age, on average, in HIV-infected patients (median age 42 at diagnosis in an Italian cohort;[83] 52 in a North American study[84]) than in HIV-uninfected patients (median age 65).[85] This suggests that HIV may accelerate the risk of HCC; however, the data are not clear. Although Patel *et al.* report a liver cancer incidence that was 7.7-fold higher in HIV-infected persons compared with the general USA population;[86] this may purely be a function of increased rates of

chronic viral hepatitis infections in HIV-infected persons. Supporting this idea, HIV co-infection was not associated with an increase in risk of HCC among US veterans with HCV.[87]

There are, however, data to suggest that an increasing proportion of liver-related deaths in HIV-infected individuals are due to HCC. A study based on nationwide surveys of deaths among HIV-infected patients in France reported an increase in the proportion of liver-related deaths attributable to HCC from 15% in 2000 to 25% in 2005.[4] This was coincident with aging of the cohort and an increase in duration of HIV infection from 10.7 years to 14.8 years.[4] Patients who died of HCC were older than those that died from other liver disease causes (48 versus 46 years, $P = 0.04$). The proportion of HCC-related deaths among HCV-infected patients in this cohort increased from 10% in 2000 to 26% in 2005.[4] Findings from this study are limited by the observational nature of the study and collection of data on HCC in fatal cases only as opposed to incident cases. This study, however, raises the question of whether the increase of HCV-associated HCC cases was related to aging or purely a function of prolonged HCV infection in the absence of the competing risk of AIDS-related death, or a combination of both. Other potential modulating factors include the presence of liver steatosis, which has been identified as an independent predictor of hepatocarcinogenesis.[30]

The American Association for the Study of Liver Disease (AASLD) recommends screening for HCC at 6-month intervals with ultrasound in all groups at high risk of HCC, largely based on data from HIV-negative patients. These include HBV carriers with cirrhosis regardless of age, and HCV-infected patients with cirrhosis, bridging fibrosis or transition to cirrhosis.[88,89] Alpha-fetoprotein (AFP) determination was judged to lack adequate sensitivity and specificity.[88] Most clinicians, however, use a combination of ultrasound and AFP for HCC screening in patients judged to be at high risk for HCC. More frequent screening has not been studied in the HIV-infected population and recommendations for screening are thus no different.

Future research

There are multiple shared factors between the HIV-infected population and the aging population, which increase the risk of liver disease. While there are some data on the impact of HIV or aging on liver disease (Table 1), it is not known if these factors act independently or synergistically; thus, there is a significant knowledge gap in understanding the impact of HIV, HAART and aging on the liver and liver disease. In each of the diseases discussed above, there are important questions that need to be answered to optimise prevention and treatment of liver-related diseases (Table 2). For example, understanding whether liver disease progresses more rapidly in older HIV–viral hepatitis co-infected patients compared with younger ones is important in deciding when treatment should be initiated. A basic understanding of the effects of aging on HBV and HCV replication and on the liver in HIV-infected compared with HIV-negative patients is also needed. Determining differences in the metabolism of HAART and the incidence of toxicity from HAART and other medications in the older individual will provide guidance regarding medication dosing. Further work to determine whether HCC develops more rapidly or whether NAFLD and NASH lead to more liver disease in the older individual is also important. Lastly, elucidation of the role of

various HAART regimens in modulating these diseases may also significantly improve our ability to prevent liver disease in this population.

Conclusion

Liver disease is a major cause of morbidity and mortality in HIV-infected patients. Current evidence suggests that older age may exacerbate this risk such that older HIV-infected patients may be at an even higher risk of liver disease. However, more data are needed to better understand the interaction of HIV and aging on liver disease. There is a need for well-designed studies on the epidemiology, pathogenesis, therapeutic and clinical outcomes of liver disease, and comorbidities in older HIV-infected patients. Such studies will inform clinicians regarding screening for and treating liver disease as the HIV-infected population ages.

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References

1. Gebo KA. HIV and aging: implications for patient management. Drugs Aging. 2006; 23:897–913. DOI: 10.2165/00002512-200623110-00005 [PubMed: 17109568]
2. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. Clin Infect Dis. 2008; 47:542–53. DOI: 10.1086/590150 [PubMed: 18627268]
3. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006; 166:1632–41. DOI: 10.1001/archinte.166.15.1632 [PubMed: 16908797]
4. Salmon-Ceron D, Rosenthal E, Lewden C, Bouteloup V, May T, Burty C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: the French national Mortalite 2005 study. J Hepatol. 2009; 50:736–45. DOI: 10.1016/j.jhep.2008.11.018 [PubMed: 19231018]
5. Soriano V, Vispo E, Labarga P, Medrano J, Barreiro P. Viral hepatitis and HIV co-infection. Antiviral Res. 2010; 85:303–15. DOI: 10.1016/j.antiviral.2009.10.021 [PubMed: 19887087]
6. Sherman KE, Freeman S, Harrison S, Andron L. Prevalence of antibody to hepatitis C virus in patients infected with the human immunodeficiency virus. J Infect Dis. 1991; 163:414–5. DOI: 10.1093/infdis/163.2.414 [PubMed: 1846395]
7. Rumi MG, Colombo M, Gringeri A, Mannucci PM. High prevalence of antibody to hepatitis C virus in multitransfused hemophiliacs with normal transaminase levels. Ann Intern Med. 1990; 112:379–80. [PubMed: 2106281]
8. Hayashi PH, Flynn N, McCurdy SA, Kuramoto IK, Holland PV, Zeldis JB. Prevalence of hepatitis C virus antibodies among patients infected with human immunodeficiency virus. J Med Virol. 1991; 33:177–80. DOI: 10.1002/jmv.1890330307 [PubMed: 1715384]
9. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. AIDS. 2010; 24:1799–812. DOI: 10.1097/QAD.0b013e32833c11a5 [PubMed: 20601854]
10. Matthews GV, Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta *et al.* AIDS. 2007; 21:2112–3. DOI: 10.1097/QAD.0b013e3282ef3873 [PubMed: 17885306]
11. Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS. 2009; 23:F1–7. DOI: 10.1097/QAD.0b013e32832e5631 [PubMed: 19542864]

12. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS. 2007; 21:983–91. DOI: 10.1097/QAD.0b013e3281053a0c [PubMed: 17457092]
13. Thomas DL. Hepatitis C and human immunodeficiency virus infection. Hepatology. 2002; 36:S201–9. DOI: 10.1002/hep.1840360726 [PubMed: 12407595]
14. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. Lancet. 2002; 359:1478–83. DOI: 10.1016/S0140-6736(02)08435-0 [PubMed: 11988247]
15. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999; 29:908–14. DOI: 10.1002/hep.510290311 [PubMed: 10051497]
16. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. N Engl J Med. 1992; 327:1899–905. DOI: 10.1056/NEJM199212313272702 [PubMed: 1280771]
17. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000; 284:450–6. DOI: 10.1001/jama.284.4.450 [PubMed: 10904508]
18. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet. 1997; 349:825–32. DOI: 10.1016/S0140-6736(96)07642-8 [PubMed: 9121257]
19. Asahina Y, Tsuchiya K, Tamaki N, Hirayama I, Tanaka T, Sato M, et al. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology. 2010; 52:518–27. DOI: 10.1002/hep.23691 [PubMed: 20683951]
20. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001; 34:809–16. DOI: 10.1053/jhep.2001.27831 [PubMed: 11584380]
21. Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med. 1995; 332:1463–6. DOI: 10.1056/NEJM199506013322202 [PubMed: 7739682]
22. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol. 2001; 34:730–9. DOI: 10.1016/S0168-8278(00)00097-0 [PubMed: 11434620]
23. Marcus EL, Tur-Kaspa R. Chronic hepatitis C virus infection in older adults. Clin Infect Dis. 2005; 41:1606–12. DOI: 10.1086/497597 [PubMed: 16267733]
24. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001; 33:562–9. DOI: 10.1086/321909 [PubMed: 11462196]
25. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002; 347:975–82. DOI: 10.1056/NEJMoa020047 [PubMed: 12324553]
26. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001; 358:958–65. DOI: 10.1016/S0140-6736(01)06102-5 [PubMed: 11583749]
27. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004; 140:346–55. [PubMed: 14996676]
28. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA. 2004; 292:2839–48. DOI: 10.1001/jama.292.23.2839 [PubMed: 15598915]

29. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med. 2004; 351:451–9. DOI: 10.1056/NEJMoa032653 [PubMed: 15282352]
30. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004; 351:438–50. DOI: 10.1056/NEJMoa040842 [PubMed: 15282351]
31. Gianmario Borroni MA, Aurora Bortoli A, Asiraghi AC, Cazzaniga M, Ceriani R, Guerzoni P, et al. Older age increases the risk of relapse in genotype-1 chronic hepatitis patients showing complete early virologic response during peginterferon and ribavarin therapy. Hepatology. 2010; 52:809A.
32. Thabut D, Le Calvez S, Thibault V, Massard J, Munteanu M, Di Martino V, et al. Hepatitis C in 6,865 patients 65 yr or older: a severe and neglected curable disease? Am J Gastroenterol. 2006; 101:1260–7. DOI: 10.1111/j.1572-0241.2006.00556.x [PubMed: 16771947]
33. Nudo CG, Wong P, Hilzenrat N, Deschenes M. Elderly patients are at greater risk of cytopenia during antiviral therapy for hepatitis C. Can J Gastroenterol. 2006; 20:589–92. [PubMed: 17001400]
34. Bhattacharya D, Umbleja T, Carrat F, Chung RT, Peters MG, Torriani F, et al. Women experience higher rates of adverse events during hepatitis C virus therapy in HIV infection: a meta-analysis. J Acquir Immune Defic Syndr. 2010; 55:170–5. DOI: 10.1097/QAI.0b013e3181e36420 [PubMed: 20622678]
35. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology. 1999; 29:328–33. DOI: 10.1002/hep.510290235 [PubMed: 9918906]
36. Howard AA, Klein RS, Schoenbaum EE. Association of hepatitis C infection and antiretroviral use with diabetes mellitus in drug users. Clin Infect Dis. 2003; 36:1318–23. DOI: 10.1086/374838 [PubMed: 12746779]
37. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. Hepatology. 2004; 40:115–9. DOI: 10.1002/hep.20289 [PubMed: 15239093]
38. Bedimo R, Westfall AO, Mugavero M, Drechsler H, Khanna N, Saag M. Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. HIV Med. 2010; 11:462–8. [PubMed: 20163481]
39. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002; 360:1921–6. DOI: 10.1016/S0140-6736(02)11913-1 [PubMed: 12493258]
40. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS. 2005; 19:593–601. DOI: 10.1097/01.aids.0000163936.99401.fe [PubMed: 15802978]
41. Spradling PR, Richardson JT, Buchacz K, Moorman AC, Brooks JT. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996–2007. J Viral Hepat. 2010; 17:879–86. DOI: 10.111/j1365-2893.2009.0124a.x [PubMed: 20158604]
42. Floreani A, Chiaramonte M, Naccarato R. Acute hepatitis in elderly patients. Arch Intern Med. 1983; 143:1829.doi: 10.1001/archinte.143.9.1829 [PubMed: 6615112]
43. Chiaramonte M, Floreani A, Naccarato R. Hepatitis B virus (HBV) in the elderly: an underestimated problem? Biomed Pharmacother. 1987; 41:121–3. [PubMed: 3607264]
44. Cleveland JL, Siew C, Lockwood SA, Gruninger SE, Chang SB, Neidle EA, et al. Factors associated with hepatitis B vaccine response among dentists. J Dent Res. 1994; 73:1029–35. [PubMed: 8006228]
45. Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. J Infect Dis. 1991; 163:1138–40. DOI: 10.1093/infdis/163.5.1138 [PubMed: 2019762]

46. Landrum ML, Fieberg AM, Chun HM, Crum-Cianflone NF, Marconi VC, Weintrob AC, et al. The effect of human immunodeficiency virus on hepatitis B virus serologic status in co-infected adults. PLoS ONE. 2010; 5:e8687.doi: 10.1371/journal.pone.0008687 [PubMed: 20084275]
47. Mai AL, Yim C, O'Rourke K, Heathcote EJ. The interaction of human immunodeficiency virus infection and hepatitis B virus infection in infected homosexual men. J Clin Gastroenterol. 1996; 22:299–304. DOI: 10.1097/00004836-199606000-00012 [PubMed: 8771427]
48. Fung J, Seto WK, Lai CL, Yuen J, Wong DK, Yuen MF. Profiles of HBV DNA in a large population of Chinese patients with chronic hepatitis B: implications for antiviral therapy. J Hepatol. 2011; 54:159–200.
49. Kawaoka T, Suzuki F, Akuta N, Suzuki Y, Arase Y, Sezaki H, et al. Efficacy of lamivudine therapy in elderly patients with chronic hepatitis B infection. J Gastroenterol. 2007; 42:395–401. DOI: 10.1007/s00535-007-2015-2 [PubMed: 17530365]
50. Dore GJ, Cooper DA, Barrett C, Goh LE, Thakrar B, Atkins M. Dual efficacy of lamivudine treatment in human immunodeficiency virus/ hepatitis B virus-coinfected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. J Infect Dis. 1999; 180:607–13. DOI: 10.1086/314942 [PubMed: 10438346]
51. Thio CL, Locarnini S. Treatment of HIV/HBV coinfection: clinical and virologic issues. AIDS Rev. 2007; 9:40–53. [PubMed: 17474312]
52. Benhamou Y, Bochet M, Thibault V, Di Martino V, Caumes E, Bricaire F, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology. 1999; 30:1302–6. DOI: 10.1002/hep.510300525 [PubMed: 10534354]
53. Matthews GV, Bartholomeusz A, Locarnini S, Ayres A, Sasaduesz J, Seaberg E, et al. Characteristics of drug resistant HBV in an international collaborative study of HIV–HBV-infected individuals on extended lamivudine therapy. AIDS. 2006; 20:863–70. DOI: 10.1097/01.aids.0000218550.85081.59 [PubMed: 16549970]
54. Floreani A. Liver disorders in the elderly. Best Pract Res Clin Gastroenterol. 2009; 23:909–17. DOI: 10.1016/j.bpg.2009.10.005 [PubMed: 19942167]
55. Price JC, Thio CL. Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol. 2010; 8:1002–12. DOI: 10.1016/j.cgh.2010.08.024 [PubMed: 20851211]
56. Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther. 1997; 61:331–9. DOI: 10.1016/S0009-9236(97)90166-1 [PubMed: 9091249]
57. Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2001; 27:426–31. [PubMed: 11511818]
58. Moyle G. Clinical manifestations and management of antiretroviral nucleoside analog-related mitochondrial toxicity. Clin Ther. 2000; 22:911–36. discussion 898. DOI: 10.1016/S0149-2918(00)80064-8 [PubMed: 10972629]
59. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. AIDS. 2007; 21:2455–64. DOI: 10.1097/QAD.0b013e3282f08cdc [PubMed: 18025882]
60. Junaidi O, Di Bisceglie AM. Aging liver and hepatitis. Clin Geriatr Med. 2007; 23:889–903. DOI: 10.1016/j.cger.2007.06.006 [PubMed: 17923344]
61. Tseng, ARJ., Walmsley, S., Sterling, S., Salit, I. Polypharmacy in older patients: a study of medication use and potential drug interactions in an aging ambulatory HIV clinic population. Reviews in antiviral therapy & infectious diseases. Abstract presented at the 1st International Workshop on HIV & Aging; 2010 Oct 4–5; Baltimore, MD, USA.
62. Marzolini C, Elzi L, Gibbons S, Weber R, Fux C, Furrer H, et al. Prevalence of comedications and effect of potential drug–drug interactions in the Swiss HIV Cohort Study. Antivir Ther. 2010; 15:413–23. DOI: 10.3851/IMP1540 [PubMed: 20516560]
63. Fountain FF, Tolley E, Chrisman CR, Self TH. Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest. 2005; 128:116–23. DOI: 10.1378/chest.128.1.116 [PubMed: 16002924]

64. Culberson JW. Alcohol use in the elderly: beyond the CAGE. Part 1 of 2: prevalence and patterns of problem drinking. Geriatrics. 2006; 61:23–7.

65. Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. J Stud Alcohol. 2002; 63:179–86. [PubMed: 12033694]

66. Nkhoma, EVV., Mynepalli, L., Logie, J. Comorbidities and co-infections among HIV patients 50 years and older. Reviews in antiviral therapy & infectious diseases. Abstract presented at the 1st International Workshop on HIV & Aging; 2010 Oct 4–5; Baltimore, MD, USA.

67. Meier P, Seitz HK. Age, alcohol metabolism and liver disease. Curr Opin Clin Nutr Metab Care. 2008; 11:21–6. DOI: 10.1097/MCO.0b013e3282f30564 [PubMed: 18090653]

68. Seitz HK, Stickel F. Alcoholic liver disease in the elderly. Clin Geriatr Med. 2007; 23:905–21. DOI: 10.1016/j.cger.2007.06.010 [PubMed: 17923345]

69. Forrest EH, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut. 2005; 54:1174–9. DOI: 10.1136/gut.2004.050781 [PubMed: 16009691]

70. Potter JF, James OF. Clinical features and prognosis of alcoholic liver disease in respect of advancing age. Gerontology. 1987; 33:380–7. DOI: 10.1159/000212907 [PubMed: 3443312]

71. Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion. 2006; 6:1–28. DOI: 10.1016/j.mito.2005.10.004 [PubMed: 16406828]

72. Guaraldi G, Squillace N, Stentarelli C, Orlando G, D'Amico R, Ligabue G, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. Clin Infect Dis. 2008; 47:250–7. DOI: 10.1086/589294 [PubMed: 18532884]

73. Crum-Cianflone N, Dilay A, Collins G, Asher D, Campin R, Medina S, et al. Nonalcoholic fatty liver disease among HIV-infected persons. J Acquir Immune Defic Syndr. 2009; 50:464–73. DOI: 10.1097/QAI.0b013e318198a88a [PubMed: 19225402]

74. Guaraldi G, Stentarelli C, Orlando G, Zona S, Carli F, Ballestri S, et al. Nonalcoholic fatty liver disease in HIV-infected persons: epidemiology and the role of nucleoside reverse transcriptase inhibitors. J Acquir Immune Defic Syndr. 2010; 53:278.doi: 10.1097/QAI.0b013e3181c990ed [PubMed: 20104126]

75. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med. 2005; 22:1141–5. DOI: 10.1111/j.1464-5491.2005.01582.x [PubMed: 16108839]

76. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004; 40:1387–95. DOI: 10.1002/hep.20466 [PubMed: 15565570]

77. Williams CH, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011; 140:124–31. [PubMed: 20858492]

78. Frith J, Day CP, Henderson E, Burt AD, Newton JL. Non-alcoholic fatty liver disease in older people. Gerontology. 2009; 55:607–13. DOI: 10.1159/000235677 [PubMed: 19690397]

79. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology. 1999; 30:1356–62. DOI: 10.1002/hep.510300604 [PubMed: 10573511]

80. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med. 2005; 352:48–62. DOI: 10.1056/NEJMra041811 [PubMed: 15635112]

81. McGovern BH, Ditelberg JS, Taylor LE, Gandhi RT, Christopoulos KA, Chapman S, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. Clin Infect Dis. 2006; 43:365–72. DOI: 10.1086/505495 [PubMed: 16804853]

82. Clifford GM, Rickenbach M, Polesel J, Dal Maso L, Steffen I, Ledergerber B, et al. Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma. AIDS. 2008; 22:2135–41. DOI: 10.1097/QAD.0b013e32831103ad [PubMed: 18832877]

83. Puoti M, Bruno R, Soriano V, Donato F, Gaeta GB, Quinzan GP, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. AIDS. 2004; 18:2285–93. DOI: 10.1097/00002030-200411190-00009 [PubMed: 15577541]

84. Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S–Canadian multicenter study. J Hepatol. 2007; 47:527–37. DOI: 10.1016/j.jhep.2007.06.010 [PubMed: 17692986]

85. O'Connor S, Ward JW, Watson M, Momin B, Richardson LC. Hepatocellular carcinoma – United States, 2001–2006 (reprinted from vol 59, pg 517–520, 2010). JAMA. 2010; 303:2349–50.

86. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med. 2008; 148:728–36. [PubMed: 18490686]

87. Kramer JR, Giordano TP, Souchek J, Richardson P, Hwang LY, El-Serag HB. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. Am J Gastroenterol. 2005; 100:56–63. DOI: 10.1111/j.1572-0241.2005.40670.x [PubMed: 15654781]

88. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53:1020–2. DOI: 10.1002/hep.24199 [PubMed: 21374666]

89. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005; 42:1208–36. DOI: 10.1002/hep.20933 [PubMed: 16250051]

Table 1
Effects of HIV, aging or the combination of both on different liver diseases

Peg-IFN, peginterferon; SVR, sustained virological response; HBV, hepatitis B virus; ART, antiretroviral therapy; ALD, alcoholic liver disease; HCV, hepatitis C virus; HCC, hepatocellular cancer; HBeAg, hepatitis B 'e' antigen; NAFLD, non-alcoholic fatty liver disease; NRTI, nucleoside analogue reverse transcriptase inhibitor

Liver disease	Effect of HIV	Effect of aging	Combined effect of HIV and aging
HCV	• Reduces rates of spontaneous recovery • Accelerates progression of chronic liver disease • Diminished treatment response with peg-IFN and ribavirin	• Reduces rates of spontaneous recovery • More rapid progression of chronic liver disease • Diminished treatment response with peg-IFN and ribavirin – Increased non-SVR – Increased relapse – Increased adverse events	• Unclear if synergistic effect of HIV infection and aging • Unclear if synergistic effect • Lower rates of SVR in genotypes 2, 3 and 5 in HIV-infected patients aged >40 years
HBV	• Reduced rates of recovery from acute infection especially with lower CD4 counts • Higher HBV replication as measured by HBV DNA and HBeAg-positive status • Uncompromised treatment efficacy of HBV- active ART compared with HIV-negative • Higher lamivudine resistance rates on therapy	• Reduced rates of recovery from acute infection • Effect on replication appears to vary based on stage of HBV infection • Uncompromised treatment efficacy of HBV-active ART therapy compared with younger patients	• Unclear if synergistic effect • No studies on combined effect of HIV and aging on HBV replication. Suggestion of increased risk of HBV associated liver related mortality with age >40 • No data on combined effect on treatment response
Medication toxicity	• Increased risk of mitochondrial toxicity leading to acute liver failure and hepatic steatosis with NRTI • Increased polypharmacy	• Increased risk of mitochondrial dysfunction with age • Increased polypharmacy	• Increased risk of mitochondrial dysfunction may raise risk of mitochondrial toxicity • Increased potential for drug–drug interactions
Alcoholic liver disease	• No studies of prevalence or course with HIV infection	• ALD prognosis worse with increasing age	• No data. However, combined effects of ART-associated mitochondrial dysfunction and age-associated mitochondrial

Liver disease	Effect of HIV	Effect of aging	Combined effect of HIV and aging
			dysfunction may potentiate risk
NAFLD	• Association with metabolic syndrome potentially induced by ART therapy and HCV infection may increase risk in HIV-infected population	• Severity associated with increasing age	• No data on prevalence and progression in older HIV-infected individuals
HCC	• Occurs at earlier age in HIV infection	• Increased risk with aging	• Potential increase in HCV-associated HCC cases with aging of HIV cohort

Table 2

Research gaps in HIV, liver disease and aging

- Effect of aging on liver function in HIV-infected individuals
- Effect of aging on liver disease progression in HIV–viral hepatitis co-infected patients
- Effect of age on natural history of viral hepatitis in HIV-infected patients
- Differences in treatment outcomes of viral hepatitis in older HIV-infected individuals
- Prevalence and risk factors for medication (antiretroviral therapy and non-antiretroviral therapy) toxicity in older HIV-infected patients
- Optimal dosing of non-nucleoside reverse transcriptase inhibitors and protease inhibitors in older HIV patients with pre-existing liver disease
- Prevalence, risk factors and progression of non-alcoholic fatty liver disease in older HIV patients
- Impact of viral hepatitis treatment on hepatocellular cancer risk in older HIV co-infected patients