CHAPTER 20

HCV / HIV Coinfection

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SECTION 1

Overview of HIV / HCV Coinfection

Introduction

Both the *human immunodeficiency virus* (*HIV*) and the *hepatitis C virus* (*HCV*) are blood-borne infections. A significant number of people are chronically infected with both HIV and HCV, a condition known as coinfection. The widespread use of increasingly effective *antiviral* therapies for HIV has greatly improved long-term survival among HIV-infected persons. As HIV survival has improved, HCV-related illness and deaths have increased among coinfected persons.[1-3] In recent years, increasing numbers of people coinfected with HIV and HCV are dying from HCV-related complications rather than HIV disease. End-stage liver disease related to HCV is considered by many HIV specialists to be the leading cause of death in HIV-positive people in the United States.[4] Coinfection has a heavier impact on certain communities, including those who are incarcerated and communities of color.[5]

The management of HIV/AIDS and *chronic hepatitis* C is complicated by the presence of the other virus. Researchers are actively studying the most effective approaches for managing coinfection. This section presents an overview of our current knowledge about how HIV and HCV influence one another in people coinfected with both viruses.

Prevalence of HCV, HIV, and HCV/HIV Coinfection

HCV infection is the most common chronic, blood-borne infection in the United States having infected an estimated 4.9 million people.[6] The World Health Organization (WHO) estimates that about 180 million people, some 3% of the world's population, are infected with hepatitis C virus (HCV). WHO further states that 130 million are chronic HCV carriers at risk of developing liver *cirrhosis* and/or *liver cancer.* It is estimated that 3 to 4 million persons are newly infected each year, 70% of whom will develop chronic hepatitis. HCV is responsible for 50% to 76% of all liver cancer cases, and 2/3 of all liver transplants in the developed world.[7]

According to the 2007 AIDS Epidemic Update, global HIV prevalence has leveled off and the number of new infections has fallen in recent years. In 2007, an estimated 33.2 million people worldwide were living with HIV (down from the 40 million estimated in 2003)[8] including an estimated 1.2 million people in the United States.[9]

Although different studies have arrived at varying numbers, most experts now believe that up to 30% of HIV-infected persons in the U.S. are coinfected with HCV.[10-12] An estimated 5% to 10% of Americans living with HCV are also infected with HIV.[12] More than 90% of hemophiliacs treated with blood products during the 1970's and 1980's became infected with HCV.[13] A study in 1998 found more than 80% of hemophiliacs over 18 years of age are infected with HCV.[14] Between 60% to 85% of adult hemophiliacs are coinfected with HIV and HCV.[15] An estimated 50% to 98% of people who acquired HIV though injection drug use are coinfected with HCV.[15] Recent studies at diverse locations and in diverse populations showed a disturbing new trend in increasing sexual transmission among men who have sex with men in HIV-positive populations.[16-18] Prior to these reports, sexual transmission of HCV was considered relatively rare.

Effects of HIV on the Natural History of Chronic Hepatitis C

Immune Response to HCV and Spontaneous Viral Clearance

The *immune system* responds to viral infection with two types of responses, a cellular response and a *humoral immunity* (*antibody*) response (see Figure 1). Cellular responses involve special *white blood cells* called *T cells*. Different kinds of T cells have different actions that help the body fight viral infection.

Humoral responses are antibody responses. Antibodies are proteins produced in response to substances the body sees as foreign such as bacteria and viruses. Antibodies are produced by white blood cells called mature *B cells* or plasma cells. Interestingly, B cells must interact with helper T cells to mature into plasma cells and begin antibody production (see Figure 2). Antibodies tag foreign invaders and cells infected by viruses or bacteria. This alerts the rest of the immune system to the presence of the invader and often leads to the destruction of the viruses, bacteria, or infected cells.

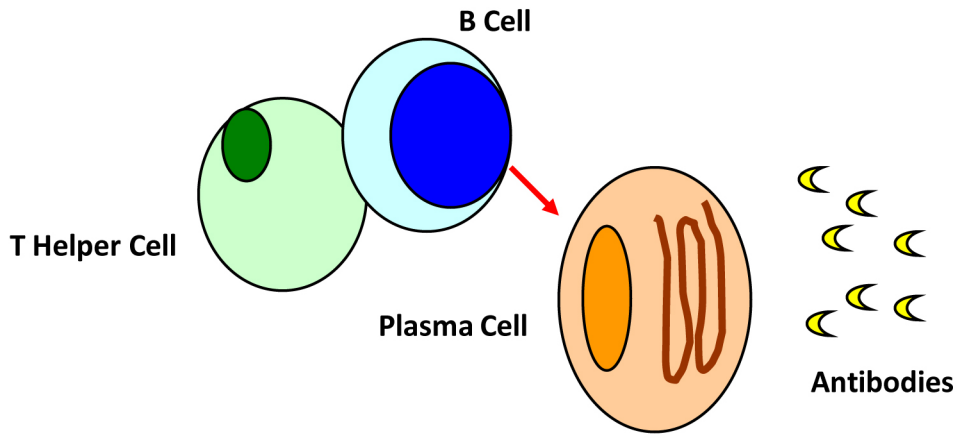
On average, 15% to 30% of people infected with HCV alone spontaneously clear the virus without consequence.[19] However, data suggest that only 5% to 10% of people with HIV spontaneously clear HCV.[20] Further, the likelihood of *spontaneous clearance* of the virus seems to decrease as the number of *T helper cells* decrease.[19-21] T helper cells are the primary target of HIV. They are killed off when HIV infection is untreated or poorly controlled. Therefore, people with well-controlled HIV disease generally have higher T helper (*CD4*) cell counts than those whose disease is poorly controlled.

Normally, people infected with HCV begin producing antibodies to the virus within several weeks after infection. Screening tests for hepatitis C detect *anti-HCV antibodies*. In recent years, researchers have found a very small number of people with apparently normal immune systems who are chronically infected with HCV but do not have any

Figure 1. Types of Immune Responses

Cellular Response	Humoral (Antibody) Response
T lymphocytes (T cells) – there are 3 types • T helpers (CD4 cells) • T suppressors • Killer T cells (NK cells)	B lymphocytes (B cells) B cells interact with T helper cells and mature into plasma cells that produce antibodies.

Figure 2. T and B Cell Interactions Leading to Antibody Production



detectable antibodies to the virus.[22-24] This appears to be a very rare situation, and researchers are actively investigating why it occurs.

While the presence of HCV without detectable anti-HCV antibodies is quite rare in people with normal immune systems, it appears to occur in 5% to 19% of people coinfected with HIV.[25, 26] Scientists believe this is probably due to the devastating effects HIV has on the immune system and the loss of CD4 cells. This notion is supported by the fact that generally, people who lack HCV antibodies have lower levels of CD4 immune cells than HIV-infected people who have HCV antibodies.[26] This concept is further supported by recent data that show higher T cell activity improves the chance of spontaneous clearance of HCV among those with HIV.[27]

Effects of HIV on HCV Disease Progression

HCV *viral loads* are significantly higher in the blood and livers of coinfected people compared to people with HCV alone.[28-30] While high HCV viral loads have been correlated with decreased response rates to *interferon-based therapy*, the effect (if any) of viral load on the progression of HCV-related liver disease among coinfected persons is undetermined.[31]

Evidence from multiple studies indicates HIV accelerates the progression of HCV-related liver disease.[32-36] A study of 547 people found the time from infection to cirrhosis was substantially shorter (7 years) in people coinfected with HIV compared to people with HCV alone (23 years).[31] Another 3-year study of 489 people found 8.4% of coinfected persons had *liver failure* (*decompensation*) compared to no cases among those with HCV only.[37] These findings are supported by a separate study that found the rate of *fibrosis* progression (liver scarring) was much faster in HCV/HIV coinfected people than in those with HCV only.[38] A group of eight studies that examined the effects of HIV on HCV-related disease progression were analyzed collectively. Researchers found that compared to people infected with HCV only, coinfected persons had twice the risk for cirrhosis and approximately six times the risk for liver failure (decompensation).[35] As in people infected with HCV alone, several studies have shown that *alcohol* consumption further accelerates the already rapid liver disease progression in those with HCV/HIV coinfection.[39]

People with HCV/HIV coinfection should avoid <u>any</u> alcohol consumption.

Coinfection may also increase the risk of liver cancer.[36] When liver cancer does occur in HCV/HIV patients, it tends to present at a younger age than in those with other causes of underlying cirrhosis.[40, 41]

Effects of HAART on HCV Disease Progression

It is important to note that the studies demonstrating accelerated disease progression associated with HIV coinfection were performed or involved data collected before the widespread use of highly active antiretroviral therapy (HAART) for HIV.

HAART was introduced in 1996 and was a substantial breakthrough in the treatment of HIV infection. For many people, HAART has transformed HIV infection from an imminent life-threatening illness to a condition more akin to a chronic disease. With HAART, HIV is often reduced to an undetectable level and T cell counts generally rebound substantially. Since the introduction of HAART, HIV-related death rates have dropped substantially and survival time has increased dramatically. While serious infections and related deaths have declined steadily in the HIV-infected population since the introduction of HAART, death rates from HCV-related illnesses have been quickly and consistently increasing (see Table 1).[2, 33, 42-46]

Table 1. Mortality Rates Due to End-Stage Liver Disease Among HCV/HIV Coinfected Persons[31]

1987 - 1995	1997 - 2000
1.6 – 13%	7.8 – 50%

In short, the introduction of HAART has enabled HCV/HIV coinfected people to live long enough to experience the effects of chronic hepatitis C. Overall, HAART also slows the progression of HCV disease in coinfected patients (compared to patients with ART or untreated).[47, 48] One study of 182 HCV/HIV coinfected people found the fibrosis stage on *liver biopsy* was lower in people who had been on *combination therapy* with a *protease inhibitor* (one of the drugs used in HAART) compared to people who had never taken a protease inhibitor. The estimated cirrhosis rates at 5, 15, and 25 years post-HVC infection are shown in Table 2.

Table 2. Estimated Cirrhosis Rates in HCV/HIV Coinfected People[49]

Years Since Infection	With Protease Inhibitors	Without Protease Inhibitors
5	2%	5%
15	5%	18%
25	9%	27%

Benhamou Y, Di Martino V, Bochet M *et al*. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. *Hepatology*. 2001;34(2):283-7.

Effects of HAART on HCV Viral Load and Liver Enzymes

Liver enzyme levels increase in approximately 10% of HIV-infected people after beginning HAART therapy.[50] Such increases have been observed in up to 30% of persons coinfected with HCV.[49-61] Some anti-HIV drugs such as nevirapine,[50-52] ritonavir,[52] and stavudine[53, 54] are more likely to cause elevations in liver enzymes than others are.[55] A group of anti-HIV drugs called *nucleoside reverse transcriptase inhibitors* (NRTIs; for example, ddI, ddC and AZT) have also been reported to cause liver enzyme elevations.[56, 57] It appears the increased susceptibility to anti-HIV drug-related liver injury among people coinfected with HCV/HIV is caused by the interplay of many factors. Some of the drugs appear to be directly *hepatotoxic*, meaning they chemically injure liver cells. People with chronic hepatitis may be more susceptible to this type of injury because an inflamed and/or scarred liver may be less capable of processing medications.

Both HCV[58] and some anti-HIV medications have the ability to damage structures called mitochondria inside liver cells. Mitochondria are the "powerhouses" of cells. They provide the energy needed for cells to function properly. When mitochondria are damaged, liver cells do not have the energy to function normally and liver damage occurs. Mitochondrial damage is thought to be one of the mechanisms of liver injury and liver enzyme elevations seen in some HCV/HIV coinfected people on HAART.[59-62] HAART-associated mitochondrial damage appears to be heightened in the presence of underlying hepatitis C.

In 2004, the HCV-HIV International Panel published treatment guidelines entitled, "Care of patients with hepatitis C and HIV coinfection."[63] With regard to the hepatotoxicity of antiretroviral drugs, the panel made this recommendation:

> Liver enzyme elevations after beginning antiretroviral therapy are more frequent in patients with underlying chronic *hepatitis B* and C. Therefore, drugs with more hepatotoxic profiles (i.e., nevirapine, ritonavir) should be used cautiously in coinfected patients. Treatment should be discontinued in patients with symptoms or *grade* 4 increases in *aminotransferase* levels… The close monitoring of these patients during the first weeks may enable them to remain on therapy, because they experience a progressive resolution of liver abnormalities without discontinuing treatment.

Effects of HCV on the Natural History of HIV/AIDS

Research has shown clearly that coinfection with HIV accelerates the natural course of HCV infection. For a number of years, it has been unclear whether the reverse held true as well. New and emerging research now indicates that overall, HCV does not appear to affect HIV disease progression or response to HAART.

A study of 416 people in Italy found patients coinfected with HCV/HIV and those infected with HIV alone progressed to AIDS at a similar rate.[64] A larger study of 1,955 people conducted in Baltimore, Maryland also found no difference in the progression to AIDS or death among coinfected persons compared to people with HIV only.[65] The authors in the large US study of 10,481 patients concluded that coinfection with HCV did not increase the risk of AIDS-defining opportunistic infections or death, and did not affect short-term *immunological* or virological response to first-line HAART.[66] Similarly, a European study of 5,957 patients found HCV did not influence the risk of HIV disease progression, but that coinfection was associated with a markedly increased risk of liver-related death.[67]

Coinfection, Lipid Metabolism, Lipodystrophy, Steatosis and Hyperglycemia

Lipodystrophy is a group of fat *metabolism* disorders commonly seen in people with HIV.[68-70] These disorders can cause several changes in the body including:

- Loss of fat in the arms, legs, buttocks, and/or face is called lipoatrophy. Such fat loss can cause the veins of the arms and legs to protrude and give the face a sunken appearance.
- Lipohypertrophy is a build up of fat stores in the gut, breasts, shoulders, and/or back of the neck. The abdomen often appears bloated and feels hard. The fat around the gut reflects an accumulation of fatty tissue in the abdominal cavity leading to a swollen look.

Some changes in fat metabolism are not visible but are nonetheless abnormal. Levels of fats such as *cholesterol* and *triglycerides* in the blood can become abnormally high with lipodystrophy. High levels of fat may increase the risk for heart disease, stroke, and other disorders.

The exact mechanisms that lead to lipodystrophy in people with HIV are being actively researched. However, it seems clear that several factors are involved including some associated with the virus itself and others associated with anti-HIV therapy. Researchers have found evidence that coinfection with HCV may contribute to the development of lipodystrophy in coinfected persons.[71] HCV damages the powerhouses of liver cells (the mitochondria), thus interrupting normal fat breakdown and storage.[72, 73] One study suggests the incidence of lipoatrophy is higher in people coinfected with HIV and HCV than it is in those infected with HIV only.[74] The redistribution of fat from the arms and legs into the abdomen also causes increased fat in the liver, a situation that can further damage an HCV-infected liver.

HAART-related lipodystrophy has been associated with another condition known as *insulin* resistance (IR).[75] People with insulin resistance have abnormally high *blood sugar* (*glucose*) levels. Some researchers have reported the incidence of IR is higher in HCV/HIV coinfected persons on HAART compared to persons with HIV only.[76] Investigators speculate HAART-related IR may result from anti-HIV medication directly impairing glucose uptake by muscle, effects of HIV per se, or indirect effects such as fat redistribution.[77] *Clinical* scientists hope to soon find effective ways to treat the metabolic abnormalities associated with HAART, HIV, and HCV/HIV coinfection.

Steatosis, or *fatty liver*, is a common finding in people living with HCV. The finding of fatty liver on biopsy can help identify patients at risk for disease progression[78, 79] or those who may respond more poorly to interferon-based therapy.[80] Previous studies have shown associations between the steatosis severity and infection with HCV *genotype* 3[81, 82], obesity[83], and diabetes[84]. However, a recent study of 708 veterans showed that steatosis is highly prevalent and more severe in HCV/HIV coinfection than in HCV infection alone.[85]

The increased prevalence and severity of steatosis in the coinfected population possibly explains the increased rate of fibrosis progression in coinfected persons. Compared to HCV infection alone, HCV/HIV coinfection was associated with a significantly increased odds ratio of steatosis. Among those who were coinfected, the fibrosis progression rate increased in a linear fashion along with the grade of steatosis.

There are several potential pathways by which HIV and HCV may interact to cause steatosis. There are differing opinions on this question. One possibility is that HIV infection itself may lead to development of steatosis by assisting HCV replication. HCV/HIV coinfected people have increased HCV RNA levels inside the liver,[86] and increased HCV viral loads have been associated with increased severity of steatosis in people with HCV alone.[87] HIV may also act in concert with HCV, disrupting *lipid metabolism* and causing steatosis.

According to data from a subset of the APRICOT HCV/HIV coinfection study, the probability of achieving sustained viral response (SVR) was not reduced by steatosis. Also, SVR significantly reduced the prevalence of steatosis in patients infected with HCV genotype 3 but not in those infected with other HCV genotypes.[88]

A recent study of 203 persons with HCV/HIV coinfection demonstrated a strong relationship between *hepatic* steatosis, fibrosis, and *hyperglycemia*. This finding supports efforts to treat HCV and to use ART regimens that have the least associated risk of hyperglycemia in HCV/HIV-co-infected persons.[89]

Harm Reduction

People with HCV/HIV coinfection are at increased risk for other infectious diseases. It is important to take steps to protect yourself from exposure to other infectious diseases.

The simplest and most effective way to protect yourself from food-borne illnesses is hand washing. Although it sounds trivial, hand washing goes a long way toward protecting yourself from many illnesses. A few simple rules to keep in mind include:

- Always wash your hands before eating or preparing food. Be sure everyone in your household does the same.
- Always wash your hands after using the restroom.
- Wash all fresh fruits and vegetables before eating.
  Commercial fruit and vegetable washes are not necessary. Simply rub the fruit or vegetable with your washed hands under running water. Fruits or vegetables with a hard exterior should be scrubbed with a clean vegetable brush. You can clean your vegetable brush in the dishwasher.

Hand washing not only protects you from food-borne illnesses but also helps prevent the spread of cold and flu viruses. Safe sex practices are also essential for coinfected persons. These practices will prevent the spread of HIV and/or HCV to others, and will protect you from being exposed to sexually transmitted infections such as hepatitis B, gonorrhea, syphilis, herpes, chlamydia, and others.

Injection drug use poses many threats to wellness. It is best for coinfected person to avoid all injection drug use and other recreational drug use. However, if you are injecting drugs, be sure to use scrupulously clean injection habits. Avoid reusing needles, and never share needles with others.

People who are coinfected and drink alcohol are at greatly increased risk of developing severe liver disease, cirrhosis, and/or liver cancer. All people infected with HCV should avoid alcohol, but it is even more important for coinfected persons. People coinfected with HCV/HIV should not drink any alcohol. If you have difficulty abstaining from alcohol, you might be addicted to alcohol. Talk with your healthcare providers about the problem. Many resources are available to help you eliminate alcohol from your life. For additional information about the effects of alcohol in HCV and treatment options, see *Chapter 3, Alcohol and Hepatitis C* and *Appendix I, How to Cut Down on Your Drinking*.

Hepatitis A and B

Due to shared routes of transmission, people coinfected with HIV and HCV are at increased risk for also contracting hepatitis B. A recent study conducted in Spain found that among people with HIV, 79% of injection drug users were also infected with both HCV and HBV. Triple infection rates among those with other risk factors ranged from 10% to 20%.[90] Unlike HIV, HCV, and HBV, hepatitis A is a food-borne illness. Hepatitis A causes an acute form of viral hepatitis; there is no chronic form of hepatitis A. Although HAV infection alone is usually a relatively mild disease, it is often a more serious

illness in people with HIV, HCV, and/or HBV. Fulminant hepatitis is a rapidly progressive condition characterized by a massive loss of liver cells and liver failure. Fulminant hepatitis is a rare complication of HAV infection (0.3% – 1.8% of cases).[91] Although there have been some conflicting reports,[92] most investigators agree that *acute hepatitis* A in people with chronic hepatitis C is associated with an increased risk for fulminant hepatitis ranging from 0% to 40%.[92-99]

Infections with HBV and HAV among HCV/HIV coinfected persons can be life threatening. All persons with HIV should be tested for HCV and HBV. Most healthcare providers recommend that coinfected persons not already infected or immune to HAV and HBV should be vaccinated against these viruses. The vaccines contain no live viruses, so there is no risk of infection from the vaccines. The two vaccines can be given simultaneously. Hepatitis A and B vaccines are available for little to no cost at public health clinics in the United States and many other countries.

If you have not been previously vaccinated or infected with HAV and are exposed to the virus, treatment with *immune globulin* is recommended.[91] Immune globulin should be given as soon as possible after exposure, but must be given within two weeks of exposure to be effective. Similarly, people who have been exposed to HBV should be treated with hepatitis B immune globulin (HBIG) as soon as possible after exposure, preferably within 24 hours.[100] The effectiveness of HBIG when administered more than seven days after exposure is unknown. The first shot in the hepatitis B vaccine series can be given at the same time as HBIG. If the HBV vaccine is indicated, it too should be given as soon as possible and preferably within 24 hours.

Summary

Overall, up to one-third of people living with HIV in the U.S. are coinfected with HCV. Coinfection with HIV adversely affects hepatitis C disease progression increasing the risk of cirrhosis, liver failure, and liver cancer.

Harm reduction is especially important for people with HCV/HIV coinfection. Vaccination against HAV and HBV is particularly important. Lifestyle choices such as safe sexual practices, avoiding recreational drug use or using clean needles, and abstaining from alcohol can enhance overall wellness and improve quality of life.

References

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853-60.
2. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis*.2001;32(3):492-7.
3. Monga HK, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001;33:240-7.
4. Martin-Carbonero L, Soriano V, Valencia E, et al. Increasing impact of chronic viral hepatitis on hospital admissions and mortality among HIV infected patients. *AIDS Research and Human Retroviruses*. 2001;17(16):1467-1471
5. CDC IDU HIV Prevention Unit, Hepatitis C Virus and HIV Coinfection, September 2002
6. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002. *Ann Intern Med*. 2006;144:705-714.
7. World Health Organization. Available at http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.htm. Accessed April 24, 2008.
8. UNAIDS. *2007 AIDS Epidemic Update.* Geneva, Switzerland. 2007. Available at http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007/. Accessed April 24, 2008.
9. HIV/AIDS in the United States. CDC HIV/AIDS Facts, March 2008. Available at http://www.cdc.gov/hiv/resources/factsheets/us.htm. Accessed April 24, 2008.
10. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2002;34(6):831-7.
11. Sulkowski M, Benhamou Y. Therapeutic issues in HCV/HIV coinfected patients. *J Viral Hepat*. 2007;14(6):371-386.
12. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med*. 2003;138:197-207.
13. Ragni MV, Ndimbie OK, Rice EO, Bontempo FA, Nedjar S. The presence of hepatitis C virus (HCV) antibody in human immunodeficiency virus positive hemophilic men undergoing HCV seroreversion. *Blood*. 1993; 82:1010-5.
14. Ewenstein B, Koerper M. Survey of diagnostic and treatment practices of chronic hepatitis C in federally-funded hemophilia treatment centers. Presented at: Medical and Scientific Advisory Council meeting. Orlando, Florida. October 1998.
15. Poles MA, Dieterich DT. Hepatitis C virus/human immunodeficiency virus coinfection: clinical management issues. *Clin Infect Dis*. 2000;31(1):154-161.

16. Danta 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 May 11;21(8):983-91.
17. Gambotti L and the acute hepatitis C collaborating group, Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. *Euro Surveill*. 2005; 10(5)
18. van de Laar TJ, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. *J Infect Dis*. 2007 Jul 15;196(2):230-8. Epub 2007 Jun 11.
19. 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.
20. Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *JAMA*. 2000;284(4):450-6.
21. Alter MJ, Margolis HS, Krawczynski K, 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.
22. Rossi G, Tucci A, Cariani E, et al. Outbreak of hepatitis C virus infection in patients with hematologic disorders treated with intravenous immunoglobulins: different prognosis according to immune status. *Blood*. 1997;90:1309-14.
23. Durand F, Beauplet A, Marcellin P. Evidence of hepatitis C virus viremia without detectable antibody to hepatitis C virus in a blood donor. *Ann Intern Med*. 2000;133:74-5.
24. Hitzler WE, Runkel S. Routine HCV PCR screening of blood donations to identify early HCV infection in blood donors lacking antibodies to HCV. *Transfusion*. 2001;41:333-7.
25. Bonacini M, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr*. 2001;26:340-4.
26. George SL, Gebhardt J, Klintzman D, et al. Hepatitis C virus viremia in HIV-infected individuals with negative HCV antibody tests. *J Acquir Immune Defic Syndr*. 2002;31(2):154-162.
27. Falconer K, Gonzalez VD, Reichard O, Sandberg JK, Alaeus A. Spontaneous HCV clearance in HCV/HIV-1 coinfection associated with normalized CD4 counts, low level of chronic immune activation and high level of T cell function. *J Clin Virol*. 2008;41(2):160-163.
28. Cribier B, Rey D, Schmitt C, Lang JM, Kirn A, Stoll-Keller F. High hepatitis C viraemia and impaired antibody response in patients coinfected with HIV. *AIDS*. 1995;9:1131-36.
29. Sherman KE, O'Brien J, Gutierrez AG, et al. Quantitative evaluation of hepatitis C virus RNA in patients with concurrent human immunodeficiency virus infections. *J Clin Microbiol*. 1993;31:2679-82.
30. Bonacini M, Govindarajan S, Blatt LM, Schmid P, Conrad A, Lindsay KL. Patients co-infected with human immunodeficiency virus and hepatitis C virus demonstrate higher levels of hepatic HCV RNA. *J Viral Hepat*. 1999;6:203-8.
31. Verucchi G, Calza R, Manfred R, Chiodo F. Human immunodeficiency virus and hepatitis C virus coinfection: epidemiology, natural history, therapeutic options and clinical management. *Infection*. 2004;33:33-46.
32. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol.* 1997;26:1-5.
33. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology.* 1999;30:1054-58.
34. Puoti M, Bonacini M, Spinetti A, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. *J Infect Dis.* 2001;183(1):134-7.
35. Bierhoff E, Fischer HP, Willsch E, et al. Liver histopathology in patients with concurrent chronic hepatitis C and HIV infection. *Virchows Arch.* 1997;430(4):271-7.
36. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4):562-9.
37. Monga HK, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection related morbidity and mortality among patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001;33:240-7.
38. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology*. 1996;24(2):289-93.
39. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. *Hepatology.* 1999;30:1054-1058.
40. Garcia-Samaniego J, Rodriguez M, Berenguer J, Rodriguez-Rosado R, Carbo J, Asensi V, Soriano V. Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C. *Am J Gastroenterol.* 2001;96(1):179-83.
41. Bräu N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol.* 2007;47(4):527-537.
42. Soriano V, Rodriguea-Rosado R, Garcia-Samaniego J. Management of chronic hepatitis C in HIV-infected patients. *AIDS*. 1999;13:539-46.
43. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. *J Infect Dis.* 1999;179:1254-8.
44. Cacoub P, Geffray L, Rosenthal E, et al. Mortality among HIV-infected patients with cirrhosis or hepatocellular carcinoma due to hepatitis C virus in French departments of internal medicine/infectious diseases, in 1995 and 1997. *Clin Infect Dis*. 2001;32:1207-14.
45. Soriano V, Martin-Carbonero L, Garcia-Samaniego J, Puoti M. Mortality due to chronic viral liver disease among patients infected with human immunodeficiency virus. *Clin Infect Dis.* 2001;33:1793-4.
46. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. *J Acquir Immune Defic Syndr.* 2000;24:211-7.
47. Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. *Lancet*. 2003;362:1708-1713.
48. Marine-Barjoan E, Saint-Paul MC, Pradier C et al. Impact of antiretroviral treatment on progression of hepatic fibrosis in HIV/hepatitis C virus co-infected patients. *AIDS*. 2004; 18: 2163-2170.

49. Benhamou Y, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, Katlama C, Poynard T; MultivirC Group. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. *Hepatology*. 2001;34(2):283-7.
50. Sulkowski M, Thomas D, Chaisson R, Moore R. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. *JAMA*. 2000;283:74-80.
51. Martinez E, Blanco J, Arnaiz J, Gatell J. Heptatotoxicity in HIV-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS*. 2001;15:1261-8.
52. Sulkowski M, Thomas D, Mehta S, Chaisson R, Moore R. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. 2002;35:182-9.
53. Gisolf EH, Dreezen C, Danner SA, Weel JL, Weverling GJ. Risk factors for hepatotoxicity in HIV-1-infected patients receiving ritonavir and saquinavir with or without stavudine. *Clin Infect Dis*. 200;31:1234-9.
54. Spruance SL, Pavia AT, Mellors JW, et al. Clinical efficacy of monotherapy with stavudine compared with zidovudine in HIV-infected, zidovudine-experienced patients. *Ann Intern Med*. 1997;126:355-63.
55. Sulkowski MS. Hepatotoxicity associated with antiretroviral therapy containing HIV-1 protease inhibitors. *Semin Liver Dis*. 2003;23(2):183-94.
56. Saves M, Raffi F, Clevenbergh, P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-contained antiretroviral regimen in HIV-infected patients. *Antimicrob Agents Chemother.* 2000;44:3451-5.
57. Brinkman K, ter Hofstede JM, Burger DM. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS*. 1998;12:1735-44.
58. Okuda M, Li K, Beard MR, Showalter LA, Scholle F, Lemon SM, Weinman SA. Mitochondrial injury, oxidative stress, and antioxidant gene expression are induced by hepatitis C virus core protein. *Gastroenterology.* 2002;122(2):366-75.
59. Moyle G. Hyperlactatemia and lactic acidosis during antiretroviral therapy: causes, management and possible etiologies. *AIDS Rev.* 2001;3:150-6.
60. Lonergan J, Behling C, Pfander H, Hassanein T, Mathews W. Hyperlactatemia and hepatic abnormalities in 10 HIV-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis*. 2000;31:162-6.
61. Batisse D, van Huyen J, Piketty C, et al. Severe liver mitochondriopathy with normal liver histology and normal lactate levels in patients receiving nucleoside analogs. *AIDS*. 2002;16:2370-1.
62. Sutinen J, Kakkinen A, Westerbacka J, et al. Increased fat accumulation in the liver in HIV-infected patients with antiretroviral therapy associated lipodystrophy. *AIDS*. 2002;16:2183-93.
63. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with hepatitis C and HIV coinfection. *AIDS*. 2004;18:1-12.
64. Dorrucci M, Pezzotti P, Phillips AN, Lepri AC, Rezza G. Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. *J Infect Dis*. 1995;172:1503-8.
65. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *JAMA*. 2002;288:199-206.
66. Sullivan PS, Hanson DL, Teshale EH, et al. Effect of hepatitis C infection on progression of HIV disease and early response to initial antiretroviral therapy. *AIDS* 20(8): 1171-1179.
67. Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis*. 2005;192(6):992-1002.
68. Carr A, Samaras K, Burton S. et al. A syndrome of lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998;12:F51-8.
69. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet*. 1998;351:1881-3.
70. Saint-Marc T, Partisani M, Poizot-Martin I. et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS*. 1999;13:1659-67.
71. Duong M, Petit JM, Piroth L, et al. Association between insulin resistance and hepatitis C virus chronic infection in HIV-hepatitis C virus-coinfected patients undergoing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001;27(3):245-50.
72. Barba G, Harper F, Harada T. et al. Hepatitis C virus core protein shows a cytoplasmic localization and associates to cellular lipid storage droplets. *Proc Natl Acad Sci USA*. 1997;94:1200-5.
73. Barbaro G, Di Lorenzo G, Asti A. et al. Hepatocellular mitochondrial alterations in patients with chronic hepatitis C: ultrastructural and biochemical findings. *Am J Gastroenterol*. 1999;94:2198-2205.
74. Zylberberg H, Nalpas B, Pol S, Bréchot C, Viard JP. Is there a relationship between hepatitis C virus infection and antiretroviral-associated lipoatrophy? *AIDS*. 2000;14(13):2055.
75. Faraj M, Lu HL, Cianflone K. Diabetes, lipids, and adipocyte secretagogues. *Biochem Cell Biol*. 2004;82(1):170-190.
76. Duong M, Petit JM, Piroth L, et al. Association between insulin resistance and hepatitis C virus chronic infection in HIV-hepatitis C virus coinfected patients undergoing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001;27(3):245-250.
77. Grinspoon S. Mechanisms and strategies for insulin resistance in acquired immune deficiency syndrome. *Clin Infect Dis*. 2003;37(Suppl 2):S85-90.
78. Castera L, Hezode C, Roudot-Thoraval F., et al., Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C and paired liver biopsies. *Gut*. 2003;52:288–92.
79. Patton HM, Patel K, Behling C, Bylund D, Blatt LM and Vallee M et al. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. J Hepatol. 2004;40:484–490.
80. Monto A, Alonzo J, Watson JJ, et al, Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol, *Hepatology.* 2002;36:729–36.
81. Sharma P, Balan V, Hernandez J, et al., Hepatic steatosis in hepatitis C virus genotype 3 infection: does it correlate with body mass index, fibrosis, and HCV risk factors? *Dig Dis Sci. 2004*:49:25–9.
82. Hu KQ, Kyulo NL, Esrailian E, et al., Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. *J Hepatol.* 40 (2004), pp. 147–154.

83. Sanyal AJ, Contos MJ, Sterling RK, et al., Nonalcoholic fatty liver disease in patients with hepatitis C is associated with features of the metabolic syndrome. *Am J Gastroenterol.* 2003;98:2064–71.
84. Gaslightwala I, Bini E, Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection. *J Hepatol.* 44(6):1026-1032.
85. Bonacini M, Govindarajan S, Blatt LM, et al, Patients co-infected with human immunodeficiency virus and hepatitis C virus demonstrate higher levels of hepatic HCV RNA. *J Viral Hepat.* 1999;6:203–8.
86. Rubbia-Brandt L, Quadri R, Abid et al., Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol*. 2000;33:106–115.
87. Bonnet F, Lawson-Ayayi S, Thiebaut R. A cohort study of nevirapine tolerance in clinical practice: French Aquitaine Cohort, 1997-1999. *Clin Infect Dis.* 2002;35:1231-7.
88. Rodríguez-Torres M, et al. Hepatic steatosis in HCV/HIV co-infected patients: correlates, efficacy and outcomes of anti-HCV therapy: a paired liver biopsy study. *J Hepatol.* 2008 May;48(5):756-64. Epub 2008 Feb 7.
89. Mehta S, Thomas D, Torbenson M, Moore R, and Sulkowski M. Liver histology, ART, and hyperglycemia in HCV/HIV coinfected adults. *CROI* 2006. Abstract 165.
90. Rodriguez-Mendez ML, Gonzalez-Quintela A, Aguilera A, Carballo E, Barrio E. Association of HCV and HBV markers in Spanish HIV-seropositive patients in relation to risk practices. *Hepatogastroenterology*. 2003;50(54):2093-7.
91. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 1999;48(No. RR-12):1-54.
92. Bianco E, Stroffolini T, Spada E, et al. Case fatality rate of acute viral hepatitis in Italy: 1995-2000. An update. *Dig Liver Dis*. 2003;35(6):404-8.
93. Williams I, Bell B, Kaluba J, Shapiro C. Association between chronic liver disease and death from hepatitis A, United States, 1989–92 [Abstract A39]. IX Triennial International Symposium on Viral Hepatitis and Liver Disease. Rome, Italy, April 1996.
94. Akriviadis EA, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. *Ann Intern Med*. 1989;110:838–9.
95. Willner IR, Uhl MD, Howard SC, Williams EQ, Riely CA, Waters B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. *Ann Intern Med*. 1998;128:111–4.
96. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med*. 1998;338:286–90.
97. Keefe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol.* 1995;90:201–5.
98. Vento S. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *J Viral Hepat*. 2000;7(Suppl 1):7-8.
99. Reiss G, Keeffe EB. Review article: hepatitis vaccination in patients with chronic liver disease. *Aliment Pharmacol Ther*. 2004;19(7):715-27.
100. Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR.* 2001;50(No. RR-11):1-42.