Acute hepatitis C and HIV coinfection

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Hepatitis C is a common infection worldwide, but acute infection is often asymptomatic and difficult to diagnose. People coinfected with HIV and hepatitis C might progress to chronic liver disease more quickly. We present a case of a man infected with HIV with sexually acquired acute hepatitis C and discuss the immunology, natural history, and epidemiology of acute hepatitis C and coinfection with HIV. Several recent reports have documented acute hepatitis C among men who have sex with men who engage in high risk sexual practices and often have concomitant genital ulcer disease. We review treatment options for the medical management of acute hepatitis C and coinfection with HIV.

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Introduction

Hepatitis C is a common infection among people infected with HIV, ranging from 10–40% among most cohorts studied.[1] Use of intravenous drugs or receipt of blood products are common risk factors among many people that are coinfected. Recent increases in coinfection have been noted in many countries among populations of men who have sex with men.

Since acute hepatitis C is often an asymptomatic infection, many patients infected with HIV are diagnosed through routine hepatitis screening and during the chronic phase of disease. People infected with HIV with symptomatic acute hepatitis C infection can present with a wide range of symptoms, from mild scleral icterus to vague abdominal discomfort to severe hepatitis needing admission to hospital. These patients will have antibody to hepatitis C and detectable virus. Some patients with acute hepatitis C will rapidly clear infection. This infection presents clinically as a patient with detectable antibody to hepatitis C, but without detectable hepatitis C viral load (on repeated measurements). It is important to identify acute hepatitis C infection among people infected with HIV because early treatment is associated with better response than treatment of chronic hepatitis C.

Case report

A 40-year-old man infected with HIV presented reporting tan stools, anorexia with weight loss of about 4·5 kg, and "yellow eyes" for 2 weeks.

Infection with HIV was diagnosed 6 years earlier. Antiretroviral drugs had been started 4 months earlier with CD4-T-cell count reaching a low of 109 cells per mL (9%). Medical history included rectal herpes, Kaposi's sarcoma (cutaneous and rectal), *Pneumocystis jirovecii* pneumonia, thrush, immune reconstitution progressive multifocal leukoencephalopathy, and depression. The antiretroviral drug regimen of tenofovir, emtricitabine, lopinavir, and ritonavir was well tolerated. The CD4-T-cell count increased to 146 cells per mL (12%) and HIV RNA viral load was 100 copies per mL after 8 weeks of treatment with antiretroviral drugs. Other drugs included levetiracetam, valacyclovir, and citalopram. Alcohol consumption by the patient was infrequent, only two drinks weekly, and he admitted to occasional use of recreational drugs (MDMA or ecstasy), but strictly denied use of intravenous drugs. He had unprotected receptive anal intercourse with his partner of several years and occasional anonymous partners with whom he used condoms for receptive contact. There was no serologic evidence of hepatitis A, B, or C 10 months before presentation.

The patient was afebrile with normal vital signs. On physical examination, he was thin, his eyes were mildly icteric, and seemed uncomfortable. Abdominal examination revealed that the tip of his spleen was palpable and that he had tenderness in his right-upper quadrant. The patient had neither arthritis nor anogenital ulcers. Raised transaminases were noted in the patient (table 1 shows laboratory findings and table 2 shows the results of hepatic tests), he was admitted to the hospital and his treatment with antiretroviral drugs was stopped.

The differential diagnosis included drug-related hepatotoxicity (protease inhibitor or levetiracetam) or hepatotoxicity related to the use of recreational drugs, acute viral hepatitis (A, B, or C), immune reconstitution illness from viral hepatitis or mycobacterial infection, disseminated herpes simplex, Epstein-Barr virus, cytomegalovirus hepatitis, autoimmune hepatitis, and Wilson's disease.

Hepatitis C viral load established the diagnosis of acute hepatitis C seroconversion. The hepatitis C viral load was 6·5 $\log_{10}$ IU/mL (figure) and the genotype was 1. Hepatitis A IgM and hepatitis B surface antigen were negative. An abdominal ultrasound was normal and his symptoms improved substantially by discharge from hospital on the sixth day since admission. A week later his antiretroviral drugs were restarted and treatment for acute hepatitis C

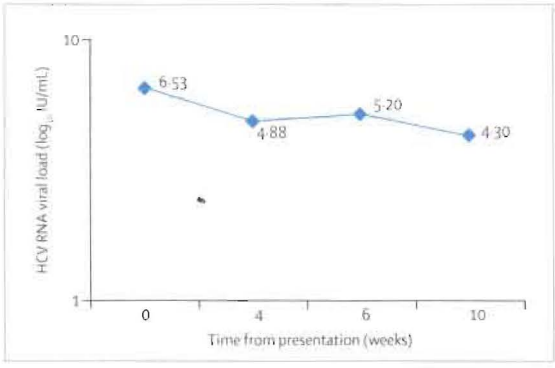

Figure: Hepatitis C RNA viral load from initial presentation before treatment

	On admission	Reference range
White cell count (per μL)	6	4·0–8·5
Haemoglobin (g/dL)	12	13·5–17·5 (men)
Haematocrit (%)	36	40–50 (men)
Mean corpuscular volume (fL)	95	80–97
Platelets (per μL)	313 000	140 000–440 000
Lactate dehydrogenase (U/L)	534	91–180
Creatinine (mg/dL)	1·2 (baseline 0·9)	0·7–1·2
Albumin (g/dL)	3·3	3·5–5·0
International normalised ratio	0·9	1·0
Thyroid stimulating hormone (μIU/mL)	1·8	0·34–5·6
CD4 (cells per mL)	229 (16%)	468–1599 (31–57%)
HIV RNA viral load (copies per mL)	Fewer than 80	Fewer than 80
Hepatitis C antibody IgG	Positive	Negative
Hepatitis C RNA viral load (log_{10} IU/mL)	6·53	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis B surface antibody IgG	Negative	Negative
Hepatitis A antibody IgM	Negative	Negative
Epstein-Barr virus antibodies	Negative	Negative
Cytomegalovirus viral load (copies/mL)	Negative	Negative
Rapid plasma reagin	Non-reactive	Non-reactive
Antinuclear antibody	Negative	Negative
Anti-smooth muscle antibody	26	20–30, weak positive
Mitochondrial antibody	Negative	Negative
Ceruloplasmin (mg/dL)	43	17–66

Table 1: Laboratory findings on admission

	Aspartate aminotransferase (IU/L)	Alanine aminotransferase (IU/L)	Alkaline phosphatase (IU/L)	Bilirubin (mg/dL; total/direct)
Reference range	10–42	17–63	38–126	0·3–1·6
3 months before admission	19	17	89	0·8/0·1
2 weeks before admission	87	144	124	1·0/0·2
Hospital day 1	958	1363	219	
Hospital day 2	752	1256	216	4·8/2·7
Hospital day 3	898	1616	250	11·7/7·7
Hospital day 5	630	1385	241	8·7/5·8
Hospital day 6	331	957	208	4·4/2·5
3 days after discharge	57	256	129	2·2/1·0
3 weeks after discharge	67	126	139	1·3/0·5

Table 2: Liver test results

was considered. Given his rapid virological response to antiretroviral drugs 4 months earlier, immune reconstitution to an earlier viral hepatic infection was thought possible but unlikely because of his clinical presentation and high risk sexual activity. It was decided to treat him. The precise timing of the patient's infection with hepatitis C virus could not be ascertained because there were no stored samples from earlier visits.

Because the patient did not spontaneously clear the infection after 10 weeks (although viral load had decreased substantially in the absence of treatment), it was deemed preferable to start treatment with pegylated interferon-α2b (1·5 μg/kg per week) and ribavirin (800 mg orally daily) for 24 weeks rather than waiting for possible spontaneous viral clearance. A rapid virological response was noted at 4 weeks and continued through 24 weeks of treatment. Adverse effects included anaemia, headaches, and worsening depression. The patient remained adherent to his antiretroviral regimen with an undetectable HIV viral load throughout his treatment. He achieved a sustained virological response with undetectable hepatitis C virus RNA viral load 24 weeks after completing treatment. A year after completing his treatment, he continues to do very well and his hepatitis C virus RNA and HIV viral loads remain undetectable. Ongoing prevention efforts have included discussion of minimising risky sexual behaviour, encouraging regular condom use, and vaccination for hepatitis A and B.

Virology and immunology

Hepatitis C virus is a single-stranded RNA flavivirus first identified in 1989. It has one large open reading frame encoding a polyprotein of 3020 aminoacids with structural (including envelope E1 and E2) and replicative functions (NS3, NS4, and NS5). The envelope region is the most mutable, specifically in hypervariable region 1, a 30 aminoacid region of E2. Hepatitis C virus has been classified into six genotypes with 60% sequence homology between the viral strains. Although hepatotropic, hepatitis C virus does not integrate into host DNA and infects only a minority of liver cells. Replication of the virus (detection of a negative-strand RNA intermediate) has also been shown to happen less frequently in peripheral blood mononuclear cells (PBMCs), but the importance of this is unclear.[7] Non-replicative hepatitis C RNA has been identified in saliva, urine, ascites, and semen, but blood has been proven to be the predominant mode of transmission.[1] Hepatitis C virus RNA viral load is higher among patients coinfected with hepatitis C virus and HIV than in people with monoinfection.[4,5] Mechanisms of receptor-mediated cell entry and viral spread are areas of active investigation.

Immunological studies of acute infection with hepatitis C virus in humans have focused on adaptive T-cell immunity and have shown that clearance of the virus during the acute phase needs an effective CD4 and CD8 T-cell response.[6–8] Few studies have evaluated the adaptive T-cell immune response during acute hepatitis C in patients coinfected with HIV. Danta and colleagues[9] evaluated T-cell function specific to hepatitis C virus in a cohort of patients infected with HIV (mean CD4-T-cell count 554 cells per mL) with acute infection with hepatitis C virus compared with patients only infected with hepatitis C virus. Interferon γ ELISPOT responses were substantially reduced by coinfection with HIV, especially against non-structural proteins (1/10 *vs* 5/8; p=0·008). Studies of patients chronically infected with HIV and hepatitis C virus have more clearly shown the effect of low CD4-T-cell count on T-cell responses specific to hepatitis C viruses.[6,10] Coinfected patients with CD4-

	Population	Prevalence of hepatitis C virus	Incidence of hepatitis C virus	Risk factors or possible associations	Miscellaneous
Fox[40]	155 MSM recently infected with HIV, London, no IVDA, 8% asymptomatic	0%	7% over 7 years	Recreational drugs (91%), fisting (73%), active sexually transmitted infection (55%)	..
Richardson[41]	948 MSM, London STD clinic, no IVDA	0%	0·37 cases per 100 person years	Infection with HIV (RR 7·9)	Incidence increased from 1·6 to nine cases per 1000 person years (2003–06)
Buffington[42]	6041 males, US STD/HIV clinics, 15% IVDA	51% in IVDA, 1·5% in MSM, 3·6% in others	..	..	..
Danta[43]	111 MSM infected with HIV, 2% IVDA, England, 93% asymptomatic	..	..	Multiple partners, unprotected anal intercourse, fisting, use of sex toys, history of STD, group sex, recreational drug use	Five clusters explain 78% sequences
Dougan[44]	225 MSM coinfected with HIV and HCV, Europe	..	..	Multiple partners, unprotected anal intercourse, fisting, group sex, club drugs	Many with STD coinfection
Matthews[45]	120 patients with acute infection with hepatitis C virus, Australia (of 22% infected with HIV, all were MSM)	..	..	80% of people not infected with HIV admitted IVDA, 1% MSM; 46% of people infected with HIV admitted IVDA, 50% MSM	..
Van de Laar[46]	1836 MSM, Amsterdam, 27% infected with HIV, 0·2% IVDA	1·3%	0·07/100 person years overall, 0·18/100 person years in people infected with HIV	Infected with HIV	Incidence in MSM infected with HIV increased from 0·08/100 person years (before 1999) to 0·87/100 person years (after 2000)
Wang[47]	67 patients with acute hepatitis C virus (antibody or RNA), USA, 64% asymptomatic, 66% IVDA	..	..	IVDA, nosocomial, most patients with unknown risk factor had high risk sex (MSM, partner infected with hepatitis C virus, sex worker, >6 partners)	..
Santantonio[48]	214 patients newly infected with hepatitis C virus (antibody and RNA), Italy, 32% asymptomatic, 3% HIV	..	..	IVDA, nosocomial, high risk sex (MSM, partner infected with hepatitis C virus, >2 partners in previous 6 months)	..
Serpaggi[49]	12 MSM with HIV and acute HCV (antibody and RNA), Paris, 83% asymptomatic, no IVDA	..	..	Unprotected anal intercourse	25% with STD (syphilis, chlamydia), 83% genotype 4 and closely related
Turner[50]	308 MSM infected with HIV, London, 8% IVDA	..	0·92/100 person years	Multiple partners, unprotected anal intercourse, fisting, use of sex toys, recreational drug use	..
Alary[51]	1085 MSM with HCV (antibody), Montreal	2·9%	0·04/100 person years	IVDA	..
Gambotti[52]	29 MSM infected with HIV with acute HCV (antibody or RNA), Paris, 83% asymptomatic, no IVDA	..	..	Multiple partners, unprotected anal intercourse, fisting	41% active STD (mostly syphilis)
Gotz[53]	17 MSM, 7 with recent HCV (antibody and RNA), 86% infected with HIV, 86% LGV proctitis	..	..	Infected with HIV, multiple partners, fisting	..
Rauch[54]	3327 patients infected with HIV, (antibody screen every 6 months), Swiss HIV Cohort	33% overall, 90% in IVDA	0·64/100 person years, IVDA 7·4/100 person years, MSM 0·7/100 person years		..
Amin[55]	1649 patients infected with HIV	16·1% overall, 93% in IVDA, 3·4% in MSM	..	IVDA	..
Browne[56]	27 patients, incident HCV (antibody), London HIV/STD clinic, 26 MSM, 93% infected with HIV, 89% asymptomatic	..	..	84% recent unprotected anal intercourse, 36% syphilis, 8% IVDA	..

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cell depletion (CD4-T-cell count of fewer than 500 cells per mL) had a more limited hepatitis C virus specific CD8 T cell interferon γ response ($p<0·0002$).[11] Furthermore, recurrence of hepatitis C viraemia in patients coinfected with HIV and previously controlled hepatitis C virus was inversely associated with CD4-T-cell count.[10] Overall, studies of patients with acute and chronic infection with hepatitis C virus show substantial deficits in cellular immunity to the virus, which is related to the level of CD4-T-cell depletion.

The importance of humoral immunity to hepatitis C virus during acute infection is incompletely understood. One study[17] characterised the antibody response as predominantly low titre, restricted primarily to the IgG1 subclass, and delayed in onset. Only a quarter of patients developed neutralising antibodies by 8 months after seroconversion. Mehta and colleagues[11] provided some evidence supporting partial protective immunity since persons with earlier infection were half as likely to develop new hepatitis C viraemia compared with those without

	Population	Prevalence of hepatitis C virus	Incidence of hepatitis C virus	Risk factors or possible associations	Miscellaneous
(Continued from previous page)					
Ghosn[54]	5 MSM infected with HIV with acute HCV (antibody and RNA), Paris	..	..	Multiple partners, unprotected anal intercourse, active early syphilis	..
Diamond[57]	833 MSM, Seattle	1%	..	IVDA	..
Fletcher[58]	16 MSM infected with HIV with HCV, London	.	.	Unprotected anal intercourse, fisting	50% recent STD (87% syphilis)
Hammer[59]	981 repeatedly tested for HIV, 5·4% infected with HIV, San Francisco	2·5% overall, 2·1% in MSM	0 cases	IVDA, infection with HIV, >50 years	..
Marx[60]	1631 patients, India, active IVDA excluded	3% women, 2% men	..	Genital ulcers (women); MSM, HSV2 antibodies (men)	.
Romanowski[61]	6668 patients, Canada STD clinic, 2·4% HIV, 42% IVDA, two-thirds with a history of STD	3·4%	..	IVDA (RR 60), HIV (RR 2·6), history of STD (RR1·7)	66% report STDs
Saxton[62]	1852 MSM, New Zealand, 2·9% infected with HIV, 37% history of STD	1·8% (self report)	..	IVDA, infection with HIV, income less than US$20 000	..
Filippini[63]	106 patients infected with HIV, 30% MSM, no IVDA, Italy	15·1% (5·2% in HIV controls)	..	Infection with HIV, MSM	..

MSM=men who have sex with men. UAI=unprotected anal intercourse. IVDA=intravenous drug abuse. HCV=hepatitis C virus. STD=sexually transmitted disease. RF=risk factor. RNA=HCV RNA PCR. LGV=lymphogranuloma venereum. OR=odds ratio. RR=relative risk.

Table 3: **Study outcomes outlining possible sexual transmission of hepatitis C among men who have sex with men (reverse chronologic order)**

	Number treated, population	Regimen	Treatment timing	Sustained virological response by genotype (%)
Calleri[64]	46 patients in Italy, 57% IVDA, 76% asymptomatic, 57% genotype 1 and 4	Pegylated interferon for 12 weeks	2 weeks after peak alanine aminotransferase	1 (68), 2 (80), 3 (89), 4 (33), 5 (100)
De Rosa[65]	23 IVDA in Italy, two infected with HIV, 65% genotype 1 and 4	Pegylated interferon for 12 weeks	2 weeks after diagnosis	1 (83), 2 (100), 3 (83), 4 (0)
DeRosa[66]	19 patients in Italy, 74% asymptomatic, 58% genotype 1, three infected with HIV	Pegylated interferon for 12 weeks	4-5 weeks after peak alanine aminotransferase	1 (73), 2–3 (75)
Kamal[67]	92 patients in Egypt, Germany, and USA, 10% IVDA, mostly genotype 1 and 4	Pegylated interferon for 8 weeks vs 12 weeks vs 24 weeks	After 8–12 week observation	1 (64), 2 (100), 3 (100), 4 (92), spontaneous resolution (22)
Wiegand[68]	89 patients in Germany, no IVDA, 19% asymptomatic, 67% genotype 1 and 4	Pegylated interferon for 24 weeks	11 weeks after infection	Genotype not available (71)
Broers[69]	14 patients in Switzerland (8 completed therapy), 81% IVDA, 41% asymptomatic	Pegylated interferon for 24 weeks	After 5 week observation	1 (60), 2 (0), 3 (63), spontaneous resolution (19)
Santantonio[70]	16 patients in Italy, 25% IVDA, 25% asymptomatic, 38% genotype 1 and 4	Pegylated interferon for 24 weeks	After 12 week observation	1 (83), 2 (100), 3 (100), spontaneous resolution (39)
Delwaide[71]	28 patients, 22% asymptomatic, 46% IVDA, 66% genotype 1	Interferon for 8 weeks	8 weeks after presentation	1 (83), other (50)
Nomura[72]	30 patients in Japan, 10% IVDA	Interferon for 4 weeks (24 weeks if relapse), 8 weeks vs 52 weeks postinfection	After 8 week observation	1B (56), other (100), after 8 weeks (87), after 52 weeks (40), spontaneous resolution (12)
Gerlach[73]	36 patients in Germany, 15% asymptomatic, mostly genotype 1 and 4, 27% IVDA	Interferon (10) and ribavirin (10), pegylated interferon (2) and ribavirin (4) for 14–61 weeks	After 23 week observation	1 (75), 2 (100), 3 (100), 4 (0), spontaneous resolution (52)
Jaeckel[74]	44 patients in Germany, 61% genotype 1, 20% IVDA	Interferon for 24 weeks	13 weeks after infection	Genotype not available (98)

MSM=men who have sex with men. IVDA=intravenous drug abuse.

Table 4: **Acute treatment of monoinfection with hepatitis C virus**

previous infection (12% *vs* 21%). Pestka and colleagues[14] noted that patients who had resolved acute infection were more likely to have rapid neutralising antibody levels than patients with persistent infection. However, humoral immunity alone seems to be insufficient in controlling viral replication in part because of the rapid mutability of envelope proteins and the fact that not all persons who clear infection have measurable neutralising antibody concentrations. Few studies specifically analysed the humoral immune response to acute hepatitis C virus

	Study design	Number treated, population	Regimen	Treatment TIMING	Sustained virological response by genotype (%)
Dominguez[28]	Prospective	14 patients in Paris infected with HIV, 72% asymptomatic, 28% genotype 1, no IVDA, median CD4-cell count 345	Pegylated interferon and ribavirin for 24 weeks	After 12 week observation	1 (75), 3 (100), 4 (60), spontaneous resolution (4)
Serpaggi[27]	Retrospective	10 MSM in Paris infected with HIV, 83% asymptomatic, 92% genotype 1 and 4, no IVDA, median CD4-cell count 625	Interferon for 24 weeks	7 weeks after presentation	0
Vogel[29]	Prospective	36 MSM in Germany infected with HIV, 91% genotype 1 and 4, no IVDA, median CD4-cell count 416	Pegylated interferon with or without ribavirin for 24 weeks (27) vs 48 weeks (9)	Immediate, then protocol amended to wait 12 weeks	1 (60), 2 (0), 3 (100), 4 (50), spontaneous resolution (27)
Gilleece[26]	Prospective	27 MSM in London infected with HIV, most genotype 1, 2% IVDA, median CD4-cell NA	Pegylated interferon and ribavirin for 24 weeks	After 12 week observation	1 (55), other (100), spontaneous resolution (24)
Vogel[28]	Retrospective	11 patients infected with HIV, 18% asymptomatic, 9% IVDA, median CD4-cell 507	Interferon (2), pegylated interferon (4), pegylated ribavirin (5) for 11–48 weeks	2–5 weeks after diagnosis	1 (88), 2 (100), 4 (100)

MSM=men who have sex with men. IVDA=intravenous drug abuse.

Table 5: Treatment for acute hepatitis C virus in patients coinfected with HIV

infection in the setting of coinfection with HIV; however, there is evidence that the humoral immune response is delayed in the setting of coinfection.[15]

In addition to these studies of the B cell and T cell adaptive immune response, several studies have shown the importance of the innate immune response to infection with hepatitis C virus and the ability of this virus to subvert this response. One recent study[16] identified the ability of the NS3/4A protease of hepatitis C virus to directly cleave an intracellular protein needed for the recognition of double-stranded RNA and the initiation of the interferon response to infection with hepatitis C virus. The role of coinfection with HIV on the interferon response to infection with hepatitis C virus is not well understood. Other innate immunity studies of infection with hepatitis C virus have identified the importance of natural killer cells and the expression of a particular natural killer cell receptor HLA genotype in the clearance of hepatitis C virus.[17] Given that perturbations in frequency, phenotype, and function of subsets of natural killer cells have been shown in both infection with HIV and hepatitis C virus, it could be postulated that coinfection might lead to an exaggeration of these derangements.[18] Several groups of investigators are actively identifying individuals acutely infected with hepatitis C virus with the goal of a more complete understanding of an effective immune response in early infection with hepatitis C virus.[19]

Natural history of hepatitis C virus with or without coinfection with HIV

Most acute infections with hepatitis C virus will become chronic. A systematic review of people acutely infected with hepatitis C virus showed an average spontaneous viral clearance of 25% (95% CI 0·22–0·29, range 0–80%) at least 6 months after diagnosis.[20] Risk factors for progression to chronic infection include asymptomatic infection, male sex, African-American ethnicity, and coinfection with HIV.[20–23] Villano and colleagues[24] did a prospective evaluation of people that were active abusers of intravenous drugs, and showed that 30% developed acute hepatitis C over 8 years; those people with lower viral loads of hepatitis C virus were more likely to clear the infection, and alanine aminotransferase values were not associated with viraemia.

There are few prospective analyses of the natural history of acute hepatitis C during infection with HIV. In one descriptive study,[14] two of nine people—with their infection with HIV well controlled and superinfection with hepatitis C virus—had spontaneous clearance. Although many treatment studies of acute hepatitis C allow for spontaneous viral clearance before treatment, clearance rates vary widely and treatment trials might have an inclusion bias for those patients who are more likely to clear infection. Spontaneous resolution rates of 4–27% have been reported in coinfection with HIV,[25–29] which is similar to the clearance rate of 26% in monoinfection with hepatitis C virus.[20] One natural history study showed that 353 people infected with HIV were less likely to clear acute infection with hepatitis C virus (14% *vs* 7%), especially in those with lower CD4-T-cell counts.[22] Another cohort of 62 patients with acute hepatitis C showed low spontaneous resolution rates (15–19%), irrespective of HIV status.[30] Further investigation should reveal more of the natural history of people with coinfections, although one important issue in identifying clearance rates is the difficulty in establishing precise timing of infection with hepatitis C virus.

Pathologically, there is recent evidence that acute infection with hepatitis C virus might lead to direct, immediate liver fibrosis.[31] The study followed 11 men who have sex with men infected with HIV and acutely infected with hepatitis C virus. Liver biopsies were done

3–21 weeks after the onset of hepatitis (and before the beginning of treatment) and 82% showed moderately advanced fibrosis. This is a fibrosis progression rate that is five-times greater than in people acutely infected with hepatitis C only. This study had insufficient follow-up to establish whether patients responded to treatment or developed progressive liver disease.

Although our review is focused on acute hepatitis C and HIV, there are a few pertinent outcomes studies examining people with chronic hepatitis C and HIV. A recent meta-analysis of hepatic outcomes in coinfections with HIV and hepatitis C virus[37] showed a doubling of risk of cirrhosis and a six-times increased risk of end stage liver disease compared with patients only infected with hepatitis C virus. Other studies evaluating HIV-related outcomes (adjusted for the use of antiretroviral drugs) have shown modest or minimal additional risk of progression to AIDS or death among patients coinfected with hepatitis C virus.[41] However, recent studies in the era of antiretroviral drugs showed an increased risk of death in people with coinfection.[44] One multivariate survival analysis[3] found shorter time from date of diagnosis of HIV to death among patients that were coinfected (hazard ratio 2·5). An increase in mortality due to infection with hepatitis C virus was also shown in an analysis of 84000 US death certificates from 1995 to 2004. Among the 5·2% of people coinfected with HIV and hepatitis C virus during 2004, the mean age at death was 48 years compared with 56 years among people only infected with hepatitis C virus.[45] Chronic coinfection with HIV and hepatitis C virus seems to be associated with an increased morbidity and mortality compared with infection only with hepatitis C virus.

Epidemiology and sexual transmission

According to the US Center for Disease Control and Prevention National Notifiable Disease Surveillance System, the incidence of acute hepatitis C has fallen substantially over the past 15 years, from 2·4 to 0·3 cases per 100000 population. This report documents 19000 acute infections with hepatitis C virus and 3·2 million people with chronic infection reported in 2006. However, recently, there has been a 19% increase in reported cases between 2005 and 2006. Reported risk factors for infection with hepatitis C virus include use of intravenous drugs (54%), multiple sexual partners (36%), and a sexual partner infected with hepatitis C virus (10%).[46]

There are large epidemiological studies that have associated use of intravenous drugs with infection with hepatitis C virus.[1,47] However, evidence linking incident infection with hepatitis C virus to sexual transmission has been conflicting. Longitudinal studies of heterosexual couples over the past 20 years have shown minimal to no risk of sexual transmission during long-term monogamy.[48] In a large prospective cohort of people infected with HIV identified over 16 years, those with a history of abuse of intravenous drugs had an incidence of hepatitis C virus of 7·4 cases per 100 person years, whereas those without a history of abuse of intravenous drugs had an incidence of hepatitis C virus of 0·23 cases per 100 person years. By comparison, men who have sex with men without a history of abuse of intravenous drugs had an incidence of hepatitis C virus infection of 0·7 cases per 100 person years.[49]

A recent review examined sexual transmission as a risk factor for hepatitis C infection and found limited evidence of an association.[50] However, there have been several reports over the past 10 years citing possible sexual transmission of hepatitis C among men who have sex with men (table 3). These cohorts are unique when compared with earlier hepatitis C cohorts, because of high risk sexual activity without substantial exposure to intravenous drugs. Specific sexual practices strongly associated with incident infection with hepatitis C virus include fisting, group sex, club drugs, and number of sexual partners.[44,45,51] In one recent study,[51] fisting was the most significant risk factor associated with sexual transmission and the only variable associated with incident infection with hepatitis C virus. People engaging in two or three high-risk practices in a group setting (receptive or insertive anal intercourse or fisting) had an increased risk of acute infection with hepatitis C virus through sex.[44] Although these studies report minimal rates of abuse of intravenous drugs, evaluation of sex as a risk factor is limited by self-reporting of high-risk behaviours.

Many of the recent reports of acute infection with hepatitis C virus have been described among men who have sex with men coinfected with HIV. Few studies have looked specifically at HIV as a putative cofactor for increased transmissibility of hepatitis C virus. A retrospective analysis done in a cohort of 948 men who have sex with men in London, UK, from 2000 to 2006[42] documented 1·5 cases of acute hepatitis C per 1000 person years compared with a case rate of 12 per 1000 person years in men who have sex with men infected with HIV. Similarly, a case–control study in Italy[43] documented an increase in prevalence of antibody against hepatitis C virus from 5% in men who have sex with men to 15% in men who have sex with men with concomitant infection with HIV. In an evaluation of 120 people acutely infected with hepatitis C virus in Australia, 50% of men who have sex with men infected with HIV cited sexual risk factors, whereas the majority of heterosexual people not infected with HIV had a history of abusing intravenous drugs.[46] Furthermore, there is some biological plausibility to an enhanced risk of transmission of hepatitis C virus in coinfection with HIV and hepatitis C virus, because higher quantitative titres of hepatitis C virus have been described in the plasma, seminal fluid, and salivary secretions of people with coinfected with HIV.[52]

A common association among these reports of men who have sex with men with incident infection with hepatitis C virus is concomitant sexually transmitted infection. This is particularly worrying because of

recent reported increases in sexually transmitted infections among men who have sex with men including early syphilis, lymphogranuloma venereum (LGV), and fluoroquinolone resistant *Neisseria gonorrhoeae*.[16,35] Fox and colleagues[41] reported 11 hepatitis C virus seroconversions among 155 men who have sex with men infected with HIV and noted 55% of these men had a sexually transmitted infection. In several recent reports from Paris and London,[37,42,55,58] 25–50% of men who have sex with men infected with HIV with acute hepatitis C had a sexually transmitted infection. Additionally, a cluster study in the Netherlands[53] traced 17 men who have sex with men contacts (infected with HIV but not abusers of intravenous drugs) of an index case coinfected with HIV, hepatitis C virus, and LGV and reported that 41% had been recently infected with hepatitis C virus and 82% had LGV. Sexual transmission is supported by the use of phylogenetics to link transmission pairs with viral sequencing. Three recent studies with phylogenetic analyses identified clusters of infection that were genetically linked (high sequence homology of variable domains E1/E2, NS5B, or HVR1), and were organised as separate monophyletic groups with unique sexual transmission events.[37,44,47] In conclusion, when considering risk factors for infection with hepatitis C virus, there is accumulating evidence for sexual transmission of hepatitis C among men who have sex with men. Infection with hepatitis C virus by sexual transmission might be more efficient in the setting of concomitant sexually transmitted infection or infection with HIV associated with high risk sexual behaviours.

Treatment of acute hepatitis C

Treatment outcomes for acute hepatitis C are derived from prospective cohort trials that include various regimens with differing treatment duration (table 4). All these studies define the primary endpoint, sustained virological response (SVR), as an undetectable hepatitis C viral load 24 weeks after completion of treatment. More recent studies have allowed 5–12 weeks for spontaneous viral clearance before starting treatment.

A pivotal trial in the treatment of acute hepatitis C showed a 98% SVR in patients who received interferon alfa-2b for 24 weeks.[72] The durability of this response has been shown over 2·6 years.[73] Review of subsequent treatment trials with pegylated interferon at 1·0–1·5 μg/kg per week showed SVRs ranging from 57–94%.[58,59] Only one trial used ribavirin in combination with interferon (81% SVR) and thus its role as adjunctive treatment remains uncertain.[73] Most trials have examined 24-week duration of therapy, although three recent studies showed an SVR of 72–74% after 12 weeks of treatment.[63-65] In all studies reviewed, the best outcomes are reported for those persons who are symptomatic or are infected with hepatitis C virus genotype 2 or 3.

Search strategy and selection criteria

Ovid Medline 1950 to June, 2008, was searched with the keywords "acute hepatitis C" or "hepatitis C treatment" or "hepatitis C transmission". This produced a list of 7550 citations when combined with "and" for acute hepatitis C, 155 articles on transmission and 195 treatment articles remained. Hepatitis C articles were also combined with searches of keywords "HIV" or "AIDS" or "sexually transmitted infections" or "sexually transmitted diseases" or "genital diseases, male" or "genital ulcer". All subheadings were included. This led to an additional 688 articles reviewed, of which eight remained after combination with acute disease. Searches were limited to the English language and reference lists were used to find additional citations.

It remains unclear when it is appropriate to begin treatment. In the treatment trials reviewed that allowed 12 weeks for spontaneous viral clearance, 12–52% of people had resolution of infection before the beginning of treatment.[41,73] Thus, treating patients immediately might lead to unnecessary treatment. However, waiting for prolonged periods might also be detrimental, because several trials have shown that promptly starting treatment (after 8–12 weeks) is associated with a high SVR.[41,73] Recommendations at present suggest ongoing evaluation up to 12 weeks to detect spontaneous resolution before starting treatment.[74]

There is more limited information available on management of acute hepatitis C in patients infected with HIV (summarised in table 5). Available studies are small, exclude those with low CD4-T-cell counts (mean 473 cells per μl), and use combination regimens of interferon and ribavirin. People coinfected with HIV and hepatitis C virus seems less likely to respond to appropriate treatment with SVR rates ranging from 0–91% in various studies.[27,28] One recent prospective multicentre trial designed specifically to evaluate the use of combination therapy showed overall SVR of 61% but did not show additional benefit of interferon and ribavirin compared with interferon alone.[27] The European AIDS network will be doing a multicentre study on the use of combination therapy as well as comparing treatment of 24–48 weeks duration.

In summary, although 26% of people with acute hepatitis C will clear the virus spontaneously within the first 10 weeks after infection, people infected with HIV seem less likely to eradicate infection spontaneously. In the absence of spontaneous clearance, antiviral treatment seems to be effective in viral eradication. Therefore, early identification and treatment (if needed) of patients with acute hepatitis C virus would have a substantial effect on this prevalent infection among patients infected with HIV. At present, treatment guidelines for acute infection with hepatitis C virus in the setting of coinfection with HIV recommend

pegylated interferon and weight-based ribavirin for 24 weeks or more, pending further evaluation of the use of combination therapy.[74,75]

Ongoing controversy and research questions

There are several areas of research relevant to the management of patients infected with HIV with acute hepatitis C. To identify acute infection with hepatitis C virus, appropriate diagnostic screening among men who have sex with men with high risk behaviours might be appropriate. Also, the importance of concurrent sexually transmitted anogenital ulceration in infection with hepatitis C virus needs to be explored. The optimum treatment regimen including when to start treatment, the duration of treatment, and need for concomitant ribavirin needs further evaluation, particularly in people infected with HIV. Clinical advances will also be based on a more complete understanding of the pathogenesis of hepatitis C and its earliest interactions with the host immune system.

Contributors

JDO as primary author collected data, wrote the paper, and made revisions on the basis of reviewer comments. MK and HR assisted with writing the paper and data collection; they also made key edits. AG provided funding source and edits. KW contributed to design of the paper, edits, and data interpretation.

Conflicts of interest

We declare that we have no conflicts of interest.

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