

Characteristics of hepatitis C virus infection in HIV-infected people

Curtis L Cooper MD FRCPC, Andrew D Badley MD FRCPC, Jonathan B Angel MD FRCPC

CL Cooper, AD Badley, JB Angel. Characteristics of hepatitis C virus infection in HIV-infected people. *Can J Infect Dis* 2001;12(3):157-163.

Knowledge pertaining to hepatitis C virus (HCV)/human immunodeficiency virus (HIV) co-infection is currently incomplete or conflicting. Several points are well studied, however. Plasma HCV RNA levels are higher in matched HIV-infected people than in HIV-seronegative control subjects and are inversely correlated with CD4⁺ T lymphocyte counts. HCV genotype does not appear to influence this value. Co-infected individuals develop histological and clinical features of HCV liver disease more rapidly than HIV-seronegative patients. Co-infected individuals appear to respond to interferon-alpha therapy equally as well as HIV-seronegative HCV-infected adults, but minimal information exists regarding the efficacy and toxicity of combination HCV therapy (interferon-alpha plus ribavirin) in this population. Adverse consequences of highly active antiretroviral therapy in co-infected patients include hepatic toxicity and, in a minority of patients, an 'immune restoration syndrome'. It is unclear whether long term, highly active antiretroviral therapy positively or negatively influences the natural history of HCV infection.

Key Words: *Antiretrovirals; HCV; Hepatitis; Hepatitis C virus; HIV; Human immunodeficiency virus*

Caractéristiques de l'infection à virus de l'hépatite C chez les personnes porteuses du VIH

Les connaissances actuelles sur la co-infection à virus de l'hépatite C (VHC) et à virus de l'immunodéficience humaine (VIH) sont incomplètes et contradictoires. Cependant, plusieurs éléments de la co-infection font l'objet d'études. Ainsi, le taux plasmatique d'ARN du VHC est plus élevé chez les personnes également infectées par le VIH que chez les sujets témoins séronégatifs à l'égard du VIH et il est en corrélation inverse avec le nombre de lymphocytes T CD4. Le génotype du VHC ne semble pas influencer sur cette valeur. Les personnes co-infectées présentent des manifestations cliniques et histologiques d'atteinte hépatique plus rapidement que les personnes non porteuses du VIH. Par ailleurs, les patients co-infectés semblent réagir autant au traitement à l'interféron alpha que les patients infectés par le VHC mais non par le VIH; il existe toutefois très peu d'information sur l'efficacité et la toxicité du traitement associant l'interféron alpha à la ribavirine dans ce groupe de patients. Parmi les effets indésirables du traitement antirétroviral hautement actif chez les personnes co-infectées, mentionnons l'hépatotoxicité et, dans une minorité de cas, le syndrome du rétablissement des défenses immunitaires. On ne sait pas encore si l'administration prolongée du traitement antirétroviral hautement actif a une influence positive ou négative sur l'évolution spontanée de l'infection à VHC.

*This article is the winner of The Canadian Journal of Infectious Diseases Trainee Review Article Award for 1999-2000
Division of Infectious Diseases, Ottawa Hospital General Campus, Ottawa, Ontario*

Correspondence: Dr Curtis L Cooper, Room G12, 501 Smyth Road, Ottawa Hospital General Campus, Ottawa, Ontario K1H 8L6.

Telephone 613-737-8924, fax 613-737-8925, e-mail Ccooper@ottawahospital.on.ca

Hepatitis C virus (HCV) infects approximately 2% of the North American population (1); however, within certain high risk groups, including people with hemophilia and intravenous drug users, this prevalence is much higher (2-5). Approximately one-third of human immunodeficiency virus (HIV)-infected people are HCV-seropositive (6). Among intravenous drug users with HIV, this rate increases to at least 50% and up to 90% in many surveys (2,5,7). Many aspects of HCV infection and its natural history remain incompletely understood or unstudied. This is also true of HIV/HCV co-infection. The present article identifies aspects of HCV infection in HIV-infected individuals that are well understood and reviews the current knowledge surrounding other relevant, yet unresolved, issues (Table 1).

DIAGNOSIS OF HCV INFECTION

The diagnosis of HCV infection is based on the detection of immunoglobulin G antibodies to HCV envelop, core and nonstructural HCV antigens. Blood specimens are initially screened by enzyme-linked immunoassays (EIA), and positive results are confirmed by the recombinant immunoblot assay. If positive, chronic infection is demonstrated by the detection of plasma HCV RNA by using polymerase chain reaction (PCR) technology. Although first-generation tests have sensitivities as low as 50%, third-generation kits, which test for multiple antigens, are reported to be highly sensitive and specific in immune competent hosts (8). Diagnosis of HCV in HIV/HCV co-infected patients is more challenging because up to 15% of patients are negative or indeterminate by EIA despite HCV viremia (9-11). This is, in part, due to assay sensitivity issues as well as HCV antibody seroreversion, a process in which initially positive HCV antibody measures become negative (12). Newer EIA systems may eliminate both of these problems. In one study, an assessment of an HIV-seropositive cohort by third-generation assay showed greater than 99% sensitivity and specificity (8). Although these results are impressive, patients at risk but with negative anti-HCV antibody tests by EIA and/or recombinant immunoblot assay should be tested for plasma HCV RNA by PCR assay until additional studies confirm the enhanced sensitivity of newer EIA kits.

HCV VIRAL LOAD

In immune competent hosts, HCV RNA levels vary greatly among people infected with HCV and do not correlate with the rate of liver disease progression (13,14); however, they do help predict a patient's response to therapy. The value of HCV RNA levels in predicting disease progression and response to therapy in HIV/HCV co-infected patients is unknown. It is well documented that HCV RNA plasma levels are higher in HIV-co-infected individuals than in HIV-seronegative persons with HCV (15-18). This has been demonstrated in studies controlling for age, HIV viral load, CD4⁺ T lymphocyte count or other risk factors for HCV progression (18). Several reports reveal a significant inverse correlation between absolute CD4⁺ T lymphocyte number and

TABLE 1
Hepatitis C virus (HCV)-related disease parameters in human immunodeficiency virus (HIV) co-infected individuals

Parameter	Observation in HIV co-infection (compared with HCV infection alone*)
Reliability of serology for screening	Decreased
HCV viral load	Increased
Histological evidence of disease on liver biopsy	Increased
Rate of fibrosis	Increased
Rate of progression to clinical liver disease	Increased
Response to HCV drug therapy	Unresolved
Adverse events related to HCV drug therapy	Unresolved

*See text for details

HCV RNA viral load (18,19). In contrast, Mir et al (20) found no correlation between CD4⁺ T lymphocyte count and plasma HCV RNA level. Overall, however, these data suggest that impaired host immunity leads to an elevation in plasma HCV load. This is further supported by the observation that HCV viral load in chronically infected persons increases following HIV infection (16).

In addition to immune status, CCR5Δ32 heterozygosity may influence HCV viral load in co-infected patients (21). Receptor heterozygosity has been associated with slower progression of HIV disease (22). When 16 CCR5 wild-type (WT)/Δ32 co-infected patients were compared with 55 CCR5 WT/WT co-infected patients, a significantly lower HCV viral load was found in the former. This group was also more likely to clear spontaneously HCV infection completely (six of 19 [31.6%] versus nine of 57 [15.7%]). The CCR5 receptor likely does not directly influence HCV infection because HCV does not use this receptor for cell entry. One potential explanation for these findings is that antigen-specific immunity, including that against HCV-specific antigens, is preserved in heterozygous persons because the rate of HIV-induced immune destruction is reduced in this population. This relative preservation of immunity may allow for enhanced control of HCV viral load and greater clearance of HCV infection.

Other potential predictors of HCV viral load have been assessed. Severity of hepatic insufficiency does not appear relevant to HCV RNA viral load in immune competent hosts (23). Conversely, Dragoni et al (18) demonstrated a significant increase in HCV viral load in HIV-co-infected patients with end-stage liver disease compared with those without co-infection (18). This may be explained, however, by lower CD4⁺ T cell counts in the former group. As with HIV-seronegative persons, HCV genotype does not appear to influence viral load in co-infected people (15,24).

PROGRESSION TO LIVER DISEASE

Several studies have indicated that HIV infection is an independent risk factor for the presence of liver disease in HCV infection (25-30). A greater degree of portal, periportal and lobular inflammation, and centrilobular fibrosis has been observed with co-infection (31,32). In another study matched for duration of HCV infection, age, sex, alcohol use and route of infection, core liver biopsies were performed in 54 HIV/HCV co-infected patients with a median CD4⁺ T lymphocyte count of 320 cells/ μ L and were compared with liver biopsies from 53 HCV-infected individuals (25). Based on the Metavir Group Histological scale (30,33), perisinusoidal fibrosis in those without portal fibrosis was observed in 10 of 27 (37%) co-infected patients versus five of 32 (16%) HIV-seronegative people. These results may be relevant because perisinusoidal fibrosis is postulated by some as evidence for early HCV-induced liver disease (25). In patients with CD4⁺ T cell counts below 200 cells/ μ L, histological evidence of cirrhosis was seen in five of 11 (45%) compared with six of 58 (10%) patients with higher CD4⁺ T cell counts. These results have been duplicated elsewhere (25), and suggest that both initial and later stage hepatic injury are more common in co-infected individuals. One limitation of these studies is that although approximately two-thirds of co-infected patients were on antiretroviral therapy, details regarding the duration of use and correlation with fibrosis scores were not provided (25). The potential importance of other factors, such as antiretroviral therapy, in explaining the prevalence of liver disease in co-infected individuals is supported by the fact that the three classic histological lesions associated with HCV infection (ie, steatosis, bile-duct injury and lymphoid nodules) were not more frequently identified in co-infected patients (25).

Evidence that HIV infection affects the rate of hepatic fibrosis has been reported (26). In this study, fibrosis progression rates were calculated by dividing Metavir fibrosis stage values by the estimated years of HCV infection. The estimated median duration of HCV infection before cirrhosis was 26 years (range 22 to 34 years) in co-infected patients versus 38 years for HIV-seronegative people (range 32 to 47 years) and was statistically significant. Furthermore, this study provided additional evidence that impaired immunity (CD4 count less than 200 cells/ μ L) and alcohol consumption greater than 50 g/week were independently associated with rapid progression to cirrhosis. Sex was not found to be an independent predictor of fibrosis rate.

Lesens et al (34) and Dragoni et al (18) have demonstrated that progression to clinically evident liver disease is also accelerated in co-infected individuals. In the former study (34), 81 co-infected people with hemophilia infected between 1978 and 1985 were assessed for persistent bilirubin elevation greater than 21 μ mol/L; ultrasound-demonstrated ascites; hepatic encephalopathy; histological evidence of cirrhosis or hepatocellular carcinoma; and esophageal or gastric varices. Alternative explanations for liver disease, including opportunistic infections, malignancies and alcohol,

were ruled out before attributing these end points to HCV infection. The mean estimated time between HCV infection and any of these end points was 17.2 years. Twenty-two (27%) met at least one of these criteria compared with 5.7% in a matched HCV-infected, HIV-seronegative cohort. Based on this analysis, an odds ratio for progression to these clinical measures of liver disease was 7.4 (95% CI 2.2 to 22.5). Unfortunately, no attempt was made to correlate antiretroviral use with these hepatic end points. Dragoni et al (18) showed that a low CD4⁺ T cell count was correlated with clinical end stage liver disease.

Although the natural history of HCV infection appears to be accelerated in the presence of HIV infection, significant liver disease still requires many years to develop. Rapid deterioration in hepatic status after HIV infection in patients with pre-existing HCV infection has, however, been described as well (28).

Even in the absence of HIV infection, debate continues as to whether HCV genotype influences the rate of liver disease progression (35-42). In a study of 119 HIV/HCV co-infected patients, the clinical course did not differ based on HCV genotype (35). A limitation of this study is that the end points assessed, which included a 30% decrease in Karnofsky index, 20% loss of body weight, AIDS-defining illness, death and 50% or greater fall in CD4⁺ T cell count, were more specific to HIV than to HCV-induced end-stage liver disease. Further investigation of this issue is required.

RESPONSE TO ANTI-HCV THERAPY

Several studies suggest that HIV-infected patients treated with interferon-alpha (INF- α) for HCV infection have sustained response rates (defined as absence of detectable plasma HCV RNA six months following the completion of INF- α) that are comparable with those of HIV-uninfected persons (43-45). Sustained response rates of 20% to 36% were reported among those participants who completed their course of therapy. Poor responses have been reported in those patients with CD4⁺ T lymphocyte counts below 200 cells/ μ L (44-46).

The current standard of care for the treatment of HCV infection in the absence of HIV infection is combination therapy with INF- α and ribavirin (13,14,47). Overall sustained response rates of 40% to 50% have been reported; however, this depends on several factors including HCV genotype, plasma RNA level, presence of cirrhosis, age and sex. There are minimal data evaluating this form of therapy in co-infected individuals (9,48-51). At six months, end of treatment response rates of 50% to 70% were observed in cohorts of 19, 20 and seven co-infected participants, respectively (9,48,49). In another study, all four patients on combination therapy for 12 months were found to have undetectable HCV viral loads (50). In a study of 18 co-infected patients, 11 were able to complete a six-month course of dual therapy (51). Of these, five achieved biochemical and virological sustained responses six months after completing therapy. Drug toxicity was a major factor limiting patient ability to complete combination therapy (50,51). Anemia, related to the use of rib-

avirin, was a frequently reported serious adverse event (five of 21, 23.8%), but was successfully managed with dose reduction and/or erythropoietin (50). Other frequently observed adverse events seen in co-infected patients include constitutional symptoms and depressed mood (50,51). It remains unclear whether these side effects are more common in co-infected populations.

EFFECT OF ANTIRETROVIRAL THERAPY ON THE COURSE OF HCV

Several groups have attempted to identify direct antiviral activity of antiretrovirals on HCV. Neither nucleoside reverse transcriptase inhibitors (NRTIs) (52,53) nor protease inhibitors (54,55) have such an effect. There are no data assessing non-nucleoside reverse transcriptase inhibitor (NNRTI) activity against HCV.

It is unknown whether HCV-induced liver disease progression is affected by antiretroviral therapy. The prevalence of HCV-induced fibrosis in co-infected patients was assessed as a function of antiretroviral use in 122 co-infected patients and compared with 122 matched, HIV-seronegative patients (26). Rates did not differ significantly among patients receiving highly active antiretroviral therapy (HAART) (single protease inhibitor plus double NRTI therapy), double NRTI therapy, single NRTI and no antiretroviral therapy. No patient was on NNRTI therapy. Duration of HAART, double NRTI and single NRTI use was 12.1, 33 and 30 months before liver biopsy, respectively.

As indicated, several studies have described an inverse relation between CD4⁺ T lymphocyte count and plasma HCV RNA level (18,19). One question that remains is whether an increase in CD4⁺ T lymphocyte count after introduction of HAART (56-58) is associated with a reduction in plasma HCV RNA level. At least one study described a reduction in HCV viral load by greater than 0.5 log₁₀ at 12 months in seven of 16 patients on HAART with HIV viral loads below 50 copies/μL (59). In this cohort, HCV viremia became undetectable in four patients. The mean CD4⁺ T lymphocyte increase at 12 months was 210 ± 18 cells/μL. These results suggest that prolonged suppression of HIV replication associated with immunological restoration may result in improved immune control of HCV infection. This issue remains unresolved, however, because a recent study suggests that HCV viral loads may actually be higher in antiretroviral-treated patients (20). A possible explanation for these seemingly conflicting results, as suggested by Rutschmann et al (54), is that HCV viral load may transiently increase following initiation of HAART as a result of cytotoxic T lymphocyte-mediated lysis of HCV-infected cells, with the release of HCV. After several months, as this process resolves, plasma HCV RNA levels may return to baseline or actually fall below initial levels (60). It may be that only after a prolonged period of time is immunity restored sufficiently to reduce HCV viral load and possibly clear the infection (59).

An 'immune restoration syndrome' has been described after introduction of HAART in co-infected individuals

(61,62). Combination antiretroviral therapy has been highly effective in suppressing HIV viral load with resulting beneficial immunological effects, including increased absolute (62,63) and naive CD4⁺ T lymphocytes (64), and improved antigen-specific cell-mediated immunity (65). Improved HCV-specific immunity may actually exacerbate HCV-induced transaminitis, induce HCV seroconversion in previously HCV-infected but seronegative individuals, and increase plasma HCV RNA levels (61). Resulting hepatic decompensation and death have been described (61,66). The reason for increased HCV RNA levels and hepatic injury is not fully understood but likely results in part from increased immune-damage to HCV-infected hepatocytes with resulting HCV release (61). Despite the grave consequences of this syndrome, the incidence is low and should not preclude antiretroviral therapy in co-infected individuals.

Unfortunately, both NRTIs (67-69) and protease inhibitors (70,71) have well established hepatic toxicity. These toxicities have negative implications in patients with and without HCV co-infection (70,72). Most studies, but not all (70), suggest that antiretroviral hepatic toxicity is more frequently observed and more severe in co-infected patients (54,60,72,73). Both protease inhibitors and NRTIs were noted to elicit transaminitis in HCV-infected patients newly started on antiretroviral therapy at a frequency almost three times that seen in HCV-negative patients (72). An odds ratio of 6.1 (95% CI 2.2 to 6.7) for grade 3 or 4 transaminitis was reported for protease inhibitor use in this study. A recent prospective cohort study raised specific concerns about the use of ritonavir in HCV-infected people (70). A 30% (95% CI 17.9% to 44.6%) incidence of grade 3 or 4 elevation in alanine aminotransferase or aspartate aminotransferase was described compared with 8.1% with other protease inhibitors and 5.7% (95% CI, 1.2% to 12.9%) with nucleoside analogue-based therapy. NNRTIs may also be hepatotoxic in co-infected people, but the frequency of this manifestation remains to be established (74).

EFFECT OF HCV ANTIVIRAL THERAPY ON HIV COURSE AND THERAPY

One concern requiring further investigation relates to the effect of HCV antiviral therapy on the pharmacokinetics and pharmacodynamics of antiretroviral agents. Ribavirin, a purine analogue, antagonizes the anti-HIV activity of pyrimidine analogues (zidovudine, ddC, d4T) by inhibiting phosphorylation (75,76). Conversely, ddI (purine analog) levels are increased substantially *in vitro* by ribavirin (76). The potential *in vivo* influence of ribavirin on NRTI levels and activity should be considered before initiating HCV therapy in antiretroviral-treated, HIV-infected individuals. The effects of ribavirin on NNRTI and protease inhibitor levels are unknown.

Rapid and irreversible decline in CD4⁺ T lymphocyte count after the use of INF-α has been described in HIV-infected patients (77,78). More frequently, however, a transient decrease occurring between the sixth and 14th week of therapy is observed (77); this is seen in 10% to 15% of treated

patients. This decline is likely evidence of redistribution from the circulating compartment to lymphoid tissue rather than lymphocyte destruction. Despite the effect on CD4⁺ T lymphocyte counts, INF- α therapy may be particularly beneficial in co-infected persons based on several studies demonstrating a 1.5 to 2.0 log reduction in HIV viral load with high dose INF- α therapy (79,80). A modest HIV viral load reduction was reported with combination ddI and low dose INF- α (52); however, no clinical benefit was described with this combination therapy or with zidovudine and INF- α (53). Ribavirin also has modest activity against HIV in vitro (81), but a clinical benefit has not been shown (82).

INITIATING HCV THERAPY IN HIV CO-INFECTED PEOPLE

It is generally accepted that people infected with both HCV and HIV should not be excluded from drug therapy (83,84). As in HIV-seronegative individuals, therapy should be reserved for those with HCV virus detected by PCR, sustained alanine aminotransferase greater than 1.5 times baseline, and histological evidence of necrosis, inflammation or fibrosis on liver biopsy (82). Patients should be clinically stable in terms of both HIV infection and other medical illnesses. Additional contraindications to HCV therapy include psychiatric instability, predicted poor adherence and pregnancy. Patients, if on antiretroviral therapy, should be tolerating these medications well, be adherent to this therapy and have stably suppressed viral load measurements for three to six months while on therapy. HCV drug treatment for individuals not on antiretroviral therapy is reasonable in those with CD4⁺ T lymphocyte counts greater than 200 cells/mL. Given concerns regarding loss of CD4⁺ T cells with INF- α , HCV therapy should generally be avoided in patients with counts below 200 cells/mL.

As with HIV-seronegative patients, close clinical and laboratory monitoring is necessary. Given the hematological suppressive effects of ribavirin and INF- α , hemoglobin and leukocyte monitoring (including CD4⁺ T cells) is vital. Transaminase levels will increase in a large proportion of co-infected patients after the introduction of HCV drug therapy. As long as the patient remains clinically stable and there is no evidence of clinical or biochemical liver function deterioration, it seems reasonable to follow these patients without discontinuing HCV therapy.

Further research is vital before clear, evidence-based guidelines for HCV therapy in HIV co-infected patients can be developed and widely implemented.

SUMMARY

Much remains to be learned about HCV infection in HIV-seropositive persons. The weight of evidence suggests that co-infected people have higher HCV viral loads, develop liver fibrosis more rapidly and present with clinical evidence of cirrhosis sooner than patients infected with HCV alone. Weakened immunity, as a result of HIV infection, appears to have a permissive role in HCV-mediated liver disease.

Insufficient data are available to determine whether immune restoration following HAART results in improved outcome in terms of HCV-induced disease parameters. Antiretroviral liver toxicity continues to complicate HIV treatment and, in particular, the management of co-infected individuals. HCV treatment with agents, including INF- α and ribavirin, continues to be assessed in HIV/HCV co-infected patients. These assessments will, it is hoped, result in therapy that is more effective and better tolerated than those regimens currently available.

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