

Bidirectional Interaction between Cytomegalovirus and Hepatitis C Virus after Liver Transplantation: A Critical Review of the Clinical Evidence

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Abstract

Purpose: *A bidirectional interaction between cytomegalovirus and hepatitis C is hypothesized to adversely affect the outcome of liver transplantation for chronic hepatitis C. This article reviews the clinical data on this hepatitis C virus-cytomegalovirus interaction.*

Methods: *Review of (i) studies that assessed the impact of cytomegalovirus on hepatitis C virus viremia, recurrent hepatitis C, fibrosis, cirrhosis, graft failure, and mortality and (ii) studies that assessed the impact of hepatitis C virus on cytomegalovirus load, infection, and disease.*

Results: *Eleven studies investigated the impact of cytomegalovirus on hepatitis C outcomes. Seven of these studies reported potential associations of cytomegalovirus with (i) time to recurrent hepatitis C and fibrosis, (ii) severity of recurrent hepatitis C and fibrosis, and/or (iii) incidence of allograft failure and mortality. In contrast, four studies failed to demonstrate these associations. On the issue of hepatitis C virus influencing cytomegalovirus outcomes, two studies reported a higher incidence of cytomegalovirus disease in liver recipients with severe recurrent hepatitis C, while two studies failed to show the association between hepatitis C virus positivity and cytomegalovirus load, infection, and disease after liver transplantation.*

Conclusion: *This comprehensive review highlights the conflicting results of studies on the association between hepatitis C virus and cytomegalovirus after liver transplantation. The contrasting findings could be accounted for by several factors including variability in case definitions and endpoints, patient populations, clinical practices such as anti-cytomegalovirus prophylaxis and interferon therapy, among others. In our view, despite these conflicting results, the proven association between cytomegalovirus and overall transplant outcomes (and possibly hepatitis C virus pathogenicity) should warrant an aggressive cytomegalovirus prevention strategy in hepatitis C virus-infected liver transplant recipients. (Trends in Transplant. 2008;2:148-56)*

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Key words

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Introduction

Liver transplantation has evolved as an increasingly important modality for the treatment of many end-stage liver diseases. In 2007, a total of 6,492 liver transplants were performed for various indications in the USA¹. Overall, the most common indication for liver transplantation is end-stage liver disease caused by chronic infection with hepatitis C virus (HCV), an RNA virus that infects 3% of the human population or an estimated 170 million people worldwide²⁻⁵.

While liver transplantation prolongs and improves the quality of life of many individuals with end-stage HCV-induced cirrhosis⁶, the long-term outcome of this procedure is impeded by recurrence of HCV infection involving the liver allograft, and this is often characterized by an accelerated course. After liver transplantation, HCV viremia persists in up to 95% of patients⁷ while allograft hepatitis C occurs in 50-60% of patients during the first year⁸. In many instances, recurrence of hepatitis C leads prematurely to cirrhosis and allograft failure that requires re-transplantation or results in death⁹. Indeed, within five years after liver transplantation, approximately 10% of HCV-infected patients will have experienced allograft failure or death². Numerous studies have been conducted to identify potentially reversible predisposing factors in an effort to reduce the adverse outcomes associated with severe hepatitis C recurrence³.

One of the correctable variables that has been implicated as a facilitator of hepatitis C recurrence is cytomegalovirus (CMV) infection⁸⁻¹⁷. Cytomegalovirus, a ubiquitous β -herpesvirus that infects 60-100% of humans, is regarded as the single most common pathogen causing significant morbidity among liver recipients^{12,13,16,18}. Without anti-CMV prophylaxis, the virus may reactivate to cause asymptomatic CMV infection in 23-85%, and symptomatic and often tissue-invasive disease in up to 50% of

liver recipients^{10,19,20}. In addition, CMV possesses potent immunomodulatory properties that could enhance allostimulation, leading to acute and chronic graft rejection and superinfections with other opportunistic bacterial, viral, and fungal infections^{13,18,21,22}. It is in this context that CMV is hypothesized to influence the clinical course of hepatitis C after liver transplantation. Conversely, HCV is also known to possess immunomodulating properties, and accordingly, it has also been hypothesized that HCV-infected patients may be at a higher risk of CMV infection²³. Taken together, CMV and HCV may exhibit a bidirectional relationship that could lead to a cycle of virus-to-virus interaction.

During the last decade, the potential interaction between CMV and HCV after liver transplantation has been the focus of several investigations. In this article, we critically review the evidence supporting and refuting this proposed viral interaction.

Methods

Publications related to this topic were identified through a search of the PubMed database using various combinations of terms such as "liver transplantation", "CMV", "cytomegalovirus", "HCV", "hepatitis C virus", and "interaction". This search strategy yielded a total of 13 unique studies that have specifically addressed the interaction between CMV and HCV^{10-18,24-27}. A detailed review of the references cited in the articles identified during the primary search was also performed. Several studies have also assessed the interaction between HCV and other viruses (such as human herpes virus 6)^{8,12,13}; however, the focus of this review is on the CMV-HCV relationship.

Review of the clinical evidence

The first study describing the negative impact of CMV on hepatitis C was reported in

1997, when Rosen, et al. described that HCV-infected liver recipients with CMV viremia were significantly more likely to develop cirrhosis and graft failure²⁶. Since then, several studies have assessed the influence of CMV on hepatitis C (Table 1), and conversely, the impact of HCV on CMV (Table 2)^{8,10-16,18,24,25,28}.

All studies have a retrospective study design and, with one exception²⁵, described populations from single centers. Study populations were as few as 39 to as many as 358 HCV-infected liver recipients. Definitions of CMV as a predictor of outcome varied from serology¹¹ to nucleic acid detection by PCR^{12,25}, viremia by culture^{10,26}, phosphoprotein (pp)65 antigenemia^{8,18,24}, and clinical definitions¹². Likewise, HCV outcomes varied from recurrence of viremia¹⁶, to histologic evidence of hepatitis^{8,12,13}, fibrosis^{8,12,13}, and cirrhosis^{8,12,13}, to allograft failure^{10,12,24} and mortality^{10,12,24}.

Impact of cytomegalovirus on hepatitis C outcomes

Eleven studies assessed the impact of CMV on hepatitis C outcomes (Table 1)^{8,10-16,18,24,26}. The rate of CMV in these 11 studies ranged from as low as 6.8%¹⁵ to a high of 59%^{8,18}. Seven of these studies have suggested, by one measure or another, that CMV negatively influences the outcome of hepatitis C^{8,10,12,13,15,26}. On the other hand, four have indicated the lack of association between CMV and hepatitis C^{11,14,16,24}.

Hepatitis C virus viremia

Hepatitis C viremia persisted in all but a very few of HCV-infected liver recipients^{8,10-16,18,24-26}. Whether CMV influenced the degree of HCV replication has been investigated by few investigators^{12,13,16}. In a subgroup analysis of 18 HCV-infected liver recipients, including six who developed short-term CMV

viremia that was preemptively treated with ganciclovir, the HCV RNA level during the first 150 days after transplantation was not significantly different between patients with or without CMV DNAemia¹⁶. In a study of 92 HCV-infected liver recipients, HCV RNA appeared to be higher at 16 weeks, but not 52 weeks, after liver transplant among 23 patients who developed compared to those who did not develop CMV disease (mean \pm standard deviation, 55.71 \pm 50.47 vs. 33.52 \pm 47.03 mEq/ml; $p = 0.1034$), although this did not reach statistical significance¹². Likewise, HCV load at one and three months were not significantly affected by CMV load, infection, or disease in a cohort of 66 HCV-infected liver recipients¹³.

Recurrent hepatitis C

Recurrence of hepatitis C occurred in 47% to 62%¹³. Several studies demonstrated that CMV facilitated the occurrence of recurrent hepatitis C^{12,13,26}. In one study, recurrence of hepatitis C was similar during the first year between those with or without CMV viremia; however, the histologic severity (Knodell score), particularly with bridging necrosis, was significantly higher in patients with CMV viremia²⁶. In a second study, a non-significant trend was observed between CMV disease and the proportions of patients with severe hepatitis C recurrence (21 vs. 8%; $p = 0.14$)¹³. In a third study, a trend toward a higher histologic activity index at 16 weeks after transplantation was observed among patients with CMV disease (mean score \pm standard deviation, 3.9 \pm 2.8 vs. 2.8 \pm 2.4; $p = 0.06$)^{10,12}. In a fourth study, recurrent hepatitis C occurred earlier among CMV-infected compared to noninfected liver recipients¹⁸.

On the other hand, three studies indicated that the incidence of recurrent hepatitis C was not significantly different between CMV-infected and noninfected patients^{8,14,18}. While the onset of recurrent hepatitis C may be earlier in CMV-infected patients, its incidence was not

Table 1. Studies that assessed the impact of cytomegalovirus on hepatitis C virus infection after liver transplantation

Study No, Authors, Year	Study population and groups	Antiviral prophylaxis	Outcome
1 Rosen, et al. ²⁶ 1997	n = 43 Group 1: CMV viremia (n = 8) Group 2: no CMV infection (n = 35)	Acyclovir for 120 days or IV ganciclovir for 7 days followed by acyclovir for 120 days	Comparable time to HCV recurrence (143.4 ± 94.7 vs. 220.9 ± 48.2 days; p = 0.47) Similar incidence of histological HCV recurrence (7 of 8 [87.5%] vs. 23 of 35 [66%]; p = 0.4) Mean total Knodell score of final biopsy was greater in Group 1 (p = 0.016), especially with bridging necrosis (p = 0.009) Incidence of allograft cirrhosis (50 vs. 11%; p = 0.027) and graft failure due to HCV (37.5 vs. 5.7%; p = 0.034) was higher in Group 1
2 Teixeira, et al. ¹⁴ 2000	n = 39 Group 1: CMV infection (n = 18) Group 2: CMV negative (n = 21)	Preemptive therapy with IV ganciclovir for 14 days	Higher mild to moderate rejection in Group 1 than Group 2 No significant difference in fibrosis stage at one year after transplant (2.13 vs. 1.17, respectively) CMV did not influence incidence and grade of histologic outcome of HCV recurrence
3 Humar, et al. ¹³ 2002	n = 66 Group 1: CMV infection (n = 26) Group 2: No CMV infection (n = 40)	Oral ganciclovir prophylaxis x 12 w for CMV D ⁺ R ⁻ patients	CMV infection, disease and DNA load were not associated with HCV viral load at 1 and 3 months after transplant Trend towards higher incidence of CMV disease in patients with severe HCV recurrence (21 vs. 8%; p = 0.14) Fibrosis score greater in patients with CMV disease (mean 1.67 vs. 0.56; p = 0.016) and those with CMV infection (mean 1.03 vs. 0.50) compared to those without CMV infection or disease, respectively CMV disease was associated with severe fibrosis (44% of patients with CMV disease have fibrosis score > 3 vs. 7% in patients without CMV disease)
4* Burak, et al. ¹⁰ 2002	n = 93 Group 1: CMV viremia (n = 25) Group 2: No CMV viremia (n = 68)	Acyclovir x 4 w or ganciclovir x 8 w	Fibrosis score at 4 months was higher in CMV viremic patients (1.05 ± 1.14 vs. 0.45 ± 0.81) Fibrosis stage ≥ 2 at 4 months (45 vs. 16.4%; p = 0.01) after transplant is more common in CMV viremic patients CMV viremia was a significant independent predictor of graft failure (RR: 3.73; 95% CI: 1.65-8.45) HCV viral load (mEq/ml) was similar between the two groups (4.1 ± 4.6 vs. 3.0 ± 4.2; p = 0.26)
5* Razonable, et al. ¹² 2002	n = 92 Group 1: CMV disease and infection (n = 40) Group 2: No CMV infection (n = 52)	Acyclovir x 4 w or ganciclovir x 8 w	Patients with CMV disease and infection had higher fibrosis stage (mean, 0.87 vs. 0.43) and hepatitis activity index (mean, 1.0 vs. 0.5; p = 0.05) at 4 months after transplantation Non-significant trend towards higher HCV load at 4 months in patients with CMV disease (mean, 55.71 vs. 35.52; p = 0.10) Allograft failure and mortality was higher in patients with CMV disease (RR: 3.708; 95% CI: 1.638-8.396; p = 0.0017)
6 Singh, et al. ⁸ 2002	n = 51 Group 1: CMV viremia (n = 30) Group 2: No CMV viremia (n = 21)	Preemptive ganciclovir upon the detection of CMV viremia	HCV recurrence was comparable (50 vs. 42.8%) Patients who received oral ganciclovir had lower total Knodell score (mean 5.2 vs. 6.9; p = 0.05) and fibrosis scores (mean, 0.44 vs. 1.005; p = 0.12)

Table 1. Studies that assessed the impact of cytomegalovirus on hepatitis C virus infection after liver transplantation (continued)

Study No, Authors, Year	Study population and groups	Antiviral prophylaxis	Outcome
7 Chopra, et al. ¹⁵ 2003	n = 58 Group 1: CMV infection (n = 4) Group 2: No CMV infection (n = 54)	Not reported	Patients with CMV infection after transplant had a higher fibrosis progression rate compared with those without CMV (mean fibrosis-free survival, 29.0 vs. 53.0 months; p = 0.0004)
8 Ceccherini-Nelli, et al. ¹¹ 2003	n = 129	Not reported	HCV RNA persisted in all but one patient No association between CMV seropositivity and pp65 and recurrent hepatitis C after transplant
9 Firpi, et al. ²⁴ 2004	n = 358 Group 1: CMV antigenemia (n = 53) Group 2: No CMV antigenemia (n = 205)	Prophylaxis with oral ganciclovir x 3 months	Median fibrosis progression was 0.8 units per year. Equal distribution of CMV in patients with slow (< 0.8 units/year) and rapid (> 0.8 units/year) (14 vs. 13%) No significant association between CMV and long-term allograft survival or histologic evidence of cirrhosis
10 Singh, et al. ¹⁸ 2005	n = 133 Group 1: CMV infection (n = 36) Group 2: No CMV infection (n = 97)	Preemptive therapy with ganciclovir	Severity of HCV recurrence as assessed by Knodell score (5.8 ± 0.7 vs. 4.9 ± 0.4) or fibrosis score (0.94 ± 0.5 vs. 0.54 ± 0.1) was comparable Recurrent hepatitis C occurred earlier in Group 1 compared to Group 2 (median, 4.1 vs. 10.4 months; p = 0.037)
11 Nebbia, et al. ¹⁶ 2007	n = 69 Group 1: CMV PCR positive (n = 21) Group 2: CMV PCR negative (n = 48)	Preemptive therapy with ganciclovir or valganciclovir	HCV replication was not significantly different between the two groups One-year liver biopsies (in 56 patients, including 17 with CMV infection) did not show significant difference between the two groups in terms of histologic grade or stage

HCV: hepatitis C virus; CMV: cytomegalovirus; PCR: polymerase chain reaction; IV: intravenous administration.

*Study numbers 4 and 5 assessed the same patient population at a single center but were different in terms of CMV definitions (CMV viremia vs. CMV disease/infection). Study 5 also investigated the effect of human herpes virus 6 and 7 on HCV outcomes.

significantly different compared to patients without CMV (55.6 vs. 49.8%; p > 0.20)¹⁸. In another study of 39 HCV-infected patients who were monitored twice-weekly and treated preemptively for CMV reactivation, the occurrence of "preemptively treated" CMV viremia did not enhance the incidence and histologic outcome of HCV recurrence during the first year after liver transplantation¹⁴.

Allograft fibrosis

In several studies, CMV-infected patients were more likely to have a higher inci-

dence or degree of fibrosis progression compared to noninfected patients^{10,12,13,15,26}. In a study of 66 HCV-infected patients, liver recipients with CMV infection and disease developed higher fibrosis scores compared to those without CMV infection (1.67 vs. 0.56; p = 0.016)¹³. In this same study, the percentage of patients with severe fibrosis (scores > 3) was significantly higher in the CMV-infected compared to the noninfected group (44 vs. 7%; p = 0.009)¹³. These findings were mirrored in a second study, which demonstrated that fibrosis scores and the proportion of patients with severe fibrosis (score > 2) were significantly higher in HCV-infected liver

Table 2. Studies that assessed the impact of hepatitis C virus on cytomegalovirus infection after liver transplantation

Study No, Authors, Year	Study group	Antiviral prophylaxis	Outcome
1 Singh, et al. ²⁸ 1996	n = 100 Group 1: hepatitis C (n = 22) Group 2: No hepatitis C (n = 78)	Preemptive therapy with ganciclovir	Incidence of CMV disease was higher in patients with recurrent hepatitis C (32 vs. 9%; p = 0.12)
2 Humar, et al. ¹³ 2002	n = 66 Group 1: hepatitis C recurrence (n = 41) Group 2: No hepatitis C recurrence (n = 25)	Oral ganciclovir prophylaxis x 12 w for CMV D ⁺ R ⁻ patients (n = 6)	Median peak CMV viral load was not significantly different between Groups 1 and 2 CMV infection (37 vs. 44%) and disease (17 vs. 8%) was not significantly different between Groups 1 and 2, respectively Trend towards higher incidence of CMV disease in patients with severe HCV recurrence (21 vs 8%; p = 0.14)
3 Nebbia, et al. ¹⁶ 2007	n = 257 Group 1: HCV-infected patients (n = 69) Group 2: Non HCV-infected patients (n = 188)	Preemptive IV ganciclovir or valganciclovir for CMV DNAemia	No significant difference in CMV DNAemia frequency, maximum viral load, doubling time, AUC, decline rate after therapy, between HCV-infected and non HCV-infected groups
4 Humar, et al. ²⁵ 2007	n = 177 Group 1: HCV-infected patients (n = 60) Group 2: Non HCV-infected patients (n = 117)	Valganciclovir or oral ganciclovir prophylaxis for 100 days	Incidence of CMV disease (16.7 vs 27.4%; p = 0.11), CMV viremia (53 vs. 53%), and peak CMV viral load (median peak, 723 vs. 543 copies/ml) was not significantly different between HCV-infected and non HCV-infected groups, respectively

CMV: cytomegalovirus; HCV: hepatitis C virus; AUC: area under the concentration curve; IV: intravenous administration.

recipients who developed compared to those who did not develop CMV viremia (45 vs. 16.4%; p = 0.01)^{10,12}. A third study further demonstrated that patients with CMV had a more rapid fibrosis progression rate compared to those without CMV (mean, 29 vs. 53 months; p = 0.0004)¹⁵.

In contrast, several studies showed a lack of significant difference in the incidence, severity, and rate of fibrosis progression between patients with or without CMV^{16,18,24}. In a cohort of 69 HCV-infected liver recipients, short-term viremia treated preemptively with ganciclovir was not significantly associated with the stage of fibrosis at one year after transplantation¹⁶. In the largest study involving 358 patients, no significant difference was

observed in the histologic degree of cirrhosis between patients with or without CMV antigenemia²⁴. In addition, there were similar proportions of CMV-infected patients who developed slow and rapid progression of fibrosis²⁴.

Allograft failure and mortality

The CMV viremic liver recipients had a markedly diminished cirrhosis-free actuarial survival by Kaplan Meier estimates²⁶. In a cohort of 93 HCV-infected liver recipients, the incidence of allograft failure (defined as cirrhosis, relisting for liver transplantation, re-transplantation, or death) was significantly higher in patients with CMV viremia compared to non-viremic patients (52 vs. 19.1%; p = 0.002)^{10,12}. In

stratifying the patients, allograft failure developed in 48% of patients with CMV disease, 35% of patients with asymptomatic CMV infection, and 17% of patients without CMV infection^{10,12}. Even after adjusting for significant confounders such as donor and recipient age, year of transplantation, and use of mycophenolate mofetil in a stepwise multivariate model, CMV was an independent risk factor for allograft failure and mortality in HCV-infected liver recipients^{10,12}. In contrast to these findings, in a cohort of 358 patients, there was no significant difference in the long-term survival of patients who did or did not develop CMV pp65 antigenemia²⁴.

Impact of ganciclovir therapy

Anti-CMV preventive strategies in the 11 studies varied from prophylaxis²⁴ to preemptive therapy^{8,18} or a combination of both. Reflecting the evolution of clinical practice since 1990, the antiviral drugs for prevention of CMV varied from acyclovir^{10,12} to ganciclovir and valganciclovir²⁴. Hence, it has been difficult to assess the impact of anti-CMV therapy on hepatitis C outcomes. In one study, however, patients who received oral ganciclovir for preemptive treatment of CMV antigenemia had significantly lower Knodell scores⁸.

Impact of hepatitis C virus on cytomegalovirus infection and disease

Since HCV is an immunomodulatory virus that may impair cellular immune responses, HCV-infected patients may be more predisposed to develop CMV disease (Table 2). This concept was illustrated anecdotally in a report of two liver recipients who developed late-onset CMV disease, despite lacking traditional risk factors¹⁷. In possibly the first cohort study that evaluated this association, the incidence of recurrent major infections was higher in liver recipients with recurrent HCV

hepatitis compared to other patients (10/22 [45%] vs. 8/78 [10%]; $p = 0.005$), including a trend towards a higher incidence of CMV disease (32 vs. 9%; $p = 0.12$)²⁸. Three subsequent studies, however, did not observe this association. The median peak CMV load, and the incidence of CMV infection and disease was not significantly different in HCV-infected patients who did and did not develop recurrent hepatitis C, although a trend towards a higher incidence of CMV disease was observed in patients with severe recurrence of hepatitis C¹³. In comparing HCV-infected from non HCV-infected liver recipients, two studies found no significant differences in the incidence of CMV disease, viremia, and peak CMV load between the two groups^{13,16}. Compared to 188 HCV-negative liver recipients, the incidence of CMV DNAemia and CMV replication dynamics observed among 69 HCV-infected liver recipients was not significantly different¹⁶. These findings were reflected in a recent multicenter study wherein the incidence of CMV disease and CMV viremia, and the peak CMV load were not significantly different between HCV-infected and noninfected liver recipients¹³.

Discussion

This comprehensive review of published clinical reports highlights the evidence for and against the bidirectional relationship between CMV and HCV after liver transplantation. On the first issue of whether CMV facilitates hepatitis C recurrence and progression after liver transplantation, several studies have strongly argued that CMV was significantly associated with recurrent hepatitis C, time to and severity of HCV-induced fibrosis and cirrhosis, and allograft failure and mortality after liver transplantation^{10,12,13,15,26,28}. One study even observed that oral ganciclovir treatment of CMV viremia was associated with lower Knodell and fibrosis scores in HCV-infected liver recipients⁸. On the contrary, there were also

several studies that have refuted these findings by demonstrating the lack of significant association between CMV and hepatitis C outcomes^{11,14,16,24}. On the second issue of whether HCV influences CMV, one study suggested that HCV-infected liver recipients are at higher risk of CMV disease²⁸, while three other studies did not show increased risk of CMV in HCV-infected compared to non HCV-infected liver recipients^{16,25}.

So why the conflicting data? We can surmise that this likely reflects variations in study design, patient populations, and clinical variables. It is important to emphasize that each of the studies analyzed different outcomes. Some studies focused on viral factors such as viral load, time to recurrence, and doubling time, whereas other studies focused on liver histology such as fibrosis stage or hepatitis recurrence. Depending on the study, the consideration of CMV as predictor was indicated by serology, PCR detection, antigenemia assays, culture, and clinical measures. Likewise, the outcomes of interest ranged from HCV viremia to incidence and time to onset of recurrent hepatitis, fibrosis, cirrhosis, graft failure, and death. Immunosuppression and antiviral prophylaxis also varied greatly across studies. Even within the same study, different patients received varying regimens of medications, tailored to their specific needs as influenced by other factors such as CMV donor and recipient serostatus and immunosuppressive drugs. A patient receiving viral prophylaxis immediately after transplantation compared with a patient receiving prophylaxis once a viral reactivation was detected, could have significantly different outcomes. Patient populations varied among the different studies, introducing yet another factor that could lead to conflicting results. All these variables, together with many other confounders that may affect outcome, such as use of interferon therapy, are likely the reasons why there is such a contrast in the results.

The potential clinical relevance of the bidirectional relationship between CMV and HCV, however, should spur the conduct of large, prospective, multicenter trials that will address this issue in a standardized manner. If the association is proven, then one can provide mechanisms to prevent CMV (i.e. a correctable risk) in order to improve the outcome of liver transplantation for HCV. Undoubtedly, a thorough understanding of this relationship will not only benefit transplant recipients, but may be extrapolated to other populations including immunocompetent individuals. Indeed, in a study of 34,204 HCV-infected patients and 136,816 control subjects without HCV, CMV was observed more commonly in the HCV-infected group, even after excluding patients that were immunocompromised by AIDS and transplantation²⁷.

Despite the contrasting findings, the clinical benefits of preventing CMV cannot be ignored. In our view, since CMV is such a preventable confounder, one can strongly argue for the aggressive prevention of CMV in all HCV-infected liver recipients^{29,30}. In our center, we adapted the approach of antiviral prophylaxis to all HCV-infected liver recipients at risk of primary or reactivation CMV disease³¹. The observation that aggressive treatment of short-term CMV viremia resulted in lower Knodell scores among HCV-infected liver recipients underscores this approach^{8,18}.

In conclusion, a thorough understanding of the relationship between CMV and HCV is needed so that physicians will be able to better manage liver recipients and improve outcomes. Despite conflicting data from current studies, the morbidity outcomes associated with HCV-CMV interaction in several studies should warrant the aggressive prevention of CMV disease in at-risk HCV-infected liver recipients. Indeed, prevention of CMV disease is standard of care in every liver transplant recipient. In this context, we strongly suggest that an aggressive implementation

of CMV prevention strategy should be ensured for all HCV-infected patients.

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