

Hepatitis and HIV Coinfection

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Epidemiology

The parallel epidemics of HCV and HIV infection became inextricably intertwined as the incidence of intravenous drug use (IVDU) increased in the population of people infected with HIV. It is estimated that up to 240,000 people are now coinfecting with HCV and HIV in the U.S. (Sulkowski 2000b). While the prevalence of HCV infection among injection drug users (IDUs) is much higher than that of HIV infection, alarming increases in the number of people coinfecting with HCV and HIV continue to be reported. Studies of various populations worldwide report coinfection in 23% to 75% of IDUs (Dieterich 1999a; Matthews 2000; Sulkowski 2000b). A study of 213 HIV-positive people-of whom 35% were coinfecting-determined that people between ages 40 and 49 had the greatest risk of being found HCV-infected. No correlation was found with gender or race (Sherman 2000).

The presence of HIV infection can diminish the accuracy HCV antibody assays. There is an increased risk of receiving both false-negative and false-positive results from HCV screening antibody tests in people with HIV infection (Zylberberg 1996b George 2000). The current USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus recommend that positive screening antibody tests for HCV in people with HIV should be confirmed with either the recombinant immunoblot assay (RIBA) or an HCV RNA test. In addition, it is recommended that HIV-positive people with undetectable HCV antibodies, but evidence of unexplained chronic liver disease, should have an HCV RNA test performed (CDC 1999).

Natural History of HCV/HIV Coinfection

Almost all studies of people coinfecting with HCV and HIV have reported that, while the progression of HIV disease is not strongly influenced by HCV infection, hepatitis C progresses more rapidly in people with coinfection (Wright 1994; Sánchez-Quijano 1995; Zylberberg 1996b; Soto 1997; Piroth 1998; Staples 1999). Most of the above studies show that people with HCV/HIV coinfection experience a faster progression to cirrhosis, and have evidence of more extensive liver damage (García-Samaniego 1997). Staples compared time from HIV diagnosis to AIDS, time from diagnosis of HIV to death, and time from diagnosis of AIDS to death, in 350 people, of whom 33% were HCV/HIV coinfecting, and found that HCV coinfection did not adversely impact any of those measurements (Staples 1999). A study of 111 HCV/HIV hemophiliacs, infected between 1979 and 1985, reported that people infected with HCV genotype 1 experienced a more rapid progression to AIDS and AIDS-related death (Sabin 1997).

When matched for other variables, on average, people who are HIV-positive have higher levels of HCV RNA than HIV-negative people (Eyster 1993, 1994; Cribier 1995; Thomas 1996; Beld 1998; Bonacini 1999). However, Cribier did not find a correlation between HCV RNA and either CD4 count or HIV RNA copy number, suggesting that there is no "direct interaction between HCV and HIV."

Relationship between HCV RNA and HIV Stage							
HIV Stage	A1	A2	A3	B2	B3	C2	C3
Number	3	19	7	10	26	1	9
% HCV RNA+	67	84	100	90	96	0	100
Mean HCV RNA (X10 ⁵)	149.5	174.6	196.9	120.5	125.5	-	83.8
(Cribier 1995)							

TABLE XX: Relationship between Serum and Hepatic HCV RNA and HCV/HIV			
	HCV	HCV/HIV	P-value
Serum HCV RNA (log copies/mL)	6.2	6.7	0.02
Liver HCV RNA (log copies/ig)	2.19	2.90	0.04
(Bonacini 1999)			

Some researchers recommend that HCV be thought of as an opportunistic infection in people with HIV because of a more rapid progression to death due to liver disease associated with HIV coinfection. Although, they note that it remains to be seen if highly active antiretroviral therapy (HAART) and suppression of HIV RNA will lower the incidence of progressive liver disease in people with HCV/HIV coinfection (Lessens 1999; Sulkowski 2000b). The following factors were shown to be associated with the higher liver fibrosis progression rate observed in HCV/HIV coinfecting people: low CD4 count, higher alcohol consumption, and age at HCV infection (>25 years old) (Benhamou 1999b).

Two major limitations exist, however, in the above data. First, the sequence of acquisition of HCV and HIV may affect the prognosis of each. HCV is much easier to transmit through parenteral exposure than is HIV, such as when sharing needles. Thus, it is possible that many people first become infected with HCV, and then, at a later date, become HIV-infected. One report showed that when a person acquired HCV and HIV simultaneously, it took much longer than normal for that person to develop antibodies to both HIV (8-9 months) and HCV (9-13 months). This person, a health care worker, had rapid progression to hepatic failure and death (Ridzon 1997); however, a subsequent report detailed another person who was simultaneously infected with HIV and HCV, who had developed antibodies to both at the expected time (one month for HIV, and four months for HCV), who was symptom-free four years later (Biron 1997). Most studies of HCV/HIV coinfecting people, however, do not report data based on the sequence of acquisition.

Second, the majority of the data about prognosis are from the pre-HAART era. There is a suggestion that HAART may alter the rapid progression of HCV, so that HCV disease progression may be closer to that observed in HIV-negative people when people are on HAART (Benhamou 1999a). Tor studied liver biopsies in 162 HCV/HIV coinfecting people on HAART who had stabilized HIV disease, and did not find any differences in liver inflammation and fibrosis, compared to age-matched HIV-negative, HCV-infected people (Tor 2000). Thus, as the immune system recovers on HAART, people with HIV infection may be able to "control" HCV, or at least live a longer time, before developing clinically significant liver damage. Much more research is acutely needed in this area; however, as discussed in the HCV pathogenesis section of this report, our understanding of mechanisms of immunologic response, liver damage, and potential control of HCV is very limited at this time.

The few studies which suggest that HCV progression is slowed in people on HAART, or protease inhibitors, have very serious limitations (see the "Treatment of Hepatitis C Virus" chapter). There is a great deal of patient selection when comparing a group of people who are on HAART to people not on HAART in any retrospective, non-randomized study. Active substance use, poor compliance, HIV RNA (viral load), CD4 (T helper) cell counts, coexistent mental illness, insurance, socioeconomic status, and other factors may contribute to the worse prognosis of HCV. None of the currently available studies provide enough comparative data to assess the comparability of these factors in the people treated with HAART compared to the people not treated with HAART. There is an urgent need for studies to address this critical issue, as it has a direct bearing on how aggressively HIV should be treated in HCV/HIV coinfecting people.

It is also unknown whether people with HIV more easily acquire HCV, and conversely, whether people with HCV more easily acquire HIV. There appears to be a much higher rate of sexual acquisition of HCV in HIV-positive men who have sex with men than in HIV-negative

heterosexuals (see section on HCV transmission). One prominent researcher I interviewed believes that having herpes lesions may greatly increase the risk of HCV transmission through sex; this may be a factor explaining the preceding observation.

Treatment of HIV in People Coinfected with HCV and HIV

In many clinics, HIV is under treated in people with HCV and HIV infection. This is in part due to unjustified fears about using protease inhibitors (PIs) in people with HCV.

While there are some legitimate concerns about the potential increased liver toxicity of PIs in people infected with HCV, several studies, as reviewed below, now show that people coinfecting with HCV/HIV can be safely and effectively treated with HAART.

Possible Mechanisms by Which HAART May Worsen Liver Function Tests in People with HCV

- PIs may cause additional direct liver toxicity or elevated plasma levels in people with HCV.
- The "immune reconstitution syndrome" may worsen the liver damage associated with HCV infection.
- HAART may result in increased production of HCV RNA.

In the first scenario, PIs may be more hepatotoxic in people with HCV, either due to elevated blood levels of the PIs, or enhanced toxicity at normal blood levels. Rutschmann reported transient increases in HCV RNA and liver enzymes in a study of 19 HCV/HIV coinfecting people treated with PIs (nine on ritonavir, seven on indinavir, three on ritonavir plus saquinavir). However, HCV RNA values returned to pretreatment levels within 17-32 weeks (Rutschmann 1998). Zylberberg and colleagues treated 22 HCV/HIV coinfecting people with HAART. (The regimens contained indinavir in 19 people, ritonavir in 2, and saquinavir in 1.) They observed no significant changes in liver enzymes or HCV RNA over a mean follow up of nine months; however, they did not perform serial liver biopsies to assess potential liver changes associated with the increased CD4 cells and decreased HIV RNA (Zylberberg 1998a). Another recent report studied 22 patients with HCV/HIV coinfection and found that after 24 months of HAART, 20/22 people had undetectable HIV RNA, but that there was no significant change in HCV RNA levels, although 3 patients had a transient increase in HCV RNA (Albizreh 1999).

Sulkowski observed increased liver toxicity with ritonavir in HIV-positive people, compared to other protease inhibitors. The increased liver toxicity seen in this series and associated with ritonavir use may have been partly due to a higher incidence of people with HCV (52%) in the study. The rate of severe liver toxicity with the use of PIs in people with HCV infection was 12.2% (Sulkowski 2000c).

Hepatotoxicity (grade)	Ritonavir	Other PI	NRTI*
0	33%	55%	63%
1 or 2	34%	36%	30%
3 or 4	32%	9%	7%
* NRTI = nucleoside reverse transcriptase inhibitor			

Sulkowski, however, concluded that:

Although hepatotoxicity may be more common in persons with chronic viral hepatitis, these data do not support withholding protease inhibitor therapy from persons coinfecting with hepatitis B or C virus. (Sulkowski 2000c)

There are also some reports of increased toxicity of nucleoside reverse transcriptase inhibitors (RTIs) in people with HCV/HIV coinfection. One retrospective review of 61 people reported that 39% had some evidence of increased liver toxicity of RTIs, defined as at least a doubling of serum alanine aminotransferase (ALT) and a 50% decrease within 14 days of stopping the drug (Hernandez 1999).

Additionally, there are some data demonstrating that blood levels of PIs may vary significantly in people with HCV, suggesting that therapeutic drug monitoring (TDM) may be useful in this population. Ritonavir levels have been shown to be higher in HIV-infected people with underlying liver disease, possibly necessitating a lower dose (Hsu A, 1998). Zilly observed that while HAART was generally well tolerated in people with HCV infection, there was a wide variation in blood levels of ritonavir, saquinavir, and indinavir. He recommended the use of TDM, or measuring of PI blood levels, to determine the correct dosing in people with chronic liver disease (Zilly 1999). The second possible mechanism by which HAART may worsen liver function in HCV/HIV coinfecting people is via an immune reconstitution syndrome, associated with increased CD4 cells, as is seen in some people with prior TB, MAC, and CMV infection when HAART is begun. The immune reconstitution syndrome can result in a transient flare, or worsening, of symptoms at sites of infection with tuberculosis (TB), mycobacterium avium complex (MAC), cytomegalovirus (CMV), herpes simplex viruses 1 and 2 (HSV-1 & HSV-2), and varicella zoster virus (VZV) (Sepkowitz 1998; Freeman 1988). This flare is due to increased immune activity at sites of prior infection, not reactivation of the infection itself. Since at least some of the liver damage from HCV infection is due to the immune reaction to HCV, the strengthened immune system could worsen the hepatitis. (See the "[HCV Pathogenesis](#)" chapter for a review of the evidence supporting the premise that the immune response is, in part, the cause of liver damage in people with HCV infection.)

John and colleagues studied three HCV/HIV coinfecting people who developed acute hepatitis when a PI-containing HAART regimen was begun. The hepatitis did not correlate with changes in HCV RNA, and liver biopsy was suggestive more of an HCV immune-mediated response rather than of PI toxicity; however, cellular immune responses to HCV were not studied in these people (John 1998). A French group reported that the increased liver enzymes occurring in people on HAART were due to the enhanced immune response in people who had HIV RNA levels below the limit of detection, and that the changes in liver enzymes did not correlate with changes in HCV RNA values (Gavazzi 1999). Another French group, however, reported a 2.5% (5/206) incidence of PI-associated hepatitis which they could not correlate with immune reconstitution, changes in HCV RNA levels, CD4 counts, or specific PIs (Zylberberg 1999).

The third possible mechanism by which HAART may worsen liver function in HCV/HIV coinfecting people is that HAART may cause increased HCV RNA production, which is observed in some people (Vento 1998). How often this occurs, and why it occurs, is not known. It is also not known whether there is enhanced liver damage as a result of the increased HCV RNA. It seems counterintuitive that improving the strength of the immune system would result in a greater production of hepatitis C virus. Mir observed that people on both PI-containing and non-PI-containing anti-HIV therapy had higher levels of HCV RNA than HCV/HIV coinfecting people not on HAART (Mir 2000). Also, there are anecdotal reports of people with non-detectable HCV RNA prior to HAART experiencing significant increases in HCV RNA soon after administration of HAART. Since this phenomenon is observed fairly early after the initiation of HAART, there may be some direct interactions with HAART and HCV that are not currently understood. These phenomena have not been well studied in clinical settings.

There are also data suggesting that immune system recovery associated with HAART may also improve the ability of the immune system to control HCV replication and the resultant liver damage. Benhamou and colleagues reported that projected rates of liver fibrosis, or scarring, decreased significantly when PI therapy is used to treat HIV. Patients who received PI-containing HAART had a lower fibrosis progression rate. This report is limited due to being a retrospective study, with potential selection bias in terms of which patients were thought healthy enough to receive PI-based regimens, as well as some questions about the linear model used to project

liver fibrosis progression rates. It is not at all clear why PI-based HAART regimens would result in less fibrosis, compared to non-PI-containing HAART regimens, which are equally effective at suppressing HIV RNA and improving CD4 cell counts. Nonetheless, these reports suggest that the treatment of HIV with HAART may reduce HCV progression rates and liver fibrosis (Benhamou 1999a; Bochet 2000).

The unjustifiable exclusion of people with HCV from many HAART trials has resulted in an unacceptable lack of data to address the above issues. As a result of this exclusion, important leads into the mechanisms of the immunologic and non-immunologic control of HCV replication, and the mechanisms by which HCV actually causes liver damage and fibrosis, have not been pursued. There are a considerable number of ways in which people with HCV have been excluded from many HAART trials, including: outright exclusion of people who have HCV infection; unnecessary limitations on pretreatment liver function test abnormalities; unnecessary exclusion of many active substance users/abusers; inaccurate perceptions about the suitability of HCV/HIV coinfecting people as study candidates; and, exclusion of people on methadone. Unless there is a scientifically valid reason to exclude people with HCV infection from HAART trials, they should be included.

Treatment of HCV in People Coinfected with HCV and HIV—General Considerations

In many clinics, HCV infection in HIV-positive people is rarely treated. Many hepatologists and pharmaceutical companies have chosen to focus HCV trials exclusively on HIV-negative people. This is due, in part, to the perception that: 1) HCV is more difficult to treat in HIV-positive people; 2) toxicities (namely hematological) will be greater in HIV-positive people; and 3) HIV-positive people have a shortened life expectancy and deaths on a study (even due to HIV-related causes) would tarnish study results. Thus, pharmaceutical companies are reluctant to test new therapies in people in which they fear their product may not perform very well.

Another problem in treating HCV/HIV coinfecting people is that there does appear to be some potential for increased toxicity due to ribavirin (RBV) in people who are HIV-infected (see below.) Some studies have reported significant rates of anemia and decreased CD4 counts in people treated with interferon (IFN) and RBV. It is unclear if this may be a result of HIV infection itself, enhanced toxicity due to some drugs used in HAART regimens, or too high a dose of RBV. Due to some early bad toxicity experiences, some clinicians are reluctant to treat HIV-positive people with IFN and RBV; however, several studies have now demonstrated that many people do well with this treatment regimen, as discussed below.

One researcher interviewed said that he had been involved in a dosing study conducted by Schering which was never published because they believed it showed that RBV at a dose as low as 600 mg was equally effective to the high doses currently recommended. If this is so, TAG believes that this is reprehensible, in that people may be needlessly exposed to potentially life-threatening toxicities so that a company can increase its profits. We call on Schering to make public all significant unpublished data they have from RBV-dosing trials ever conducted.

There is a critical need for much larger trials to be conducted on the treatment of HCV in the HCV/HIV coinfecting population. Unresolved questions (among many) that need to be addressed include: What is the lowest effective dose of RBV? What is the possible clinical impact of decreased CD4 cell counts? and Which HAART regimens are best when combined with HCV therapy?

Additionally, as trials yield data for HIV-negative, HCV-infected people and resolve the issues around IFN induction dosing, IFN daily dosing, the influence of HCV genotype, the efficacy of RBV with consensus and pegylated interferons, the efficacy of amantidine with IFN, etc., additional trials need to be conducted in HCV/HIV coinfecting people to determine if the results are applicable to this population. **TAG recommends that HCV treatment trials stratify for HIV-infection and enroll both HIV-positive and HIV-negative people in all ongoing and future HCV trials in order to gather these critical data simultaneously.**

Funding for such trials, however, is unlikely to be provided by industry, and local institutions have not shown much interest in conducting HCV therapy trials in HCV/HIV coinfecting people. There is a need, therefore, for federally provided funding, either through the R01 process, or through the establishment of an HCV/HIV clinical trials network to support such trials. Both NIAID and NIDDK should share in the funding of such mechanisms. To date, none of the NIAID-funded HIV clinical trials networks have shown much interest or ability in conducting trials in HCV/HIV coinfecting people in a timely manner.

Treatment of HCV in People Coinfected with HCV and HIV-Specific Trials

All of the major IFN trials, and subsequent trials with IFN plus RBV, excluded people who were HIV-positive. Thus, there are much fewer data on how to treat HCV in HCV/HIV coinfecting people. As discussed above, there simply is no scientific basis upon which to exclude people with stable HIV infection from HCV trials. Rapid pharmacokinetic (PK) or blood-level studies could be done to determine any potential adverse interactions among HCV investigational agents and HAART drugs in HCV/HIV-negative volunteers. The PK studies could also be done in real time on the first people to enroll in a new trial. In general, the response to IFN appears lower in HCV/HIV coinfecting people, and not enough data are yet available to determine comparable response rates with IFN plus RBV.

IFN Monotherapy Trials in HCV/HIV Coinfected People			
Study	ETR	SR (6 months)	Comments
Aguilar 1992	21/41 (52%)	-	
Boyer 1992	4/12 (33%)	1/12 (8%)	IFN 3-5 MU tiw* X 4-6 mos.
Nardiello 1992	9/21 (45%)	27%	IFN 3 MU tiw X 6 mos.
De Sanctis 1993	-	5/20 (25%)	IFN 3 MU tiw X 18 mos.
Marriott 1993	5/9 (56%)	4/9 (44%)	IFN 9 MU Daily X 3 mos., then 6 MU Daily (Only 9/14 completed therapy)
Spanish Group 1993	4/18 (22%)	-	IFN 3 MU tiw X 3 mos., then 5 MU tiw X 9 mos.
Linarcs 1994	9/17 (54%)	-	IFN 3 MU tiw X 6 mos.
Garcia-Samaniengo 1994	38/88 (43%)	-	IFN 5 MU tiw X 3 mos., then 3 MU tiw X 9 mos.
Del Pozo 1994	43/79 (54%)	-	IFN 5 MU tiw X 6 mos.
Marcellin 1994	6/20 (30%)	3/20 (15%)	IFN 3 MU tiw X 6 mos.
Mauss 1995	3/9 (33%)	2/9 (22%)	IFN 5 MU tiw X 6 mos.
Pol 1995	7/31 (23%)	0%	IFN 3 MU tiw X 6 mos.
Soriano 1995, 1996	26/80 (33%)	18/80 (22.5%)	IFN 5 MU tiw, for 3-12 mos.
Boldorini 1997	-	1/12 (8%)	No cirrhosis on follow-up
Mauss 1998	8/17 (47%)	5/17 (29%)	Only 1 completed 4 mos. of therapy
Coll 1999	19/43 (44%)	5/43 (12%) (10 had a "sustained biologic	IFN 5 MU tiw, for 6 mos.

		response")	
ETR = end of treatment response; SR = sustained response, tiw = thrice weekly			

The variables that correlated the best with response to IFN in almost all of the above studies were a higher CD4 count and genotypes other than genotype 1. In Mauss's study, the average CD4 count of responders was 525, versus 245 in non-responders (Mauss 1998). In Coll's study, the sustained virologic response rate was 11.6% in HIV-positive people versus 21.8% in HIV-negative people. They noted, however, that an additional five HIV-positive people had a "sustained biologic responses," which was similar to the rate in HIV-negative people: 23.2% versus 24.4%, respectively (Coll 1999).

Anti-HIV Effects of IFN and RBV

Concerns have been raised about the potential effects of IFN therapy on HIV replication. There were several studies of both oral and subcutaneous IFN to treat HIV prior to the HAART era. Low-dose oral IFN has not been shown to have any benefit for treating HIV infection in all but one study (Katabira 1998; Wright 1998; Alston 1999). One, pre-HAART, non-blinded study reported a survival advantage in non-AIDS, HIV-positive people (Rivero 1997). Likewise, subcutaneous IFN has not been shown to have any benefit on CD4 counts or changes in HIV RNA (Fischl 1997; Krown 1999). In the above-mentioned studies of injectable IFN, the increased toxicities included fatigue, muscle pain, and anemia. Marriott's 1993 study of IFN in HCV/HIV coinfecting people included only people who were asymptomatic with regard to their HIV infection. There was a transient decrease in CD4 counts in people with counts above 400, and there was no change in CD4 counts in people with CD4 counts below 400. None of the people in Marriott's study developed detectable p24 antigen (the much less sensitive precursor test to RNA PCR to detect HIV in the blood) (Marriott 1993).

There have been a few trials of RBV to treat HIV infection using doses ranging from 600 mg to 1,000 mg/day. These trials showed that there was no change in CD4 counts, total lymphocyte counts, p24 antigen levels, or CD4:CD8 ratios compared to placebo (Spanish Ribavirin Trial Group 1991; Ribavirin ARC Study Group 1993). The most prominent adverse side effect observed in these trials was a mild, reversible hemolytic anemia.

Based on the increased efficacy of combining IFN with RBV in HIV-negative people infected with HCV, small pilot studies have been conducted with this combination in HCV/HIV coinfecting people. There are a few concerns about the safety of RBV in HIV-positive people. The most common of these concerns are the potential for increased toxicity-especially hemolytic anemia (destruction of red blood cells)-and a potential adverse interaction between RBV and some anti-HIV drugs, particularly zidovudine (AZT, or Retrovir™), 3TC (lamivudine, or Epivir™), and d4T (stavudine, or Zerit™). RBV potentially decreases the intracellular activation of zidovudine, stavudine, and lamivudine (Baba 1987; Vogt 1987; Hoggard 1997; Kewn 1997); however, some early data conclude that this is not of clinical significance (Zylberberg 1998b). There is also some evidence that RBV may enhance the anti-HIV effect of ddl (Videx™) (Balzarini 1991), though more in-depth studies are needed to address these concerns.

IFN Plus RBV Trials in HCV/HIV Coinfection			
Study	End of Treatment Response	Sustained Response (@ 6 Months)	Comments
Landau 1999	10/20	7/20	RBV 500-600 mg bid*, Genotype 3a had the best response
Dieterich 1999b	4/8 @ 3 mos. 5/7 @ 6 mos.	-	19/21 people were on HAART, anemia in 5/21, five discontinued therapy
Sauleda	6/20	-	IFN 3 MU tiw, RBV 800-1,200 mg/day X 6 mos.

1999			Hemoglobin decreased from 15 to 13.4 gms/dl.
Weisz 2000	3 log decrease in HCV RNA	-	IFN 3 MU tiw, RBV 800-1,000 mg/day (11 patients). Compared to IFN alone (ten patients), there was a decrease in CD4 count of 300, anemia in 5/11 with RBV
Perez-Olmeda 2000	6/11	5/11	IFN 3 MU tiw, RBV 1000-1200 mg/day. All had previous IFN Rx. Seven patients discontinued therapy.
# All patients were hemophiliacs * bid: twice daily			

While the addition of RBV to IFN increases the probability of HCV RNA suppression, it also increases the risk of anemia; however, the anemia tends to respond well to both decreasing the RBV dose and to administration of erythropoietin (EPO) by injection (Weisz 2000; Dieterich 1999b).

Other HCV/HIV Coinfection Trials			
Study	Agents	End of Treatment Response	Sustained Response (@ 6 Months)
Wensing 1999	IFN plus Amantadine	1/3	-
Schlaak 1999	Interleukin-2 (1-2 MU/day)	0/7	2/7 (Occurred after cessation of IL-2)

No studies have been conducted using pegylated-interferon, with or without RBV, in HCV/HIV coinfecting people, though there are several trials planned to begin soon which will evaluate consensus IFN or pegylated-interferons, with and without RBV, in coinfecting individuals.

Timing of HIV and HCV Therapy in Coinfected People

Most clinicians interviewed by TAG recommend that in HCV/HIV coinfecting people, HIV therapy be initiated first. While it is true that most trials have shown that people with higher CD4 cell counts respond better to HCV therapy, there has not yet been a randomized study comparing simultaneous versus sequential therapy. Following good suppression of HIV RNA and some immune reconstitution, the need for treatment of the HCV should be reevaluated. Mark Sulkowski suggested treating HCV in coinfecting individuals when one or more of the following conditions exists:

- Stable HIV with good CD4 counts, where it may be possible to eradicate HCV
- Advanced liver disease, such as cirrhosis, where treatment may slow the progression of HCV liver damage
- Recurrent liver toxicity when HIV treatment is administered. (Sulkowski 2000a)

According to Douglas Dieterich:

Overcoming the therapeutic nihilism toward chronic hepatitis C in HIV-positive patients remains the greatest obstacle for those patients who are co-infected....Lowering the viral load with anti-HCV therapies can only benefit

patients by improving liver disease, and may permit the addition of protease inhibitors, which will certainly prolong the patient's life. (Dieterich 1999a)

Hepatitis A and B Vaccination for HCV/HIV Coinfected People

Vaccination for hepatitis A and B is strongly recommended for people coinfecting with HCV and HIV (CDC 1996). People with chronic liver disease can have fulminant hepatitis when infected by hepatitis A (Akriviadis 1989). In one study of 17 patients with HCV infection who acquired hepatitis A infection, seven (41%) developed fulminant hepatitis, and six (35.3%) died (Vento 1998).

There is a decreased response to the HBV vaccine after standard HBV vaccination in people infected with HIV, as measured by the amount of antibody produced to HBsAg, anti-HBs. The standard HBV vaccination program consists of three injections. Doubling the standard course in people with suboptimal production of anti-HBs (<10 units), has been shown to increase the response rate from 55% to 90%. Most of the observed increases in HIV RNA following HBV vaccination were transient (Rey 2000). It is very important that levels of anti-HBs are measured periodically after HBV vaccination in people with HIV to assure adequate protection from future HBV infection.

Liver Transplantation for HCV/HIV Coinfected People

Until very recently, only the University of Pittsburgh had performed any liver transplants for people who had liver failure and/or cirrhosis from HCV who were also HIV infected. Historically, the refusal of almost all transplant centers to perform liver transplants in this population was justified due to the very poor prognosis due to HIV infection. With the advent of HAART, however, this blanket exclusion is no longer justifiable. Now many transplant centers offer the rather weak justification that the safety of immunosuppressive drugs in HIV-infected people is not known. Several hepatologists, off the record, told TAG that they believe a major reason for many transplant centers' refusal to perform liver transplants on HCV/HIV coinfecting people is that the transplant surgeons at their institutions do not want operate on people who are HIV-positive.

While it is true that there are very limited data available on the use of immunosuppressive therapy in HIV-positive people, there is only one way to gather such data. Just Do It! The outcome of not performing transplantation in a person who is dying of liver failure is certainly well known. At the University of California-San Francisco (UCSF), the most common cause of death now in their HIV clinic is liver failure due to HCV (Wright 1999). With HAART, the risks of immunosuppression post-transplant probably will not be significantly different than in the HIV-negative HCV transplant population. **There simply is no scientific justification for the continued blanket refusal of most transplant centers in the U.S. to consider HIV-positive people for liver transplantation.**

UCSF has obtained \$1 million funding from the state of California to perform a limited number of liver transplants in people who are HIV infected; however, these patients will only have access to "low viability" livers (i.e., those rejected for transplantation in HIV-negative people) (Wright 1999; Wickware 2000). In addition, John Fung, of the University of Pittsburgh, where six HIV-positive people have already received kidney transplants, has submitted a protocol to the NIH to study liver transplantation in HCV/HIV coinfecting people (Wickware 2000).

National leadership, advocacy, and perhaps some creative lawyering are needed to address this ongoing discriminatory policy at most major transplant centers.

Obstacles to Treatment (Demographics, Local Communication, and Institute Factors)

Rarely are infectious-disease physicians and hepatologists in the same clinic. People are frequently bounced back and forth between HIV clinics and liver clinics, with each physician saying, "When your other infection is under control, then I will treat you." In other words, "You go first," with the result that the person receives treatment for neither HIV nor HCV. There is an urgent need for much better communication and interaction between infectious disease providers and hepatologists; ideally, both seeing the HCV/HIV coinfecting person together. Because there

have been so few trials of treatment for HIV and HCV, there are few data on which to make any recommendations regarding whether treatment should be initiated in stages, which viral infection should be treated first, or whether treatment should begin simultaneously. Such a treatment-strategy trial is desperately needed.

At the national level, there are overlapping interests at the National Institutes of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes, and Digestive and Kidney Diseases (NIDDK) contributing to the lack of conduct of clinical trials in the HCV/HIV coinfecting population. People in leadership positions at both institutes feel that their institute should be have control over the design and funding of clinical trials for HCV/HIV coinfecting people.

Clearly, there are some "turf" issues at both the local and national levels that need to be promptly resolved so that the trials necessary to address the complex challenges of treating the HCV/HIV coinfecting person can be funded and conducted.

Hepatitis B Virus (HBV) and HIV Coinfection Hepatitis B Virus (HBV) and HIV Coinfection

There is relatively little medical literature that addresses the natural history and treatment of HBV/HIV coinfection, and almost none that deals with the management of HBV/HCV/HIV coinfecting people. In one study, however, HIV infection was shown to result in a higher rate of HBV replication and a higher risk of cirrhosis in people with HBV/HIV coinfection (Colin 1999). This study included only homosexual men with no HCV infection, no prior therapy for HBV, and no history of intravenous drug use.

Characteristics Associated With Cirrhosis	
	R Relative Risk of Cirrhosis
HIV-positive	4.21
Age (per year)	1.14
Alcoholism	7.08
Duration of HBsAg positivity	1.08
HBeAg positivity	0.20
(Colin 1999)	

The rate of progression of HIV does not appear to be significantly influenced by HBV infection. However, the rate of spontaneous conversion from HBeAg to anti-HBe appears to be lower in HIV-positive people (Gilson 1997). In a study of hemophiliacs coinfecting with HBV and HCV, HIV infection was associated with a dramatic increased risk of end-stage liver disease (ESLD), which developed in over twice as many HIV-infected people, compared to HIV-negative, HBV/HCV coinfecting hemophiliacs (Ragni 2000). The above studies do not reflect the potential impact of HAART on the adverse effects observed associated with HBV/HIV and HBV/HCV/HIV coinfection. Whether HAART will minimize, or reverse, the poorer prognosis of HBV and HCV infection associated with HIV coinfection remains to be determined.

Effect of HIV on HBV/HCV Coinfecting Hemophiliacs		
	HIV-Negative	HIV-Positive
ESLD at age <38	0/7	6/12
Overall ESLD	7/107 (6.5%)	12/92 (13.5%)
Time to ESLD since HIV infection	7.5 years (median)	

Treatment of HBV in HBV/HIV Coinfected People

Nucleoside Analogues

Currently, there are relatively few treatment options for chronic HBV infection in HBV/HIV coinfecting people; however, some anti-HIV drugs, the nucleoside analogues, also have the ability to suppress HBV replication, at least for some period of time. These drugs include 3TC (lamivudine, or Epivir™) and adefovir (Preveon™).

HBV develops resistance to 3TC frequently in HBV/HIV coinfecting people (Dore 1999; Wolters 1999; Batisse 1999; Benhamou 1999c; Batisse 2000). The most common mutation seen associated with HBV resistance to 3TC is at the 550 position, in the YMDD region of HBV DNA polymerase gene (Batisse 2000; Benhamou 1999c; Thibault 1999).

Response to Lamivudine in HBV/HIV Coinfected People and the Development of HBV Resistance			
	HBV DNA Response	Resistance Development	Follow-up Period
Dore 1999	Median 2.7 log decrease in HBV DNA	-	52 weeks
Benhamou 1999	57/66-HBV DNA undetectable after 2 mos., 47% after 2 years, 9% after 4 years	20% per year	-
Batisse 2000	44/44-HBV DNA undetectable after 6 months	11/44	18 months (mean)

Several reports have documented a worsening of HBV infection in HBV/HIV coinfecting people when either HBV resistance developed to 3TC, or 3TC was discontinued (Altfeld 1998; Wolters 1999; Bessesen 1999). Altfeld described a person who had a worsening of HBV when lamivudine was stopped. Wolters reported two people treated with lamivudine who had a worsening of their HBV infection; one with the developed resistance to lamivudine, and the other when lamivudine was stopped. Bessesen described five people who had flares in their HBV infection when either lamivudine was stopped, or resistance to lamivudine developed. It is not clear from these few case reports if there is any benefit to continuing lamivudine once HBV resistance has developed; i.e., is there any clinical benefit from drug pressure that results in a less fit virus, as has been suggested with people with multidrug-resistant HIV?

Longer follow-up data are needed to determine the importance of both immune restoration and HBV mutations on cirrhosis incidence and clinical end-points. Studies are needed to assess whether combinations of new nucleoside analogues would be more effective than lamivudine monotherapy for long-term suppression of HBV replication in both HIV-infected and non-HIV-infected patients. (Benhamou 1999c)

These important concerns need to be addressed in clinical trials, as HBV and HIV resistance to lamivudine frequently develops, and it may be dropped out of secondary or tertiary HAART regimens.

Adefovir (Preveon™), a nucleotide analog, has been discontinued, by Gilead, from further development as a treatment of HIV in the U.S. due to problems with renal toxicity at doses of 60 mg and 120 mg a day. (On November 1, 1999, the FDA Antiretroviral Drug Advisory Committee voted not to recommend Gilead's application for accelerated approval of adefovir, at the requested dose of 60 mg a day, for the treatment of HIV.) Adefovir does, however, appear to inhibit HBV replication at doses of 30 mg, or possibly even lower. There is one 28-day adefovir trial involving 20 HBV/HIV coinfecting people; 15 received 125 mg of adefovir a day, and 5 received a placebo (Gilson 1999). HBV levels fell in all people receiving adefovir, but rose after

the drug was stopped, following the 28-day study period. Trials are ongoing to evaluate adefovir for the treatment of HBV, investigating dosing, long-term safety, and efficacy. Eison has reported a person who had HBV/HIV coinfection, with HBV resistant to 3TC, who subsequently had good HBV suppression on the combination of adefovir and abacavir (Ziagen™) for 22 weeks of follow-up (Eison 1999).

Another anecdotal report detailed resolution of chronic HBV infection after treatment of HIV with a ritonavir-containing regimen, though it is difficult to know from this single case report whether the improvement in HBV was related to the treatment for HIV or not (Velasco 1999).

There is a case report in the literature of a flare-up of HBV two months after initiation of HAART including stavudine (d4T), didanosine (ddI), and ritonavir, thought to represent disease reactivation induced by a strengthened immune system (Vullo 1998). How often this phenomenon occurs is unknown, but it may represent the same immune reconstitution syndrome discussed earlier.

Interferon (IFN) Interferon-?

In the early 1990s, there were a few small pilot trials evaluating IFN therapy for HBV/HIV coinfecting people which suggested that IFN may be useful (Marcellin 1993; Wolfel 1994; Di Martino 1996); however, the response rate of HBV to IFN therapy appeared to be lower in HIV-coinfecting people; only about 37% clearance of HBV DNA with IFN, compared to a spontaneous clearance rate of 17% in HBV/HIV coinfecting people (Lane 1994).

There have been two larger trials of IFN therapy for HBV/HIV coinfecting people. Zylberberg treated 25 HBV/HIV-coinfecting people with IFN- α 2a, 6 MU tiw subcutaneously for six months. Nine of the 25 people (36%) had serum HBV DNA decrease to non-detectable levels and were considered responders; only one reappeared after therapy was completed. In a comparison group, HBV DNA spontaneously became nondetectable in only 3/18 (16.7%). There was not a correlation observed with HBV DNA response and CD4 counts (Zylberberg 1996a). Another trial of IFN (5 MU, tiw, for six months) in 26 HBV/HIV coinfecting men, treated between 1987 and 1996, has also been reported. Seven of 26 (27%) became HBV DNA-undetectable during therapy. The only factor found to be associated with loss of HBV DNA, and conversion to anti-HBe, was a high pretreatment level of serum alanine transaminase. The CD4 count did not correlate with response to IFN therapy (Di Martino 2000). IFN may be a reasonable treatment for people with detectable HBV DNA levels who have developed resistance to lamivudine, regardless of CD4 cell counts.

There remain many unanswered questions about the treatment of the HBV/HIV coinfecting person concerning optimal agents to treat chronic HBV infection, the long-term efficacy of those agents, resistance, cross-resistance, and the potential dangers of discontinuing therapy, once it has been initiated. Hopefully, much-needed trials will be conducted promptly to address these many vital questions.

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