Antiretroviral Therapy in Patients with Hepatitis and HIV: Weighing Risks and Benefits

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Liver disease is an important complication of human immunodeficiency virus (HIV) infection. As HIV-infected patients live longer, they develop long-term manifestations of chronic HIV infection and/or treatment complications. Progressive liver disease is one of the leading causes of morbidity and mortality in this patient group. Underlying hepatitis B and/or C virus infection is extremely common. All classes of antiretroviral drugs have been associated with some hepatotoxicity, and patients often receive other potentially liver-damaging drugs. Alcohol use is common and frequently underestimated. All of these issues make liver disease an important factor in making antiretroviral decisions. Clinicians should weigh underlying disease, behavioral issues such as drugs and alcohol, and concomitant therapy when choosing antiretrovirals in such patients. We need more research in this area, especially with regard to mechanisms, risks, and management—for specific drugs and regimens—to ensure that our patients receive the benefits of antiretroviral therapy in the safest manner possible.

Liver disease has emerged as an important complication of HIV infection. Because HIV-infected patients are living longer, they are developing other long-term manifestations of chronic HIV infection and/or complications of its treatment [1–3]. Progressive liver disease has become one of the leading causes of morbidity and mortality in this patient group [4–7]. The assessment of liver disease in patients with HIV infection, particularly interpreting and dealing with elevations of hepatic transaminase levels, is complex, not the least because of the many factors that can contribute to liver disease. Underlying infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is extremely common, with increased prevalence of coinfection in certain HIV-infected populations [8–12]. All classes of antiretroviral drugs have been associated with some degree of hepatotoxicity, and patients often receive other potentially liver-damaging drugs [6, 13–17]. Additionally, alcohol use is extremely common and frequently underestimated or ignored [6, 7]. All of these issues make liver disease (both its occurrence and its avoidance) an important factor in making decisions about antiretroviral therapy (ART). The present article will attempt to examine ART decision-making in the context of liver disease. Three issues will be reviewed: (1) how underlying hepatitis virus infection affects ART, both choice of drug and timing of treatment; (2) how the risk of hepatitis may influence the choice of antiretrovirals for the treatment of certain patients; and (3) how we need to weigh risks and benefits in making ART decisions that take into consideration both known outcomes and theoretical ones.

ISSUES FOR COINFECTED PATIENTS

Coinfection with HBV and/or HCV is common in certain HIV-infected populations [8–12]. Indeed, in injection drug users especially, infections with all 3 viruses have been reported [13]. Each of the hepatitis viruses offers challenges with regard to ART.

Until recently, only lamivudine has been available for
the long-term treatment of HBV infection [8, 18]. Given that lamivudine is also effective in the treatment of HIV infection, it has been commonly used in coinfected patients. It is important to emphasize that lamivudine should be used in these circumstances at doses that are effective for HIV, and it should never be used in less than suppressive therapy, because resistance will rapidly emerge in HIV strains. There are issues with lamivudine therapy that have not yet been answered, however. A generally accepted assumption is that all coinfected patients should be treated for infection with both viruses. Indeed, in the absence of treatment for HBV infection, patients who receive potent ART may experience an immune-mediated flare in their HBV disease. However, the emergence of lamivudine-resistant HBV is almost inevitable in HBV/HIV coinfection after a period of 3–4 years [8, 18, 19]. This leads to the consideration of delaying lamivudine use in such patients, until their HBV infection warrants therapy.

The development of nucleotide antivirals with activity against HBV has changed the equation somewhat, although there are very limited long-term data to guide decisions at present. Both adefovir and tenofovir are very potent agents against HBV, even lamivudine-resistant strains [20–24]. Recent studies have shown excellent activity in coinfected patients (most of whom had received prior lamivudine therapy), with >4 log10 copies/mL reductions in HBV DNA levels over at least 24 weeks (in the case of adefovir, these were sustained for up to 72 weeks) [23, 24]. Furthermore, there is no evidence to date of the emergence of HBV isolates that are resistant to these nucleotides. Given that tenofovir is now approved for HIV infection, it is clearly a very reasonable alternative to lamivudine for initial therapy. Indeed, important research questions should now be addressed. Is tenofovir a better initial agent for coinfected patients? This may be particularly true if resistance is less likely to emerge in HBV during tenofovir therapy. Should combination therapy for HBV be offered as initial therapy? This is relevant only if tenofovir can delay the emergence of resistance to lamivudine or if combination therapy can increase the rate of clearance of the e antigen and more effectively suppress HBV.

Studies need to be done, but, pending the results of such studies, my preference would be to use combination therapy for HBV as an initial strategy, if possible.

The epidemiology of HCV infection is very similar to that of HIV infection, but there are important differences when it comes to management [9, 11, 14, 25–28]. The most important of these is that HCV infection is potentially curable with a relatively limited amount of antiviral therapy [29, 30]. There are important reasons to control HCV infection in coinfected patients [31]. In most studies of liver disease in patients with HIV infection, HCV contributes substantially to morbidity [25, 32, 33]. HCV also increases the risk of hepatotoxicity due to antiretrovirals, and HCV infection has been associated with poorer responses to effective ART [6, 15, 32, 34, 35]. In several cohort studies, the CD4 cell response to potent antiretrovirals was blunted in HCV-infected patients, compared with HCV-negative control subjects. This appears to be specific to HCV infection, as opposed to other liver disease. Although this has not been demonstrated in prospective studies, and thus may be a consequence of shared behavioral characteristics that affect adherence or toxicity, it nevertheless points to the need to try to control HCV infections. Recent data have suggested that the combination of pegylated IFN and ribavirin is effective in some patients who are coinfected [31, 36], thus raising the important question as to what the optimal time for treatment of HCV is for coinfected patients. Indeed, for patients who have not yet been treated for either viral infection, the question can be posed as to which virus should be treated first. With the current thinking in HIV management leaning toward delaying HIV therapy until later in the course of the disease, it seems reasonable to suggest that HCV infection should be treated initially in appropriately selected patients. There are good reasons to suggest that this may be a reasonable strategy. Treating HCV infection may decrease the toxicity and improve the ultimate effectiveness of ART. However, the best results with IFN therapy for HCV have been seen in patients with high CD4 cell counts—indeed, the response rate is blunted as the CD4 cell count falls (even to <500 cells/mm3). Thus, one could make a case that improving the immune system with ART should be undertaken initially to increase the chances that the patient’s HCV infection will respond to IFN-based treatment. This is obviously a situation that cries out for a randomized clinical trial. In the absence of such data, the best one can propose is that, for patients in an early stage of HIV infection and who have higher CD4 cell counts, it may be prudent to treat the HCV infection initially, especially if there is already evidence according to liver biopsy results of HCV-induced fibrosis or advanced inflammation. However, if the patient has more advanced HIV disease, HIV should be treated initially, both because of the risk of more rapid HIV progression and the possibility of improving the response to specific anti-HCV treatment.

**ART FOR COINFECTED PATIENTS**

Although multiple cohort studies have shown that coinfection increases the risk of toxicities from antiretroviral agents, it has been difficult to assess the absolute risk and to make a determination as to whether certain drugs are contraindicated in patients with liver disease. For example, in the study from Johns Hopkins by Sulkowski et al. [37], the relative risk of hepatotoxicity was 5 times higher in HCV/HIV-coinfected patients. However, the vast majority of coinfected patients (84%) tolerated ART without developing apparent drug-related toxicity.
Thus, it becomes difficult to conclude that certain drugs should not be used in patients with concomitant hepatitis.

An important area of research is to determine the impact of additional factors that affect the outcome for coinfected patients. This will enable physicians to make a reasonable assessment of risk and, therefore, to make reasonable choices. Alcohol use clearly increases the risk of liver disease. Active alcohol use also can affect adherence to therapy. What we are less certain of is whether alcohol use will increase the risk of liver damage from ART and should therefore be regarded as a relative contraindication for ART or, at least, for the use of certain antiretroviral drugs.

We have focused most of our attention on specific individual drugs and the risk of toxicity from them. However, patients do not receive individual drugs but, rather, combinations; more attention needs to be paid to whether certain combinations carry a greater risk of liver toxicity, especially in a patient whose liver is already damaged by hepatitis or alcohol. The importance of assessing the risk of toxicity with specific combinations has been recently shown for nucleoside-associated lactic acidosis. Although this complication has been described with virtually all nucleosides, the risk appears to increase with multiple nucleoside use, particularly with the pairing of stavudine and didanosine. The concept of multiple hits is an important one in the development of liver damage, and clinicians should weigh underlying disease, behavioral issues such as drugs and alcohol, and other concomitant therapy when choosing antiretrovirals in such complicated patients.

As was noted previously, patients who are seropositive for HBV or HCV have higher rates of hepatotoxicity associated with ART. What is not known is whether treatment for hepatitis changes that risk. We assume that it does, in the case of HCV infection, because we assume that the resultant decrease in liver inflammation and fibrosis will improve liver function and lessen the effects of other drugs. However, we have little information to support this belief. For HBV infection, the situation is equally uncertain. Despite the fact that most coinfected patients receive treatment for HBV, we do not know whether treatment lessens their risk of hepatotoxicity from antiretrovirals. If it does, does the development of resistance increase the risk of further toxicity?

One of the keys to the future will be to try to better predict those at greatest risk of toxicity, so that certain drugs can be avoided or preventive measures can be undertaken. It will be important to identify the mechanisms of drug toxicity, because different strategies can be planned accordingly. For toxicities that have a genetic basis, pharmacogenomic studies may allow us to identify individuals at very high risk, as seems to be the case with abacavir hypersensitivity [38, 39]. This may be a particularly attractive avenue of research for drugs, such as nevirapine, in which hypersensitivity, or at least individual susceptibility, appears to play a part in the development of toxicity.

### MANAGING PATIENTS

What should the treating physician do now? I believe that it is reasonable to advocate treating underlying hepatitis, if this is possible. Even if we do not yet know how effective this strategy is in minimizing hepatotoxicity, it is worthwhile, when indicated, to reduce the progression of viral hepatitis. Thus, patients with HBV infection should have ART that is active against both viruses; for patients infected with HCV (especially genotypes 2 and 3), treatment at higher CD4 counts may be more effective. It is important to address lifestyle and behavioral issues (such as the use of drugs or alcohol and psychiatric disease) that may increase toxicity (as well as potentially compromising adherence). It is also reasonable to avoid certain drugs and, more particularly, certain combinations (e.g., stavudine and didanosine), especially in patients with more advanced liver disease, such as symptomatic hepatitis or cirrhosis. In such patients, hepatotoxicity from medications may precipitate hepatic failure, with its high associated mortality.

It is equally important, however, to recognize that we lack sufficient information to make completely informed decisions about ART, and, in particular, to accurately assess the risk-benefit equation that is at the heart of every therapeutic decision. The first decision—to start or delay ART—is currently quite controversial, mainly because the need to control immunodeficiency is balanced in many minds by concerns about greater harm from long-term toxicities of treatment. This debate will continue as new data emerge, yet clinicians must make immediate decisions on the basis of incomplete information every day. Similar dilemmas exist for the choice of which ART to start with and which to use later. In some cases, clinical trial data give us very valuable information, but their utility in decision-making remains incomplete. Clinical trials involve comparisons of drug regimens that were in vogue when the trial started, not necessarily those in use at present. Some trials choose comparative arms that would rarely be used in practice, making their application to patient care difficult. Furthermore, clinical trials often exclude patients for whom these decisions are most difficult, such as those with underlying concomitant disease, including hepatitis. Finally, clinical trials rarely address the question physicians and patients face regularly—how to make comparisons about toxicities. Unfortunately, very few drugs are completely free of side effects, and we know of no good way of comparing the relative importance of these toxicities. Obviously a life-threatening toxicity weighs heavily in the mind of a physician, but is a rare serious toxicity more important than a common side effect that is debilitating or has long-term consequences? There is no good answer for these questions—they must be weighed on an individual basis—both depend on the relative risk of the event for that particular individual and the relative importance of the event for the patient and physician.
In conclusion, it is not possible to take hepatotoxicity or liver disease in isolation. It must be included as a factor in decision-making for ART, just as metabolic side effects and long-term cardiovascular risks should be considered. It is clear that we need more research in this area, especially with regard to mechanisms, risks and management—for both specific drugs and different regimens—to ensure that our patients receive the benefits of ART in the safest manner possible. Until then, physicians will need to rely on experience, remembering always the words of Oscar Wilde: “Experience is what we call our mistakes.”

References


