Human Immunodeficiency Virus and Coinfection with Hepatitis B and C

Lindsay A. Petty, MD\textsuperscript{a,}\textsuperscript{*}, Jennifer L. Steinbeck, MD\textsuperscript{a},
Kenneth Pursell, MD\textsuperscript{a}, Donald M. Jensen, MD\textsuperscript{b}

BACKGROUND

A disproportionate number of people with human immunodeficiency virus (HIV) are affected by viral hepatitis compared with the general population, because they are at higher risk due to similar routes of transmission of these blood-borne pathogens, as well as chronic persistence of virus in most hosts.\textsuperscript{1} Of all patients with HIV infection in the United States, about 10% are coinfected with hepatitis B virus (HBV) and 25% are coinfected with hepatitis C virus (HCV). Therefore, in total about one-third of the HIV population is affected by viral hepatitis.\textsuperscript{2,3} In the era of highly active antiretroviral therapy (HAART), liver disease has become a leading cause of morbidity and mortality associated with viral hepatitis.\textsuperscript{4} Coinfection with viral hepatitis, caused by either

\textsuperscript{a} Department of Infectious Diseases and Global Health, University of Chicago Medical Center, 5841 South Maryland Avenue, MC 5065, Chicago, IL 60637, USA; \textsuperscript{b} Department of Medicine, Center for Liver Disease, University of Chicago Medical Center, 5841 South Maryland Avenue, MC 7120, Chicago, IL 60637, USA

* Corresponding author.

E-mail address: lindsay.petty@uchospitals.edu

http://dx.doi.org/10.1016/j.idc.2014.05.005
id.theclinics.com
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HBV or HCV, is the main cause of liver disease. Multiple issues arise, including the dual toxicities to the liver from both viral hepatitis and ART, as well as the potential need for altering the selection of antiretroviral therapy (ART) in the setting of potential treatment of viral hepatitis, possibly affecting both the timing and the choice of therapy. In the setting of the release of new direct-acting antiviral (DAA) agents, the treatment of HIV/HCV-coinfected patients is rapidly evolving and improving.

EPIDEMIOLOGY AND RISK FACTORS

HBV and HBV/HIV

Hepatitis B is a DNA virus that infects humans. Although there is a trend toward decreasing prevalence of HBV, this infection remains the leading cause of chronic liver disease globally with 2 billion individuals being exposed and 350 million people with chronic infection worldwide.\(^5\),\(^6\) It is estimated that HBV is responsible for 30% of cirrhosis and 53% of hepatocellular carcinoma (HCC).\(^7\) The prevalence of HBV varies with geographic location. In regions with the highest prevalence, including sub-Saharan Africa and East Asia, 5% to 10% of adults are chronically infected. In regions with the lowest prevalence, including Western Europe and North America, less than 1% of adults are chronically infected.\(^8\)

HBV is highly contagious, more so than HIV or HCV. Given the shared modes of transmission between HIV and HBV, these infections occur together with relative frequency. Both are transmitted via perinatal, parenteral, and sexual contacts (Table 1).\(^9\) HBV can be transmitted from infected blood or bodily fluids via injection, mucous membranes, or wounds.\(^10\) HBV replicates to high titers in blood, but it can also be found in other bodily fluids, including semen, cervical secretions, and saliva.\(^11\) As in HBV infection alone, the epidemiology of coinfection of HIV/HBV varies with geographic region. It is estimated that the prevalence of chronic hepatitis B in HIV-infected individuals is 5% to 20%.\(^11\) Therefore, of the 35 million worldwide infected with HIV, 2 to 4 million are estimated to have chronic hepatitis B.\(^9\) A study of more than 16,000 HIV-infected individuals in the United States found a prevalence of 7.8% of chronic HBV for unvaccinated subjects, which is significantly higher than the less than 1% prevalence of the general population.\(^8,\)\(^12\)

### Table 1

<table>
<thead>
<tr>
<th>Mode</th>
<th>HIV</th>
<th>HBV</th>
<th>HBV/HIV</th>
<th>HCV</th>
<th>HCV/HIV</th>
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</thead>
<tbody>
<tr>
<td>Perinatal</td>
<td>10%–20%</td>
<td>5%–90%</td>
<td>10%–90% a</td>
<td>&lt;2%–7%</td>
<td>10%–20%</td>
</tr>
<tr>
<td>Sex</td>
<td>&lt;1%</td>
<td>Up to 90% b</td>
<td>Up to 90% b</td>
<td>&lt;1%</td>
<td>&lt;1%–3% c</td>
</tr>
<tr>
<td>Needle stick</td>
<td>0.30%</td>
<td>7%–30%</td>
<td>Unknown</td>
<td>1%–3%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

a Transmision risk less than 10% if HBsAg positive and HBeAg negative increases to 70%–90% if HBsAg positive and HBeAg positive.

b Depends on level of HBV DNA.

c Values are based on data from HCV serodiscordant heterosexual couples.

HCV and HCV/HIV

Hepatitis C is an RNA flavivirus that infects humans. About 3 to 4 million people in the United States are chronically infected with HCV, and 10,000 to 20,000 die each year from complications related to liver disease caused by HCV. In the United States, a recent review of death certificate data suggests that deaths related to HCV now exceed those caused by HIV (15,106 vs 12,734). The virus is most efficiently transmitted through parenteral means, including injection drug use (IDU) or contaminated blood or medical equipment. Much less commonly, it can be transmitted through sexual contact or perinatal vertical transmission (see Table 1). The predominant risk factors vary geographically. In the United States, IDU is the biggest risk factor, in particular since the initiation of blood product screening. It is estimated that 75% of all HCV infections in the United States are in people born between 1945 and 1965. The incidence of new infections in the United States has declined overall since blood product screening was instituted. However, the chronically HCV-infected population is aging, likely resulting in more cirrhosis seen in the coming years.

Given the similar routes of transmission, coinfection with HIV and HCV is common. IDU is a common means of transmitting both viruses, and 50% to 90% of injection drug users with HIV also have HCV. In addition, cohorts have shown that there is an increased risk of transmission among certain subpopulations, in particular, HIV-positive men who have sex with men (MSM). An increased incidence of newly acquired HCV has been seen in multiple cohorts. The precise cause of this increased incidence is unknown. Some studies have shown correlations with anal sex and mucosal damage, including sexually transmitted infections with genital ulcerations or certain sexual practices, and this mucosal breakdown has been hypothesized to increase risk of sexual transmission. However, a recent Swiss cohort did not show increased incidence of HCV in MSM who are HIV-negative. HIV also increases the rate of vertical transmission of HCV to newborns by 4 to 5 times. Overall, there is a high rate of HIV/HCV coinfection due to shared avenues of transmission, as well as increased rates of HCV transmission in select HIV-positive populations.

GENOTYPES

HBV

There are 8 identified genotypes of HBV, with multiple subgenotypes as well. In contrast to HCV, the genotype has a significant implication on clinical outcomes and natural history but minimal relation to the response to therapy. Genotype C, in particular, is associated with the highest risk of HCC and cirrhosis. The genotypes have characteristic geographic patterns. In the United States, genotype B and C are found in Asian individuals; genotype A2 and D are found in those of European and Middle Eastern descent. The clinical significance, if any, of subgenotypes is not yet known and routine genotype testing is not routinely performed.

HCV

There are 6 major HCV genotypes, with multiple subtypes and strains. Genotypes 1 to 3 are distributed globally, with 60% of worldwide infections caused by genotypes 1a and 1b. The different genotypes are geographically distributed, with genotype 1a mostly seen in Northern Europe and North America (genotype 1 constitutes 70% of US infections), and genotype 2 is less commonly seen, but more often in Europe than North America. In regards to interferon (IFN)-based therapy, the genotypes do influence response to treatment, with genotype 1 associated with a poorer
response compared with more favorable responses to genotypes 2 and 3.\textsuperscript{27} With directly acting agents now available for INF-free regimens, however, the outcomes have become more similar across the genotypes. The specific genotype is still likely to be used to guide DAA treatment regimen decisions.

**IL28B**

A single nucleotide polymorphism (SNP) near the IL28B gene in the human host, which encodes INF-\(\lambda\), has been identified, and this SNP appears to be a critical part of the innate immune system’s defense against HCV. For INF-based therapies, monoinfected individuals with the CC genotype of the SNP were more than 3 times as likely to clear HCV RNA compared with individuals with CT and TT genotypes, and similar spontaneous clearance differences have been seen in the coinfected population.\textsuperscript{28,29} Variations in IL28B are also associated with treatment outcomes, but mostly in genotypes 1 and 4. The influence of IL28B polymorphism on treatment outcome is attenuated but still present for regimens using the new DAA agents based on preliminary data.\textsuperscript{30}

**NATURAL HISTORY OF COINFECTED STATES**

**HBV in HIV**

The course of HBV is both variable and complex, being influenced by multiple factors, including the host immune response, viral fitness, HBV genotype, age, alcohol consumption, and coinfection with HIV, HCV, or hepatitis D virus.\textsuperscript{25} The natural history of chronic HBV includes 3 major phases of immune tolerant, immune active, and inactive carrier. Although infected individuals generally progress through these phases, some will reactivate and return from the inactive carrier state back to the immune active phase.\textsuperscript{10} The immune tolerant phase is characterized by positive HBeAg, high levels of HBV DNA but normal alanine aminotransferase (ALT) levels and no or little liver fibrosis or inflammation on biopsy. There is no cytotoxic T-cell activity against the virus, because the immune system does not recognize the virus in this phase. The immune tolerant phase predominantly occurs in individuals infected at birth via perinatal transmission from mothers who are positive for HBeAg. It is uncommon in those infected after birth. Although this phase can last for decades, liver disease does not appear to progress during this time.

Most individuals infected with HBV eventually progress from the immune tolerant to the immune active phase. ALT levels increase and evidence of liver disease can be found on biopsy. HBV DNA levels are elevated but generally lower than the prior phase, and levels decrease while progressing through this phase. A weak cytotoxic T-cell response can occur, resulting in HBeAg seroconversion and possible suppression of HBV DNA.

Following seroconversion, there are 3 possible situations. The majority progress to the inactive carrier state. It is marked by normal ALT levels, low or frequently undetectable levels of HBV DNA, and HBeAg negative; HBsAg remains detectable. Liver inflammation and fibrosis improve and can even reverse. Although most who enter this state remain here long-term, a minority will achieve HBsAg clearance. Notably, an estimated 20\% will reactivate to the immune active phase. In addition, despite seroconversion, the infected individual may sometimes remain in the immune active phase. Finally, one can revert back to HBeAg seropositivity. The latter is more common among genotypes C or F.\textsuperscript{24,25}

HIV has a significant deleterious impact on the natural history and progression of HBV infection. The HIV/HBV-coinfected population has an increased rate of
replication of HBV, as noted by higher HBV DNA levels and decreased rates of spontaneous clearance.\textsuperscript{31–33} In a prospective cohort of men, 12\% of the coinfected had loss of HBeAg at 5 years compared with 49\% of HBV-monoinfected.\textsuperscript{34} Not only does HIV increase the risk of developing chronic infection, but it also is associated with an increased rate of reactivation.\textsuperscript{31,35}

In addition, HIV is thought to result in the accelerated progression of liver disease. The coinfected have faster rates of liver fibrosis, in addition to increased rates of cirrhosis, end-stage liver disease, HCC, and liver-related mortality.\textsuperscript{32,33,36,37} A prospective study of 5293 MSM, including 326 who were positive for HBsAg, found that mortality due to liver disease was significantly higher in the coinfected (14.2/1000 person-years) compared with those with HBV alone (0.8/1000 person-years).\textsuperscript{37} Notably, there is limited knowledge on the effect of adult acquired HIV when HBV infection has been established for many years, as in perinatal transmission, as most research has been conducted in locations where HBV is acquired in adulthood.\textsuperscript{31}

Of the different phases, it is those in the immune active phase who are at the highest risk of developing HCC.\textsuperscript{24} HIV coinfection further amplifies this association. Depending on the mode of transmission and the age of acquisition, the lifetime risk of HCC in chronic HBV ranges from 15\% to 40\%. In addition, several other factors have been found to have an increased risk of HCC in chronic HBV, including male sex, age over 40, family history, smoking, alcohol, and aflatoxin exposure.\textsuperscript{24}

**HIV with HBV**

Although HIV has been found to have significant impact on the outcomes of HBV, the reverse has not been reliably demonstrated, and controversy exists regarding the effect of HBV on the natural history of HIV. A study of the EuroSIDA cohort found that chronic HBV had no impact on progression to AIDS or responses to HAART. Chronic HBV did significantly increase liver-related mortality in HIV-infected individuals.\textsuperscript{38} Two prior longitudinal studies and one retrospective study also did not find any evidence of HBV leading to HIV/AIDS progression.\textsuperscript{39–41}

Contrary to this, other observations have suggested that HBV is associated with a more rapidly progressive HIV course.\textsuperscript{42} A retrospective analysis including 64 HIV/HBV-coinfected individuals with chronic HBV showed that the risk of AIDS or death was nearly 2-fold higher among coinfected chronic HBV individuals compared with HIV-monoinfected individuals.\textsuperscript{43} An international study found that coinfected individuals had a lower baseline CD4 T-cell count with a median of 137 cells/mL compared with 159 cells/mL in HIV-monoinfected individuals before therapy.\textsuperscript{11} A meta-analysis including data on greater than 12,000 patients found that coinfected patients had worsened overall mortality. This study did not support that this difference was due to increased AIDS progression but speculated that severe hepatic complications could explain the reduced survival.\textsuperscript{41}

**HCV in HIV**

After transmission, the incubation period for HCV ranges from 2 weeks to 6 months (considered acute infection), with 80\% of individuals experiencing no symptoms.\textsuperscript{13,44} About 80\% of patients infected with HCV will develop chronic infection, and approximately one-third of those will progress to cirrhosis.\textsuperscript{13,45,46} In a recent study looking at the difference in all-cause mortality between patients with chronic HCV who achieve sustained HCV virologic response (SVR) to treatment versus those who do not, the 10-year cumulative incidence risk of liver-related mortality or transplantation was 1.9\% versus 27.4\%, respectively.\textsuperscript{47} Of those who did not achieve SVR and died, 70\% were due to liver-related causes.\textsuperscript{47}
Individuals with HIV have overall worse outcomes associated with HCV than the HCV-monoinfected population. From the start, HIV-infected persons are less likely to clear HCV viremia following acute infection.46,48 In the setting of acute HCV, clearance of HCV RNA of at least 2 log within 4 weeks of diagnosis was a strong predictor for spontaneous clearance. If not clear by 12 weeks, then the coinfected individual is likely to develop chronic HCV infection.49 In addition, the coinfected population is more likely to have higher HCV RNA viral loads and set points.46,48

HIV increases the speed of progression to liver disease compared with monoinfected individuals.46,50–52 Cirrhosis has been seen in coinfected individuals as early as 6 to 10 years after HCV infection, compared with 10 to 20 years in monoinfected individuals.1 The risk of cirrhosis or decompensated liver disease in HIV/HCV-coinfected patients is 3 times more than monoinfected patients, regardless of CD4 count.53,54 The exact mechanism of this acceleration of fibrosis is unclear. There have been multiple studies looking to explain this acceleration of fibrosis on the molecular level. Some studies have found a link to immunosuppression with low HCV-specific CD8+ T-cell responses, chronic immune activation, and increased circulation of proinflammatory cytokines.55–57 In addition, there is an increased risk of HCC in coinfected compared with monoinfected individuals.54

In a meta-analysis in the HAART era, estimates of coinfected individuals with cirrhosis were found to be 21% (95% confidence interval [CI], 16%–28%) and 49% (40%–49%) after 20 and 30 years, respectively.50 The overall risk of cirrhosis in the HAART era for coinfected compared with monoinfected individuals was slightly lower compared with a pre-HAART meta-analysis (relative risk: 2.11, 95% CI, 1.51–2.96 vs 2.92, 1.70–5.01).50 HAART has not been shown in studies to fully correct the differences between the 2 populations.50 However, initiation of ART on coinfected veterans recently showed a significant reduction in the rate of hepatic decompensation, by 28% to 41% on average.58

HIV with HCV

The effect that HCV has on HIV is controversial. One study showed impaired immune reconstitution with initiation of ART in coinfected patients.59 However, one study looking at 5957 HIV-positive patients with approximately 33% HCV prevalence did not show that HCV serostatus affected the risk of HIV disease progression, or that there were any virologic or immunologic responses to HAART that were worsened.2

Although the overall progression of immunologic responses is debatable, there is significant concern regarding the extrahepatic manifestations of HCV, especially in a population already at higher risk for cardiovascular disease and renal disease because of their HIV infection. These extrahepatic manifestations are hypothesized to be due to persistent immune activation and inflammation.60 Monoinfection with HIV infection increases the risk of cardiovascular disease and renal disease. The REVEAL-C study showed an increase in the rate of cardiovascular events, kidney disease, and some cancers in HIV-uninfected patients with chronic hepatitis C.61 In coinfected populations, persistent HCV-RNA has also been associated with an increased risk of cardiovascular disease and renal disease compared with HIV monoinfected patients.62–64

Although coinfection with HCV or HBV has been shown to be an independent risk factor for ART-associated hepatotoxicity,65 the number of patients this actually affects may be less significant, especially if certain antiretroviral agents are avoided and less hepatotoxic ones are used instead. The coinfected population is more likely to experience hepatotoxicity on ART, although more likely with nevarapine (NNRTI: nonnucleoside reverse transcriptase inhibitor), efavirenz (NNRTI), or high-dose ritonavir (PI: protease inhibitor) regimens.66–68 High-dose ritonavir regimens are no longer used.
Ritonavir is now only used to boost another PI. Only about 10% of patients receiving boosted ritonavir develop severe hepatotoxicity, however, and most cases are asymptomatic and resolve whether ARV is modified or not; this may differ based on stage of fibrosis. Stavudine (NRTI: nucleoside reverse transcriptase inhibitor) and didanosine (DDI; NRTI) are associated with increased risk of hepatotoxicity as well as substantial neurotoxicity and metabolic disorders, and thus, are no longer recommended for therapy. Raltegravir (INSTI, integrase inhibitor) has shown good safety profiles in the coinfected population and thus is one of the preferred backbone agents for patients with viral liver disease. Thus, there are multiple drug limitations in HIV/HCV-coinfected individuals based on increased risk of hepatotoxicity as well as drug-drug interactions. However, the overall risk of hepatotoxicity with ART is decreased after successful treatment of HCV infection.

**DIAGNOSIS AND SCREENING: IN THE HIV-INFECTED POPULATION**

It is recommended that all HIV-infected individuals be screened for HBV as well as HCV.

In regards to screening for HBV, initial testing for evidence of past or present HBV infection should be performed in all HIV-infected patients. This testing should include HBsAg, anti-HBc total, and anti-HBs. Those who test negative should be immunized. The presence of HBsAg on 2 occasions at least 6 months apart defines chronic HBV infection. These patients should undergo further evaluation with HBeAg, anti-HBe, HBV DNA testing as well as liver chemistries, complete blood count, and prothrombin time. A low threshold to evaluate for HBV infection should exist in patients with HIV infection if unexplained liver disease occurs, as spontaneous reverse seroconversion with the disappearance of anti-HBs and the reappearance of HBsAg can develop. The extent of liver fibrosis should also be monitored, which can be done with noninvasive testing such as transient elastometry. Indirect monitoring with ultrasound, fibrotests, and platelet counts is preferred, with biopsy helpful in the setting of discrepancies among these tests or the clinical picture. Chronic hepatitis B infection increases the risk for HCC. Thus, ultrasound should be performed every six months, plus or minus the measurement of serum \( \alpha \)-fetoprotein. The American Association of Study of Liver Disease (AASLD) does not recommend the routine use of AFP, but many practitioners use it as an adjunctive piece of data to make clinical decisions, although this is controversial.

In regards to screening for HCV infection, initial testing should involve anti-HCV detection using sensitive immunoassays. A positive result demonstrates exposure to HCV; it cannot distinguish acute versus chronic infection. False negatives may occur in the severely immunosuppressed (CD4 <100/mm\(^3\)), and true negatives may occur in acute HCV (within 12 weeks of acquisition). If a negative test result occurs in the setting of high suspicion based on risk factors (such as increased aminotransferases, high-risk sexual behavior, and IDU), then further testing should be performed for HCV RNA within 6 months to one year. In addition, if HCV antibody testing is positive, then subsequent quantitative HCV RNA should be performed. Although a positive HCV RNA test is sufficient for the diagnosis of active hepatitis C, a negative cannot exclude active viremia because of transient declines, and a repeat test should be performed. When HCV RNA is positive, HCV genotype testing should be performed because it is the best predictor of response and also will guide treatment regimens.

Liver biopsy remains the gold standard for evaluation of HCV-related disease (stage of fibrosis), and many noninvasive imaging tests or predictive indexes are
being developed and studied, and now biopsy is only used if the noninvasive modalities are not conclusive. Biopsy is no longer required prior to initiating therapy for HCV infection. The utility of these studies in the coinfected population is less defined as treatment options improve, because earlier therapy is recommended given the more rapid progression of fibrosis in this population.

**TREATMENT**

**HBV: Treatment of Monoinfection Compared with Coinfection: Limitations and Considerations**

Patients with HIV infection who are also infected with HBV should be treated for both infections (Table 2). Ultimately, the treatment goal for both HBV-monoinfection and HIV/HBV-coinfection remains the same: to decrease the morbidity and mortality associated with HBV infection. Given that multiple agents target both HIV and HBV, the treatment of these viruses is interconnected. Clinicians must be certain that the HIV regimen contains at least 2 HBV active drugs so that HBV resistance does not occur and so that HBV related immune reactivation syndrome does not occur.

The Department of Health and Human Services recommends that all coinfected patients receive ART with a dually active regimen against both HIV and HBV regardless of CD4 count. In contrast, in HBV monoinfected patients, treatment is indicated for chronic HBV if the risk of liver-related morbidity and mortality in the near future and the likelihood of achieving a successful viral response are both high. Guidelines from the American Association of Study of Liver Disease (AASLD) provide further details on when to treat incorporating multiple factors, including ALT and HBV DNA levels and liver biopsy findings.

**Treatment of HBV Only**

Treatment of HBV alone is not recommended. Such treatment in the coinfected patient can lead to resistance of both HBV and HIV if not managed carefully. If a patient refuses or is not taking ART, the options for HBV treatment are significantly limited due to the risk of creating HIV resistance if anti-HBV drugs that also have some anti-HIV activity are used. Anti-HBV drugs, including tenofovir (TDF, NRTI), entecavir (ETV, NRTI), emtricitabine (FTC, NRTI), lamivudine (3TC, NRTI), adefovir (NRTI), and likely telbivudine (NRTI), all have some activity against HIV. These drugs are all nucleoside or nucleotide analogues that target HBV DNA polymerase. It is recommended that these agents not be given without the accompaniment of a fully suppressive ART regimen due to risk of inducing HIV resistance. ETV and telbivudine have been

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<td>Treatment of HBV/HIV coinfection</td>
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</table>

| ART administered<sup>a</sup> | Preferred regimen: ART with 2 anti-HBV agents  
(TDF + FTC/3TC)  
Duration: indefinite |
| ART contraindicated/not utilized<sup>b</sup> | If HBV treatment indicated: PEG  
Duration: 48 wk  
*Do not administer without ART:* TDF, ETV, FTC, 3TC, adefovir, telbivudine  
If HBV treatment not indicated<sup>b</sup>: close monitoring |

<sup>a</sup> Recommended that all receive ART regardless of CD4 count.

<sup>b</sup> If ART is not implemented, then decision to treat HBV is based on standards for HBV monoinfection.
associated with the selection of M184V and M204I mutation, respectively.\textsuperscript{74,90,91} Adefovir and pegylated-\textit{INF-\alpha-2a} (PEG) are the only options for those not receiving ART, but there are limited data regarding the efficacy and safety of a regimen with one or both of these agents in the coinfected state. The former has limited value because it is less potent. If the HIV infection will not be treated, then the decision of when to initiate HBV therapy should follow the standards of HBV monoinfection.\textsuperscript{76}

\textbf{Treatment of Both HIV and HBV}

For coinfected individuals, ART should include 2 agents with activity against HBV. The Department of Health and Human Services guidelines for treatment of HIV infection recommend TDF/FTC as the preferred NRTI backbone for ART-naive individuals.\textsuperscript{87} These agents also have activity against HBV and it is thus also recommended for coinfected patients.\textsuperscript{76} The AASLD practice guidelines recommend TDF/FTC or TDF/3TC as the preferred treatment of those planning to receive both HBV and HIV therapy.\textsuperscript{74} TDF demonstrates activity against both wild-type and 3TC-resistant HBV and is suggested to decrease the rate of resistance to 3TC when combined with 3TC.\textsuperscript{74,92–95} TDF resistance in HBV has not yet been reported.\textsuperscript{76} TDF should be used with caution in those with renal dysfunction or at high risk for renal dysfunction. ETV, instead, can be added to a fully suppressive ART regimen.\textsuperscript{76} Long-term use of 3TC or FTC alone should be avoided, as this can select for resistant HBV.\textsuperscript{76,94,96} Resistance increases with increased duration of treatment.\textsuperscript{76} There is approximately a 20\% rate of development of 3TC resistance per year with this therapy alone in the coinfected; at 4 years, resistance is estimated to reach 90\%.\textsuperscript{94} Because 3TC-resistant HBV will have cross-resistance with other L-nucleosides, including telbivudine and FTC, this class of drugs should not be used if there is known 3TC-resistance.\textsuperscript{76}

Treatment of HBV should be continued lifelong because there is a significant risk of relapse of hepatitis exists if therapy is discontinued.\textsuperscript{76,89}

\textbf{Monitoring Treatment of HBV in the Coinfected Patient}

Appropriate monitoring is important to assess for treatment response, signs of developing resistance, or toxicity. HBV DNA and ALT levels should be monitored every 3 months; HBeAg should be checked every 3 to 6 months in HBeAg-positive individuals.\textsuperscript{31,76} The HBV treatment endpoints include viral suppression and improved liver disease.\textsuperscript{89} Viral suppression is defined as undetectable serum HBV DNA by polymerase chain reaction assay and loss of HBeAg (if previously positive). Improved liver disease is assessed by a decrease in ALT to within normal range. Complete response is defined as both biochemical and virological response, including loss of HBsAg. A response that persists while on therapy is a maintained response; a response that persists 6 or 12 months after discontinuation of therapy is a sustained response.\textsuperscript{74} Other markers of favorable response include improved liver histology and development of anti-HBe.\textsuperscript{76} In some HBV-monoinfected individuals, HBV therapy may be discontinued if multiple criteria are met, in particular including loss of HBeAg (if previously positive). However, in the HIV/HBV-coinfected patient on a stable ART regimen they are tolerating, therapy for HBV should continue lifelong.

Renal toxicity can be seen with TDF; therefore, serum creatinine and electrolytes should be checked at baseline and monitored every 3 to 6 months along with urinalysis every 6 months. If significant renal dysfunction occurs, TDF should be discontinued with alternative therapy chosen. If creatinine clearance is less than 10, then TDF should be discontinued as the pharmacokinetics have not been evaluated in nonhemodialysis patients with this level of renal dysfunction.\textsuperscript{97} Providers should also
consider holding TDF if there is a significant change from baseline while pursuing further work up to identify an etiology. Improvement of renal function can be seen. Lactic acidosis is an uncommon side effect of ETV use reported in treatment of monoinfected patients with advanced cirrhosis. Telbivudine can result in creatinine phosphokinase (CPK) elevations and myopathy; therefore, CPK should be monitored at baseline, then every 3–6 months or sooner if symptoms develop. As mentioned, lifelong therapy is recommended in the coinfected state. A flare of hepatitis B in about 30% of cases, with possible decompensated liver disease, has been associated with early discontinuation of therapy. Therefore, aminotransferases should be monitored every 6 weeks for 3 months and then every 3 months if therapy is prematurely stopped. If there is a rise in aminotransferases, then it is recommended that therapy be re-started.

The presence of HBV has been associated with an increased risk of hepatotoxicity with ART, but clinically significant hepatotoxicity remains uncommon. Thus, liver enzymes should be monitored monthly for the first 3–6 months after starting therapy and then every 3 months thereafter. It is also important to be aware of the risk of immune reconstitution inflammatory syndrome, which can be represented as a hepatitis flare in the coinfected patient within the first 6–12 weeks after starting ART. Because the hepatic damage that occurs in HBV infection is predominantly a result of the immune response against infected hepatocytes, the immune reconstitution that occurs with ART can lead to worsened liver disease which is manifested by a rise in aminotransferases or a flare of hepatitis. Such flares can be life-threatening and are part of the basis for recommending a regimen that treats HBV when administering ART. Utilizing two drugs active against HBV reduces the likelihood that IRIS will occur. In general, a higher risk of IRIS has been seen in those who initiate therapy with a lower baseline CD4 count, especially when less than 50. Additionally, a higher baseline HIV-1 viral load and more rapid decline in viral load increases the risk for the development of IRIS.

HCV: TREATMENT OF MONOINFECTION COMPARED WITH COINFECTION: LIMITATIONS AND CONSIDERATIONS

The primary goal of treatment is to achieve a sustained virologic response (SVR, defined as an undetectable HCV RNA 24 weeks after therapy completion). Some studies now use as an end point a shortened SVR period of 12 weeks because few monoinfected individuals rebound after this period. Coinfected patients who achieve SVR have lower rates of decompensated liver disease, HCC, and liver-related mortality compared with those patients who do not achieve SVR when followed for up to 10 years. Historically, the referral and initiation of HCV therapy in HIV/HCV-coinfected patients are low. This low amount is due to several factors, including lower response rates with PEG/ribavirin (RBV), medical comorbidities, neuropsychiatric comorbidities, perception of therapy, and adverse events associated with the IFN-based therapy. The coinfected population has decreased response rates to HCV therapy compared with the monoinfected population. Coinfected patients may have increased HCV quasispecies (due to increased mutational rates), and therefore, decreased treatment responses. The newer DAAs, sofosbuvir (SOF) and simeprevir (SMV), have decreased drug interactions and adverse events, with high success in both monoinfected and
coinfected individuals in early clinical trials. This high success is changing the recommendations and attitudes for treatment in the coinfected population (Table 3).

**PEG/RBV**

PEG plus RBV was used extensively for treatment of HCV in the past. With the development of directly acting agents that are highly effective and well tolerated without being combined with IFN, and often without RBV, PEG and RBV will be less clinically relevant.

PEG/RBV combinations have been studied extensively in monoinfected individuals, but there have been only a few studies in the coinfected population. Both agents exhibit nonspecific antiviral activity. Interferon is an immunomodulatory agent that stimulates host antiviral genes, whereas the mechanism of action of RBV is poorly understood. These studies are limited by fixed-dose RBV regimens and smaller sample sizes, but overall they show that coinfected patients have a decreased response to therapy in comparison with monoinfected groups (SVR is achieved in approximately 14%–35% vs 42%–46%). In the past, RBV was shown to cause mitochondrial toxicity, so DDI (NRTI) was contraindicated in coinfected patients being treated with RBV-containing regimens. Zidovudine (NRTI) is also contraindicated in combination with RBV because of increased rates of anemia. Side effects of PEG and RBV include flulike symptoms, malaise, weight loss, anemia, neutropenia, and thrombocytopenia. Contraindications to PEG/RBV therapy include a history of decompensated cirrhosis, pregnancy, inability to prevent pregnancy, uncontrolled depression, unstable cardiac or pulmonary conditions, and uncontrolled HIV with advanced immunosuppression.

**PROTEASE INHIBITOR + PEG/RBV (TELAPREVIR, BOCEPREVIR, SMV)**

Telaprevir (TVR) and boceprevir (BOC) are NS3/4A protease inhibitors, as well as CYP3A inhibitors. TVR as triple therapy (in combination with PEG/RBV) has been studied in coinfected patients, showing improved SVR rates compared with PEG/RBV (dual therapy) alone (74 vs 45%). Also in the coinfected population, a study showed increased SVR rates in triple therapy including BOC compared with standard dual therapy (63% vs 29%). Drawbacks remain in the use of these agents. First, both studies used extended courses of PEG/RBV, which is less ideal.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abbrev.</th>
<th>Mechanism</th>
<th>CYP450 Complex</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>TVR</td>
<td>NS3/4A protease inhibitor</td>
<td>CYP3A inhibitor</td>
<td>Headache, rash, dysgeusia, GI disturbance, and anemia</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>BOC</td>
<td>NS3/4A protease inhibitor</td>
<td>CYP3A inhibitor</td>
<td>Headache, dysgeusia, GI disturbance, and anemia</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>SMV</td>
<td>NS3/4A protease inhibitor</td>
<td>Metabolized by CYP3A4</td>
<td>Pruritus, rash, photosensitivity, and increased bilirubin</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>SOF</td>
<td>NS5B polymerase nucleotide analogue inhibitor</td>
<td>No interaction</td>
<td>Fatigue and headache</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>LDV</td>
<td>NS5A inhibitor</td>
<td>No interaction</td>
<td>Fatigue and headache</td>
</tr>
</tbody>
</table>
In addition, there is significant potential for drug-drug interactions between TVR/BOC and multiple ARVs, although it is unclear how clinically significant these may be.116,117 Finally, side effects continue to limit therapy for both protease inhibitors. Most common side effects of BOC include headache, dysgeusia, gastrointestinal (GI) disturbance, and anemia.117 Most common side effects of TVR are rash and pruritus, GI disturbance, and anemia.118 It seems likely that both BOC and TVR will have little role in the therapy for HCV if current results of more recently developed DAAs are confirmed by subsequent trials.

SMV is an NS3/4A protease inhibitor. It is metabolized primarily by cytochrome P450 3A4 (CYP3A4), so drug interactions remain a concern.116 It provides pan-genotypic activity in a once-daily pill, although it cannot be used as monotherapy. A phase III, open-label, single-arm study investigated SMV plus PEG/RBV in treatment-naive and treatment-experienced coinfected patients. Overall, 74% achieved SVR12, and 89% of patients met criteria allowing shortened therapy (24 weeks), with 78% achieving SVR12.119 Virologic failures occurred, mostly because of emergence of mutations. In multiple studies, patients with Q80K mutations, a polymorphism found commonly (48% in the United States) in genotype 1a, showed a lower response to therapy, and therefore, baseline testing is recommended before using SMV.119–121 In regards to drug-drug interactions with ARV, healthy controls demonstrated no significant interactions with TDF, rilpivirine (NNRTI), or raltegravir; however, there were alterations in SMV concentrations when dosed with EFV or darunavir/ritonavir (DRV/RTV, PI).122 Adverse events include pruritus, rash, photosensitivity, and increased bilirubin.119 Simepravir is likely to have a role in treating HCV when combined with other potent DAAs, but not with BOC or TVR.

NUCLEOTIDE INHIBITORS (SOF)

SOF is a nucleotide analogue inhibitor of the NS5B polymerase. It provides pan-genotypic activity in a once-daily pill with high barrier to resistance and no clinically significant ART drug interactions.118 It is not metabolized by the P450 enzyme complex. Preliminary data suggest that SOF + RBV treatment is safe with different ART regimens and may be equally safe and efficacious in patients that are coinfected compared with monoinfected, without HCV viral breakthrough.118,123 Drug studies in healthy persons found no significant interactions with EFV, TDF, FTC, DRV/RTV, rilpivirine, and raltegravir.116,124

A 12-week triple therapy study looked at 23 coinfected patients treated with SOF in combination with PEG and weight-based RBV. In the setting of genotype 1 infection, 89% of the 19 coinfected patients who completed the trial achieved SVR12.125 This achievement showed comparable efficacy to the larger trial of monoinfected individuals.121 Phase III PHOTON-1 investigated SOF + RBV without INF and demonstrated achievement of SVR12 in 76%, 88%, and 67% of coinfected participants with HCV genotypes 1, 2, and 3, respectively.123

OTHER AGENTS IN DEVELOPMENT (COFORMULATIONS)

Newer coformulations of DAAs have demonstrated similar sustained response rates of greater than 90% in treatment-naive and experienced patients. Recently submitted to the US Food and Drug Administration (FDA), a coformulation of ledipasvir (LDV), an NSSA inhibitor, with SOF, may soon be available.126 This option shows promise with increased ease of use because of decreased pill burden as a fixed dose once-daily regimen, as well the first all oral regimen for HCV genotype 1. In the ELECTRON trial, LDV/SOF + RBV or GS-9699 was studied in the hard-to-treat population with
advanced fibrosis or cirrhosis, and 100% achieved SVR12. Another agent, an oral three DAA regimen plus RBV (Dasabuvir + RBV twice daily, ABT-450/ritonavir/Ombitasvir once daily), showed in SAPPHIRE-I and SAPPHIRE-II to have excellent outcomes in the HCV-monoinfected population, including the more difficult to treat genotype 1a.

Studied also in the HIV/HCV-coinfected population, a new 2 DAA combination, MK-5172 and MK-8742, with or without RBV, has shown post-treatment sustained response rates above 90% for genotype 1 HCV patients, although this is still early data.

Overall, there has been little studied of these newer combination agents thus far in the coinfected population, but the treatment of both the HCV-monoinfected and HIV/HCV-coinfected patient will continue to rapidly change in the near future as more data is obtained. All-oral, interferon free regimens are on the horizon for all genotypes.

**CASE SELECTION FOR HCV THERAPY AND ART**

Decision of when to start therapy for HCV depends on stage of disease, patient readiness, and comorbidities. Minimal disease can be monitored, but in the coinfected population, even mild disease may be appropriate for therapy given the acceleration of fibrosis in this population.

ART is recommended for all coinfected patients, regardless of CD4 count. However, if the CD4 count is greater than 500, it may be reasonable to delay ART until treating their HCV to prevent drug interactions and risk of hepatotoxicity, as eradication of HCV with treatment may decrease the likelihood of drug-induced liver injury.

**PRACTICE GUIDELINES RECOMMENDATIONS**

New guidelines were recently released by the AASLD and the Infectious Diseases Society of America to help guide the treatment of HCV in the setting of rapidly evolving therapy. Special attention was paid to the HIV/HCV-coinfected population. Because of its prolonged treatment course, adverse effects, and poor response rates, PEG/RBV alone or in combination with TVR or BOC is not recommended for the treatment of patients with HCV genotypes 1, 2, 3, or 4 who are coinfected with HIV. Triple-therapy recommendations for the treatment of HIV/HCV-coinfected individuals are based on genotype, IFN-eligibility, Q80K polymorphism in genotype 1a, and prior treatment response. The mainstay of therapy still includes PEG/RBV, but now typically with the addition of SOF or SMV. Interferon-based therapies will likely be falling out of therapy in the United States within the next 6–12 months. In addition, these recommendations help guide ART choice (Table 4). Treatment of acute HCV has been shown to improve SVR rates, but the ideal treatment regimen has yet to be defined.

**MONITORING TREATMENT OUTCOME AND MANAGING ADVERSE EVENTS**

When using IFN-based therapies, HCV RNA levels should be monitored at baseline, week 4, week 12, week 24 or end of treatment, and 24 weeks after treatment. Additionally, CBC, CMP, and depression should be monitored every 2 weeks for the first month, then every month thereafter. SOF and RBV without PEG, in contrast, require less monitoring, and the FDA has endorsed SVR12 as an endpoint. Standard laboratory tests, including a complete blood count and comprehensive metabolic panel, should be monitored at 2, 4, 8, 12, 16, 20, and 24 weeks, to help identify
expected adverse events. Additionally, TSH should be monitored every 3 months. Coinfected women experience a higher rate of adverse events than coinfected men, and pregnant women should not undergo therapy with PEG/RBV. Anemia is one of the most significant adverse effects of RBV, with dose-reduction still the recommended initial strategy, although some recommend the use of epoetin or transfusions. Thrombocytopenia and leukopenia are significant adverse effects of PEG, and dose reduction remains the initial strategy, although other management options, including eltrombopag and filgastram, are sometimes used. Depression is another significant adverse effect of PEG, which can be managed with the use of antidepressants or mood stabilizers.

OTHER ISSUES
Cost and Access to Care

There is significant concern that with the improved but costly therapies now available for HCV, certain populations will get treatment more easily than others. In resource-poor nations, HCV treatment will likely remain difficult. In developed nations, HCV may become a disease of those with difficult access to care and/or more difficult to
treat, requiring PEG/RBV, such as those likely to be coinfected (homeless, active injection drug users, alcoholics, and illegal immigrants). Awareness and advocacy will become a complementary part of therapy, especially in the coinfected population. Payers are currently reviewing indications for treatment based on disease severity which may be less relevant in the coinfected population given the more rapid progression of disease.

Primary and Secondary Prevention

Both the World Health Organization and the Advisory Committee on Immunization Practices advise universal infant HBV vaccination. All individuals with HIV should be vaccinated against HBV if they do not have evidence of immunity or prior infection as defined by the presence of anti-HBsAb. All patients should be assessed for response by obtaining anti-HBs titers at one month after series completion.

HIV-positive individuals tend to have lower response rates and durability to vaccination. While immunocompetent patients respond to hepatitis B vaccination at rates greater than 90%, HIV-infected patients have been found to respond at rates of 24–56%. Low CD4 counts and high viral loads are associated with decreased immunization success. It is generally recommended that a standard vaccination schedule be initially followed. All who present to care should receive vaccination regardless of CD4 count as a response can be seen even with a low CD4. Anti-HBs titers should be obtained 1 month after completing the series. If immunity is not achieved, as defined by the development of anti-HBsAb, revaccination using a double dose and/or 3 to 4 doses can be used. At our institution, if there is no response to the initial vaccine series, then we are in the habit of repeating the vaccination series at a double dose. Although vaccination is important, patients should also be educated about transmission risks and avoidance of high risk behaviors.

In contrast, there is no vaccine for hepatitis C. Preventing the spread of HCV involves avoiding unnecessary or unsafe injections, contaminated needles, or blood products, use of injection drugs or needle-sharing, unprotected sex, sharing sharp personal products that may be contaminated with blood, and tattoos or piercings with contaminated needles. In addition, education and prevention to help prevent first infections, as well as recurrent HCV infections in high-risk groups, should be a mainstay of therapy in the HIV population.

If an HIV-infected patient is found to be coinfected with HCV, they should have hepatitis A and B vaccination to prevent other hepatotoxic viruses. Those coinfected with HBV should receive hepatitis A vaccination as well. In addition, they should be regularly monitored for chronic liver disease every 6 months with a CMP, CBC, and INR. According to the AASLD, individuals with cirrhosis should be screened for HCC with an ultrasound every 6 to 12 months, and while controversial some practitioners also use AFP.

SUMMARY

In HIV-infected individuals, coinfection with HBV and/or HCV is common due to shared modes of transmission. It is known that HIV accelerates progression of liver disease and results in increased morbidity and mortality associated with viral hepatitis, but it is less clear if viral hepatitis has a direct effect on HIV. Treatment of viral hepatitis improves outcomes and should be considered in all HIV patients. Treatment of HBV without HIV is not advised because resistance can occur in both viruses. As the new DAAs for HCV become available, treatment will become easier with less adverse
effects, less drug-drug interactions, and dramatically increased rates of success expected. There will still remain complications in the treatment of HCV in the coinfected population because of the need for continued PEG/ RBV regimens when possible, and issues with cost and access to care.

REFERENCES


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