Antiretroviral Therapy for Hepatitis B Virus–HIV–Coinfected Patients: Promises and Pitfalls

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Coinfections with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are common globally. HIV infection modifies the course of HBV infection by increasing rates of chronicity, prolonging HBV viremia, and increasing liver-related morbidity. To minimize the emergence of HIV and/or HBV resistance, as well as the emergence of liver enzyme flares, the treatment of both infections should be coordinated. Lamivudine or emtricitabine monotherapy readily selects resistant strains in the YMDD motif of the polymerase gene. Adefovir monotherapy has moderate effectiveness in HIV-HBV–coinfected patients who have YMDD mutation. If HBV treatment can be deferred until combination antiretroviral therapy for HIV infection is needed, the combination of tenofovir plus lamivudine or emtricitabine provides potent HBV therapy and a solid backbone for HIV combination antiretroviral therapy, and it likely decreases the emergence of HBV resistance.

EPIDEMIOLOGY AND NATURAL HISTORY OF HIV–HEPATITIS B VIRUS (HBV) COINFECTION

HIV infection and HBV infection are both sexually transmitted diseases. Coinfections are common globally, because the risk factors for acquisition are the same [1–3]. In the United States and Europe, >50% of HIV-infected men who have sex with men have evidence of past HBV infection, and 7%–10% have chronic HBV infection, which is defined as the persistence of surface antigen in the serum for at least 6 months. Dual infections may be even more problematic in regions of the world with a high or intermediate prevalence of HBV infection (figure 1), where early childhood infections and higher rates of chronicity are common.

HIV-infected adults who develop acute HBV infection are less likely to eliminate HBV, compared with HIV uninfected adults (23% of HIV-HBV–coinfected adults develop chronic HBV infection, compared with 4% of HBV-infected persons without HIV infection) [6]. There is a decreased likelihood of HBV clearance through a broad cellular response in HIV-infected persons with lower CD4+ T cell counts, compared with HIV-infected persons with higher CD4+ cell counts, at the time of HBV acquisition. In the absence of treatment, HIV-HBV–coinfected patients have higher HBV DNA levels and a longer duration of viremia, but lower transaminase values, compared with patients who are infected only with HBV. This prolonged period of HBV replication may increase horizontal and vertical transmission of HBV in areas of the world with a high prevalence of HIV-HBV coinfection [7].

Despite of this apparent phase of immunotolerance, HIV-HBV–coinfected persons have higher liver-related morbidity rates than do persons with either infection alone. Among 5293 men observed in the Multicenter AIDS Cohort Study, HIV-HBV–coinfected men were almost 19 times more likely to die of liver disease than were those infected with HBV alone, and they were >8 times more likely to die of liver disease than were those infected with HIV-1 alone [8]. In HIV-HBV–coinfected men, the mortality rate attributable to liver disease was highest for subjects with a nadir CD4+ T cell count of <100 cells/mm^3 and for those with heavy alcohol consumption [8]. Alcohol use (proportional to the extent and duration of use) and HBV infection produce an additive effect in terms of progression to fulminant hepatitis, aggressive chronic liver disease, and hepatocellular carcinoma [9]. The increased risk of alcohol toxicity in HIV-HBV–coinfected persons may be a result of more frequent hepatic steatosis associated with alcohol use and/or antiretroviral-associated mitochondrial toxicity. The influence of these cofactors can be reduced by counseling to reduce al-
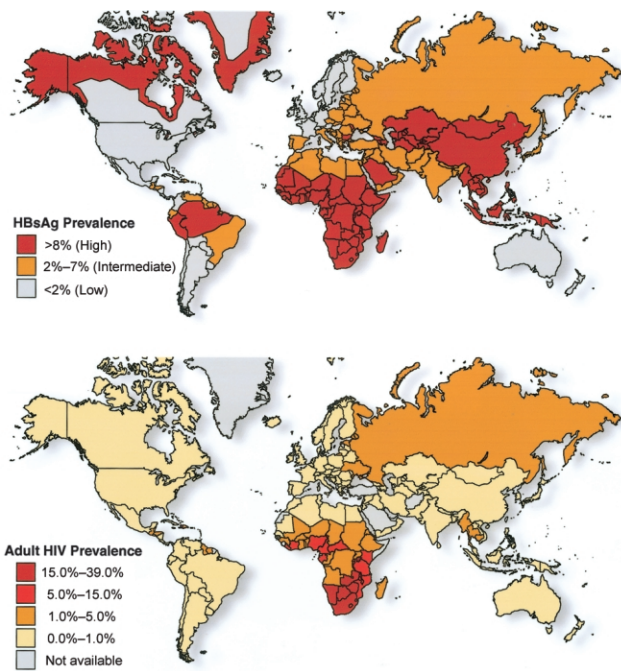
Figure 1. The global geographic distribution of chronic hepatitis B virus infection and HIV infection. From [4, 5]. HBsAg, hepatitis B surface antigen.

cohol consumption and use of less-toxic antiretroviral therapies [10]. Other factors associated with progression of liver disease are older age, elevated alanine aminotransferase (ALT) level, and high HBV DNA levels [11].

During the initial stage of chronic HBV infection, serum HBV DNA levels are high and hepatitis B early antigen (HBeAg) is present. In the majority of patients who have undergone seroconversion from HBeAg to anti-HBe (i.e., the loss of HBeAg with development of antibodies to HBeAg), HBV DNA levels decrease to $<10^5$ copies/mL, ALT levels normalize, and hepatic inflammation decreases. The majority of patients who develop HBeAg seroconversion remain in the inactive surface antigen carrier state, which is marked by detectable hepatitis B surface antigen (HBsAg), undetectable HBeAg and HBV DNA, and minimal hepatic inflammation. Patients in the inactive carrier state usually have a benign clinical course, although HBV infection may reactivate in up to 30%, with progression of liver disease [12]. Because coinfection with HIV reduces the frequency of spontaneous HBsAg and HBeAg seroconversion, the prevalence of HBeAg-negative chronic hepatitis is lower in HIV-HBV–coinfected patients [9].

Occult HBV infection is defined as the presence of HBV DNA in the serum or liver of patients without HBsAg [9]. The reported prevalence of occult HBV infection in HIV-1–infected persons ranges from <1% to 89.5% [13, 14]. Possible reasons for the wide range of reported prevalence include (1) intermittent HBV replication not captured by isolated samples; (2) different methods used to quantify HBV replication and dif-

ferent assay sensitivities among studies; (3) inconsistent reporting of antiretroviral treatment with lamivudine, emtricitabine, or tenofovir; and (4) HCV-HBV coinfection, which may interfere with HBV DNA load quantification, because the HCV core protein binds to HBV DNA, thereby suppressing HBV replication [13]. The clinical relevance of occult HBV in HIV-1 infected persons is uncertain. One recent study did not find an increased risk of liver enzyme elevations in occult HBV-HIV–coinfected persons after the start of combination antiretroviral therapy [15].

A group of patients who have chronic hepatitis with expression of HBV DNA but who have no detectable HBeAg has been recognized. These patients tend to have more severe hepatic inflammation and a higher likelihood of cirrhosis. The discordant test results (HBV DNA positive but HBeAg negative) are often due to HBV mutants that cannot produce HBeAg because of mutations in the precore or core promoter. The likelihood of these mutants is related to the duration of infection, as suggested by an older age at presentation. Precore mutations occur mainly in persons infected with HBV genotypes other than A; non-A genotypes are uncommon in the United States, where genotype A predominates, but are very common in Mediterranean, European, and Asian countries [16].

THE GOALS OF HBV TREATMENT IN HIV-HBV–COINFECTED PATIENTS

The decision to treat HBV infection in coinfected persons is based on careful consideration of the need for combination antiretroviral therapy for HIV infection, the severity of liver disease, the likelihood of response, and potential adverse events [17, 18]. HIV-infected persons with active HBV replication (i.e., they test positive for HBsAg and have detectable HBV DNA) and elevated transaminase levels (i.e., >2 times the normal level) should be considered for HBV treatment, even if the criteria for commencement of combination antiretroviral therapy for HIV infection have not yet been satisfied. In the context of HIV infection, HBV infection progresses more rapidly to cirrhosis, with lessening response to HBV treatment regimens as immunodeficiency progresses [18]. Control of HIV infection is the usual priority when treating HIV-HBV–coinfected patients. HBV treatment goals are the same for persons with coinfection as for persons with HBV infection alone—namely, normalization of the ALT level, improvement in liver histology findings, and suppression of HBV DNA.

Initially, all persons with chronic HBV infection should have HBeAg, anti-HBe, and HBV DNA levels measured to classify the stage of chronic HBV infection [19]. HBV DNA level—the measurement of HBV load—reflects viral replication and is important for diagnosis, prognosis, and treatment monitoring. Various methods are commercially available to measure HBV DNA level. Because the usual viral load unit provided in treat-

ment guidelines [9, 17] is copies per milliliter, results reported in other units should be converted to copies per milliliter for comparison [19]. Real-time PCR is superior to other methods for quantifying HBV DNA level with regard to sensitivity, specificity, and reproducibility [20]. In real-time PCR, a fluorescent-labeled oligonucleotide probe binds specifically to the PCR amplicate. The measurement of the fluorescence intensity allows quantification of the product. HBV DNA suppression correlates with histological improvement in patients receiving HBV therapy [21]. Viral eradication is not a feasible goal, because current anti-HBV therapy does not eliminate covalently closed circular DNA, the template for pregenomic RNA formation in infected hepatocytes.

In HBeAg-positive persons, HBeAg seroconversion is a durable end point that correlates with a sustained response after the cessation of treatment in patients with HBV infection alone. A baseline liver biopsy performed before the initiation of combination antiretroviral therapy should be considered for HIV-HBV–coinfected patients, because advanced fibrosis is more likely to occur in HIV-infected persons, and severe hepatitis flares can lead to liver failure and death in persons with poor hepatic reserve [22].

LIVER ENZYME FLARES IN COINFECTED PATIENTS RECEIVING COMBINATION ANTIRETROVIRAL THERAPY

Flares of liver enzymes in HIV-HBV–coinfected patients have a variety of possible causes. In chronic HBV-infected patients who experience HBV suppression while receiving antiretroviral therapy, flares have been reported upon the discontinuation of lamivudine [23], emtricitabine [24], or tenofovir [25] treatment or with the emergence of lamivudine (emtricitabine) resistance [9]. Less likely causes of flares in HIV-HBV–coinfected persons are HBeAg or HBsAg seroconversion or superinfection with another hepatitis virus (e.g., hepatitis A or D virus).

Liver histologic findings can worsen rapidly in patients during a flare and can improve significantly upon flare resolution. The higher prevalence of HBV-related cirrhosis and hepatocellular carcinoma in men may be mediated by a higher frequency of flares in men. HIV-HBV–coinfected patients are more prone to develop flares when they begin receiving combination antiretroviral therapy, and the flares may be erroneously attributed to drug-related hepatotoxicity [25]. Combination antiretroviral therapy can trigger an immune reconstitution syndrome in which immune responses against HBV antigens are augmented [26]. These immune reconstitution flares usually occur within 3 months after a person starts combination antiretroviral therapy, and they may be followed by normalization of ALT levels and clearance of HBV DNA. To prevent HBV flares, active HBV replication should be controlled before or in conjunction with the initiation of combination antiretroviral therapy. Although

clear evidence is lacking that suppression of HBV replication before the commencement of combination antiretroviral therapy prevents immune reconstitution flares, we concur with others who recommend using combination therapy with lamivudine (or emtricitabine) and tenofovir in the combination antiretroviral regimen for all HIV-HBV–coinfected patients with active HBV replication, especially those with cirrhosis [22].

The most common cause of a late flare during combination antiretroviral therapy is the emergence of lamivudine-resistant strains of HBV, which are marked by an increase in HBV DNA and the appearance of the YMDD mutation. Flares that occur after cessation of antiviral therapy have been observed in persons who stop taking lamivudine, emtricitabine, adefovir, or tenofovir [23, 27–29].

Risk factors for serious flares after antiviral cessation include elevated transaminase levels at the time that therapy is started and the presence of severe fibrosis. Flares that occur after antiviral therapy has been stopped should be treated by resumption of antiviral treatment, preferably with at least 2 HBV-active drugs in combination.

REVIEW OF HBV-ACTIVE AGENTS

Although HBV is a DNA virus, replication occurs through an RNA intermediate, requiring a viral reverse transcriptase/polymerase. The HBV reverse transcriptase lacks the proofreading function found in other polymerases. As a result, HBV exhibits a mutation rate >10-fold greater than that of other DNA viruses, and it more closely resembles the HIV retrovirus in this regard. To minimize the selection of drug-resistant HIV and/or HBV, management of both infections must be carefully coordinated.

Five drugs have been approved by the US Food and Drug Administration (FDA) for treatment of chronic hepatitis B: IFN-α-2b (in 1992), lamivudine (in 1998), adefovir dipivoxil (in 2002), entecavir (in March 2005), and pegylated IFN-α-2a (in May 2005). Although tenofovir and emtricitabine have not been licensed by the FDA for treatment of chronic hepatitis B, both agents are known to be highly active against HBV, so data regarding these drugs will be reviewed as well (table 1).

IFN. IFN-α, available in pegylated form (which permits once-weekly dosing), is most effective for HBeAg-positive patients with high ALT levels (>2 times the upper limit of normal) and low HBV DNA levels [30]. It can be used for a limited treatment duration (16 weeks) in HBeAg-positive patients. IFN use is limited by different adverse events (flulike symptoms, psychiatric effects, bone marrow suppression, and thyroid dysfunction) and is contraindicated in cirrhotic patients. Liver enzyme flares during IFN treatment are more common among HIV-infected persons than among HIV-negative persons [31].

Published trials about IFN treatment in HIV-HBV–coinfected patients were conducted before the combination anti-

Table 1. Summary of hepatitis B virus (HBV)/HIV activity and resistance features for HBV-active agents from clinical studies involving HIV-HBV–coinfected persons.

Drug	HBV response rate	Activity against HIV	Resistance risk	Resistance pattern	FDA licensed for treatment of HBV infection in the United States	Reference(s)
IFN-α	In HIV-infected patients: HBeAg seroconversion at 3 years, 4 (15%) of 26 patients; undetectable HBV DNA, 7 (27%) of 26 patients	None	None	Not applicable	Yes	[31]
Lamivudine	Greater loss of HBeAg in lamivudine arms (7 of 32 patients); median $\log_{10}$ change in HBV level in lamivudine arms at 1 year, -2.7 ($n = 48$); 40% of subjects in lamivudine arms had undetectable HBV DNA level (<400 copies/mL) at 1 year	Yes	YMDD mutants at 1 year, 25%; YMDD mutants at 2 years, 52%	V173L, L180M, M204I/V	Yes	[32, 33]
Emtricitabine	Mean decrease in HBV DNA level, $-3.4 \log_{10}$ copies/mL at 56 days; maintained after 48 weeks of treatment in more than one-half of patients	Yes	YMDD mutants at 2 years, 19%	M204I/V	No	[9, 34]
Entecavir	In coinfected patients with YMDD mutants, the mean decrease in the HBV DNA level was $-3.66 \log_{10}$ copies/mL at 6 months; 57 (84%) of 68 patients had an HBV DNA level <400 copies/mL or a ≥2-$\log_{10}$ reduction from baseline	No	Undefined	V173L, L180M, A184G, S202I, M204I/V, M250V	Yes	[35]
Adefovir	Loss of HBeAg in 3 (10%) of 29 patients, with 2 (7%) of 29 having seroconversion to HBeAb when adefovir was added to lamivudine in coinfected patients by 1 year; 7 (24%) of 29 patients had a HBV DNA level <200 copies/mL	Low	None at 3 years	A181V, N236T	Yes	[36]
Tenofovir		Yes	None at 1 year	A194T	No	[37]
Substudy 903	Mean decrease in the HBV DNA level among 11 coinfected, ART-naive subjects, 3.0 $\log_{10}$ copies/mL (lamivudine arm) vs. 4.7 $\log_{10}$ copies/mL (lamivudine plus tenofovir arm)	…	…	…	…	…
Substudy 907	Mean decrease from baseline at 6 months in the HBV DNA level among 10 coinfected, ART-experienced subjects, 4.9 $\log_{10}$ copies/mL (maintained for 1 year); 2 of 10 lost HBeAg; 1 of 10 became HBeAb positive	…	…	…	…	…

NOTE. ART, antiretroviral therapy; FDA, US Food and Drug Administration; HBeAg, hepatitis B early antigen.

retroviral era. The poorer response to IFN in HIV-HBV–coinfected patients, compared with HBV-monoinfected patients, may be a reflection of HIV-mediated immunosuppression. One study found that HIV-HBV–coinfected persons with lower $CD4^+$ T cell counts had poorer responses to IFN and higher rates of reactivation of HBV infection [31]. In HIV-HBV–coinfected patients with high $CD4^+$ T cell counts, elevated ALT levels, and low HBV DNA levels, IFN may be a candidate for initial HBV treatment, because one can avoid antiretroviral toxicity and resistance to nucleoside and nucleotide analogues.

Lamivudine. Lamivudine is a nucleoside analogue that inhibits both HIV and HBV reverse transcriptase. Although it was approved at a dosage of 100 mg daily for patients with HBV infection alone, it should be administered at 150 mg twice daily or 300 mg daily as part of a combination antiretroviral regimen in HIV-HBV–coinfected patients to prevent emergence of drug-resistant HIV.

HBeAg seroconversion has been reported in 22%–29% of HIV-HBV–coinfected patients who receive lamivudine [32, 38, 39], whereas undetectable HBV DNA levels were achieved in 40%–87% of patients [32, 38, 39]. In both HIV and HBV, lamivudine monotherapy readily selects for resistant strains in the YMDD motif of the polymerase gene. Continuation of lamivudine treatment after the emergence of a YMDD mutant may still provide some benefit; however, improvement in HBV-related histopathological stage does not appear to be sustained after the emergence of resistant mutants [12].

Emtricitabine. Emtricitabine is structurally identical to lamivudine, aside from the addition of 1 fluorine in one of the rings. The effective dosage for treatment of HBV infection (200 mg once daily) is the same dosage used for HIV treatment. In the US Public Health Service and International AIDS Society guidelines, these drugs are considered interchangeable. Resistance to emtricitabine, also through YMDD mutants, seems to occur more slowly than with lamivudine [9].

Entecavir. Entecavir is a nucleoside analogue that causes rapid suppression of HBV but that has no significant activity against HIV. In HIV-HBV–coinfected patients, a dosage of 1.0 mg per day is recommended from the start of treatment. Resistance to entecavir results from the accumulation of multiple changes in the HBV polymerase, including those linked to lamivudine resistance. Entecavir is an option for coinfected patients who require HBV treatment but whose HIV disease does not yet require combination antiretroviral therapy. It may also be useful as HBV salvage therapy in coinfected patients with YMDD mutants [35].

Adefovir. Adefovir is a nucleotide reverse-transcriptase inhibitor approved at a dosage of 10 mg per day for chronic hepatitis B. It is active against lamivudine-resistant virus in HBeAg-positive and HBeAg-negative patients. No evidence of mutations in the HIV reverse-transcriptase codons (K65R or K70E) were reported after 1 year of adefovir use at HBV treatment doses [36]. When adefovir was added to lamivudine in HIV-HBV–coinfected patients, undetectable HBV DNA levels were achieved in only 25% of subjects, and 45% of subjects achieved HBV DNA levels <1000 copies/mL [36].

Tenofovir. Tenofovir is a nucleotide reverse-transcriptase inhibitor effective against many nucleoside-resistant HIV mutants and against lamivudine- and adefovir-resistant HBV [40]. Made by the same manufacturer as adefovir, tenofovir is not yet licensed in the United States or Europe for treatment of HBV infection. Because tenofovir and adefovir have overlapping renal toxicity and similar structures, these agents should not be used in combination.

Tenofovir has shown comparable activity to adefovir against HBV in HIV-HBV–coinfected persons. Among 52 HBV-HIV–coinfected patients receiving tenofovir or adefovir in addition to their combination antiretroviral regimen, the HBV DNA mean log_{10} change from baseline at 1 year was -4.44 in the tenofovir arm and -3.21 in the adefovir arm [41]. In the 903 Study [37], patients receiving tenofovir plus lamivudine had a greater decrease in HBV DNA levels and reduced YMDD resistance, compared with those receiving lamivudine as their only HBV-active drug. A recent retrospective study [36] suggests that tenofovir is effective against lamivudine-resistant HBV strains in HIV-HBV–coinfected patients who are receiving combination antiretroviral therapy. In this study, 16 (30%) of 54 HBeAg-positive patients and 9 (82%) of 11 HBeAg-negative patients developed undetectable HBV levels while receiving a tenofovir-lamivudine combination regimen.

THE ROLE OF COMBINATION THERAPY IN COINFECTED PATIENTS

The goals of HBV treatment in the HIV-HBV–coinfected patient not only include HBV suppression, but also the prevention of HBV and HIV reverse-transcriptase resistance mutations associated with drug resistance. For the coinfected patient who does not yet need combination antiretroviral therapy but who does need HBV treatment, pegylated IFN, entecavir, and adefovir are suitable options. IFN treatment does not lead to resistance, but it is appropriate for only a narrow group of HIV-HBV–coinfected persons: those with high $CD4^+$ T cell counts, HBeAg-positive patients, and those with high ALT levels and low HBV DNA levels. Entecavir and lamivudine share some HBV drug-resistance mutations, so resistance to the entire regimen could probably occur readily. Entecavir and adefovir have a low probability of inducing HIV resistance and can be used together in combination.

Another option for HIV-HBV–coinfected persons with preserved immune function is to defer HBV treatment until com-

bination antiretroviral therapy is needed, at which time a combination antiretroviral regimen including tenofovir and either lamivudine or emtricitabine should be chosen. The rates of drug resistance with lamivudine monotherapy are 50% after 2 years and 90% after 4 years [38], suggesting that lamivudine or emtricitabine should be used in combination with another agent. Rates of resistance with tenofovir are lower, such that more data are needed to determine whether this agent can be used as the only agent with activity against HBV. A recent randomized trial of HIV-HBV–coinfected patients (both lamivudine-naive and lamivudine-experienced subjects) found that combination therapy with tenofovir and lamivudine as part of combination antiretroviral treatment was superior in terms of HBV DNA suppression than was tenofovir or lamivudine administered alone [42].

We recommend performing a baseline HBV DNA test in HIV-HBV–coinfected patients who receive antiviral therapy. Testing at 3-month intervals, as with HIV load testing, is reasonable. HBV resistance should be clinically suspected if there is a 1-log_{10} increase in the HBV DNA level from the patient's lowest on-treatment level. HBV resistance to all drugs except IFN can be confirmed with genotyping assays involving sequencing of the HBV polymerase gene. Mutations associated with IFN resistance have not been identified.

PREEXPOSURE PROPHYLAXIS AND POSTEXPOSURE PROPHYLAXIS CONSIDERATIONS

Chemoprophylaxis with tenofovir or combined tenofovir-emtricitabine has been demonstrated to prevent simian immunodeficiency virus transmission in nonhuman primates [43, 44]. Clinical trials of chemoprophylaxis with tenofovir or tenofovir-containing regimens for prevention of HIV infection are being planned or are in progress. Zidovudine administered in combination with lamivudine is frequently used for postexposure prophylaxis, which is recommended by the US Public Health Service for patients who present within 72 h after a significant exposure to an HIV-1–infected partner [45].

Discontinuation of chemoprophylaxis in persons with chronic active hepatitis B may pose a risk of an HBV hepatitis flare. All available information about the risk of hepatitis flares is derived from persons who start anti-HBV therapy with elevated liver enzyme levels or clinically significant cirrhosis. Persons who commence antiviral therapy for chemoprophylaxis with normal liver enzyme levels and no clinical signs of cirrhosis may have much lower risk. Until more information is available from clinical trials, use of anti-HBV agents for chemoprophylaxis should be closely monitored with prior HBsAg testing and serial liver function tests performed monthly for 3 months after chemoprophylaxis has been stopped.

CONCLUSIONS

HIV-HBV coinfection is common worldwide. Several nucleosides and nucleotides used as part of a combination antiretroviral regimen have activity against HBV. In HIV-HBV–coinfected patients, antiretrovirals should be selected and monitored to minimize the risk of HBV and HIV resistance. Nucleotide analogues (adefovir and tenofovir) select for HBV resistance less commonly than do nucleoside analogues (lamivudine and emtricitabine). Fortunately, the 2 drug types do not share resistance mutations, allowing several options for initial, salvage, and combination regimens. Given the rapid rates of mutation of HBV and the frequent occurrence of resistance to some antiviral agents, the use of combination regimens is likely to be beneficial. In treatment-experienced patients, the types of HBV mutations present should help guide treatment selection.

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