

Perspective

Hepatitis B Virus Treatment in HIV-infected Patients

Hepatitis B virus (HBV) infection is common in HIV-infected persons and is associated with increased risk of liver-related morbidity and mortality. Agents available to treat HBV infection in coinfecting patients include lamivudine, entecavir, emtricitabine, adefovir, tenofovir, peginterferon alfa, and the recently approved telbivudine. Treatment decisions should take into account a number of factors, including antiretroviral therapy status, HBV genotype, prior experience of lamivudine, and the need to avoid drug resistance in both HIV- and HBV-infected persons. This article summarizes a presentation on treatment and management of HBV infection in HIV-infected patients made by Chloe L. Thio, MD, at the 9th Annual Ryan White CARE Act Clinical Update in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org.

It is estimated that 1 to 1.25 million persons in the United States (US) have hepatitis B virus (HBV) infection. The incidence of infection decreased by 67% between 1990 and 2002, reflecting at least in part the use and efficacy of HBV immunization. However, between 1999 and 2002, incidence rates increased by 5% in men aged 20 to 39 years, and by 20% in men and 31% in women aged 40 years or older (age groups that are also at increased risk of HIV infection). Coinfection with HIV is common. It is estimated that approximately 10% of HIV-infected individuals also have chronic HBV infection. Coinfecting patients have increased risks of rapid progression of HBV liver disease, liver-related mortality, antiretroviral therapy-related hepatotoxicity, and hepatic failure as part of an immune reconstitution syndrome. Figure 1 shows the marked increase in liver-related mortality in coinfecting patients in a study of 5293 men with or without HIV or HBV infection (Thio et al, *Lancet*, 2002).

Case 1: Patient With No Prior Antiretroviral Therapy

A 28-year-old white man is referred for elevated liver function tests. He has a history of hypertension and review of

systems shows fatigue and decreased appetite. Physical exam shows no jaundice and no right-upper quadrant tenderness or hepatosplenomegaly. Laboratory tests show alanine aminotransferase (ALT) of 126 IU/mL and total bilirubin of 0.6 mg/dL, and the patient is positive for HBV surface antigen (HBsAg). What test is most helpful in initially characterizing the patient's HBV infection:

1. HBV DNA,
2. Liver biopsy,
3. HBV envelope antigen (HBeAg),
4. 1 and 3, or
5. 1, 2, and 3?

This patient should be tested for both HBV DNA and HBeAg. Acute HBV infection is indicated by an IgM antibody response to HBV core antigen (HBcAg). Chronic infection is indicated by presence of HBV surface antigen (HBsAg) for more than 6 months. Individuals who have responded to HBV vaccine exhibit anti-HBs antibody, and those with past infection exhibit both anti-HBs antibody and anti-HBc antibody. The patient's HBsAg-positive status indicates chronic infection.

Among patients with chronic infection, active infection is indicated by HBeAg-positive status, which is often accompanied by ALT greater than 2 times the upper limit of normal, HBV DNA level greater than 1×10^5 copies/mL ($\sim 2 \times 10^4$ IU/mL), and evidence of disease on liver biopsy. Patients

who are HBeAg-negative also may have active infection, with similar ALT levels and positive liver biopsy but may have lower HBV DNA levels (eg, greater than 10^4 copies/mL [$\sim 2 \times 10^3$ IU/mL]) than HBeAg-positive patients. HBeAg-negative patients without active infection, "healthy carriers," tend to have normal ALT levels and undetectable, or very low, HBV DNA levels and would be unlikely to have significant findings on liver biopsy. Figure 2 provides an idea of how serologic markers, liver function tests, and clinical and immune states are correlated in the natural history of HBV infection. HBV/HIV-coinfecting patients who are HBV-inactive carriers require monitoring for HBV DNA and ALT (eg, every 6-12 months) to promptly detect reactivation of HBV infection.

The patient is found to have HIV infection, with a CD4+ cell count of 500/ μ L. He is HBsAg-positive, HBeAg-positive, and anti-HBe antibody-negative, has HBV DNA of 5×10^6 IU/mL, and stage 1 to 2 fibrosis on liver biopsy. What other tests should be done:

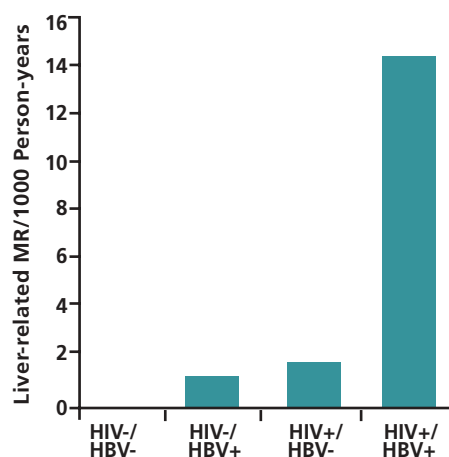


Figure 1. Liver-related mortality rate (MR) per 1000 person-years in 5293 men with (+) or without (-) hepatitis B virus (HBV) or HIV infection. Cohort included 326 men who were HBV surface antigen-positive (HBsAg+). Adapted from Thio et al, *Lancet*, 2002.

Dr Thio is an Associate Professor of Medicine at The Johns Hopkins University in Baltimore, Maryland.

1. Ultrasound or computed tomography (CT) scan and measurement of alpha-fetoprotein,
2. Total hepatitis A virus (HAV) antibody,
3. HBV genotype,
4. 1 and 2, or
5. 1, 2, and 3?

Patients with HBV infection are at increased risk for hepatocellular carcinoma, which should be ruled out by ultrasound or CT scan and testing for alpha-fetoprotein. They are also at increased risk of more fulminant HAV infection; HAV antibody should be assessed, and the patient should receive hepatitis A vaccine if he is antibody-negative.

HBV genotyping is becoming increasingly useful in HBV-disease management, as more is learned about associations of genotype with disease progression (including risk of hepatocellular carcinoma) and response to HBV treatment. For example, in a recent trial comparing peginterferon alfa with peginterferon alfa plus lamivudine in patients without HIV infection, response measured as HBeAg loss occurred in 29% and 44% of patients, respectively, at end of treatment at week 52 ($P = .01$), with the response rate increasing to 36% in the monotherapy group and decreasing to 35% in the combination group at end of follow up at week 78 ($P =$ not statistically significant [NS]; Janssen et al, *Lancet*, 2005). The

study indicated that the addition of lamivudine did not provide benefit and showed that HBV genotype influenced response at end of follow up. Among all patients, response at week 78 was observed in 47% of 90 patients with genotype A, 44% of 23 patients with type B, 28% of 39 patients with type C, and 25% of 103 patients with type D. Types A and D are the most common in the United States, and there was a statistically significant increase in response for type A versus type D (odds ratio, 2.4; 95% confidence interval, 1.3-4.6; $P = .01$) in the study. There currently are no data on association of genotype with response in coinfecting patients.

In addition to the findings already noted, genotyping shows the patient to be infected with HBV genotype A. His plasma HIV RNA level is 12,000 copies/mL. What treatment should he receive:

1. Lamivudine,
2. Entecavir,
3. Tenofovir,
4. Peginterferon alfa, or
5. 2 or 4?

US Food and Drug Administration (FDA)-approved therapies for HBV infection consist of: the L-nucleoside analogues, lamivudine, telbivudine, and entecavir; the nucleotide analogue, adefovir; and peginterferon alfa. Agents with activity

against HBV that are available but not FDA-approved include the nucleoside analogue emtricitabine, and the nucleotide analogue tenofovir. Lamivudine, emtricitabine, and tenofovir have intrinsic anti-HIV activity. Adefovir, a forerunner of tenofovir, also has anti-HIV activity but is given at lower doses in HBV infection than those associated with anti-HIV activity. Adefovir is not used for HIV treatment because doses with anti-HIV activity were associated with severe renal toxicity. Peginterferon alfa has some anti-HIV activity but is not associated with HIV resistance. Given the patient's HIV RNA and CD4+ cell count, he can begin treatment for HBV infection before antiretroviral therapy for HIV is considered. To avoid the emergence of HIV resistance that would arise with suboptimal suppression of viral replication and compromise future treatment, the agents with intrinsic anti-HIV activity should not be used to treat HBV infection. Of the choices listed, one option for the patient is peginterferon alfa; however, it has yet to be assessed in patients with coinfection. Entecavir is also an option since published data do not show evidence of anti-HIV activity. Other options, which are not listed, include initiating antiretroviral therapy early or adefovir.

Case 2: Patient On Antiretroviral Therapy

A 42-year-old HIV-infected man presents with elevated liver enzymes. He has received zidovudine, lamivudine, and efavirenz for the past 3 years and has a CD4+ cell count of 350/ μ L and plasma HIV RNA level below 50 copies/mL. He is HBsAg-positive and HBeAg-negative, with HBV DNA of 3.6×10^5 IU/mL. What should you do with his medications:

1. Replace zidovudine with tenofovir,
2. Continue current medications,
3. Add entecavir,
4. Replace lamivudine with emtricitabine, or
5. None of the above?

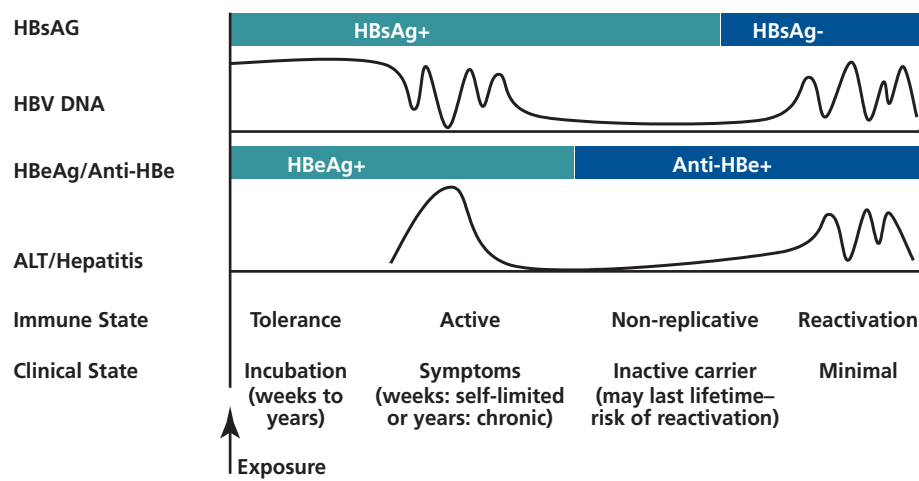


Figure 2. Natural history of hepatitis B virus (HBV) infection. HBsAg indicates HBV surface antigen; HBeAg, HBV envelope antigen; anti-HBe, antibody to HBe; ALT, alanine aminotransferase; +, positive; -, negative.

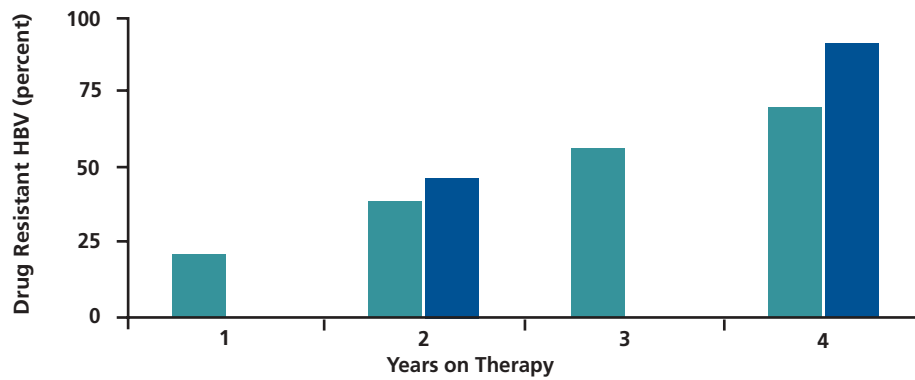


Figure 3. Development of hepatitis B virus (HBV) resistance to lamivudine (LMV) in HBV monoinfection (light green) or HBV/HIV coinfection (dark blue). Adapted from Benhamou et al, *Hepatology*, 1999; Liaw et al, *Gastroenterology*, 2000; Chang et al, *J Gastroenterol Hepatol*, 2004.

The patient has been receiving lamivudine for 3 years as part of a antiretroviral therapy regimen that remains effective in suppressing HIV replication. HBV resistance to lamivudine develops more rapidly in coinfecting patients than in HBV–monoinfected patients (Figure 3), with approximately 90% of coinfecting patients having HBV resistance after 4 years of treatment. The emergence of resistance is clinically evidenced by increases in transaminases. For example, in one study ALT flares (greater than 3 times the upper limit of normal) showed statistically significant increases in patients with lamivudine resistance, as well as statistically significant increases as the duration of presence of lamivudine resistance lengthened. Hepatitis flares occurred in about 20% of patients with no evident lamivudine resistance, about 35% of those with presence of resistance mutations for less than 1 year, and about 75% of those with mutations present for more than 4 years. Hepatic decompensation and liver-related adverse events increased after 4 years of lamivudine resistance (Lok et al, *Gastroenterology*, 2003).

In this patient, the lamivudine is needed for his HIV infection. Although data exist suggesting that continuing lamivudine despite resistance might still benefit the patient in terms of continued reduction in HBV DNA and maintained loss of HBeAg, growing evidence, on hepatitis flares and the association of such flares with worsened liver dis-

ease, argue against continuing lamivudine alone in the setting of resistance.

The patient's medications need to be changed to provide additional anti-HBV activity. Among potential drugs that may be substituted or added are adefovir, tenofovir, and entecavir. Adefovir does not appear to be as effective in treating HBV infection as tenofovir. In a cohort of

35 coinfecting patients with lamivudine-resistant HBV, 48-week outcomes with adefovir treatment (10 mg/d) were relatively poor, including reduction in HBV DNA to below 1000 copies/mL in 6%, HBeAg loss in 8.6%, and ALT normalization in 14%, although responses appeared to improve over longer durations (Figure 4; Benhamou et al, *J Hepatol*, 2006). There is a concern that adefovir treatment might result in HIV that is resistant to tenofovir; no evidence of resistance was found in the above study or in other limited experience with adefovir in this setting. AIDS Clinical Trial Group (ACTG) study 5127 was performed to demonstrate noninferiority of tenofovir 300 mg compared with adefovir 10 mg in reducing HBV DNA in 52 coinfecting patients on stable antiretroviral therapy, who had HBV DNA levels above 100,000 copies/mL and HIV RNA levels below 10,000 copies/mL (Peters et al, *CROI*, 2005 and *Hepatology*, 2006). The time-weighted average reductions in HBV DNA at 48 weeks with tenofovir versus adefovir were 4.03 versus 3.12 log₁₀ on

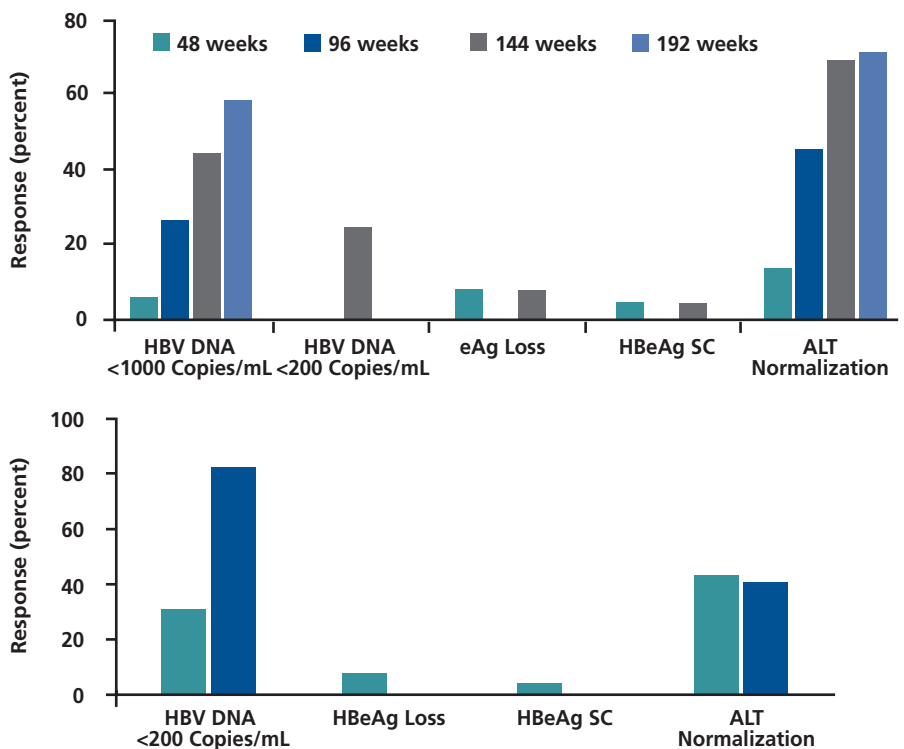


Figure 4. Top: Outcomes of adefovir treatment in observational cohort of 35 patients with lamivudine-resistant hepatitis B virus (HBV); n=31 at 48 weeks and n=29 at 144 weeks. Adapted from Benhamou et al, *J Hepatol*, 2006. Bottom: Outcomes of tenofovir treatment for 12 months in observational cohort of 65 patients with lamivudine-resistant HBV. Adapted with permission from Benhamou et al, *Hepatology*, 2006. SC indicates seroconversion; ALT, alanine aminotransferase; eAg, envelope antigen; HBeAg, HBV envelope antigen; +, positive; -, negative.

Table 1. Outcomes with Tenofovir or Lamivudine or the Combination at 24 Weeks

	Lamivudine-naive			Lamivudine-experienced		
	Tenofovir (n=10)	Lamivudine (n=11)	Tenofovir + Lamivudine (n=6)	Tenofovir (n=12)	Lamivudine (n=9)	Tenofovir + Lamivudine (n=11)
Change in HBV DNA (Log ₁₀ copies/mL)	- 4.66	- 3.31	- 5.03*	- 3.41*	- .82	- 3.93*
HBV DNA <400 Copies/mL (ITT)	40%	36.4%	50%	16.7%	0%	36.4%
ALT Normalization (ITT)	30%	63.6%	50%	25%	0%	36.4%

* $P < .05$ compared with lamivudine-alone group. ITT indicates intent-to-treat analysis; HBV, hepatitis B virus; ALT, alanine aminotransferase. Adapted from Nelson et al, CROI, 2006.

intent to treat analysis and 4.76 versus 3.48 log₁₀ on an as-treated analysis, respectively. In a cohort study of tenofovir in coinfecting patients with lamivudine-resistant HBV, 1-year outcomes were better than those reported in the adefovir cohort study, including greater proportions of patients with HBV DNA levels reduced to below 200 copies/mL and greater proportions of patients with ALT normalization (Figure 4; Benhamou et al, *Hepatology*, 2006). In a trial comparing entecavir with continued lamivudine for 24 weeks in 68 coinfecting patients with lamivudine-resistant HBV, mean HBV DNA of 9.13 log₁₀ copies/mL and mean HIV-1 RNA of 2 log₁₀ copies/mL, entecavir (n = 51) reduced HBV DNA to below 300 copies/mL in 6% compared with 0% with lamivudine. The mean decline in HBV DNA was 3.65 log₁₀ copies/mL with entecavir compared with an increase of 0.11 log₁₀ copies/mL with lamivudine (entecavir package insert).

One study evaluated the combination of lamivudine with tenofovir in HBV-monoinfected patients. Patients without prior lamivudine exposure had a significantly greater reduction in HBV DNA with the combination therapy than with lamivudine alone (Table 1; Nelson et al, CROI, 2006). Among lamivudine-experienced patients, both the combination therapy and tenofovir alone significantly reduced HBV DNA compared with lamivudine, with the combination appearing to improve other outcomes as well, despite the prior lamivudine exposure.

There are few data on HBV resistance to adefovir, tenofovir, and entecavir (Borroto-Esoda et al, *J Hepatol*, 2006; Colonno et al, *J Hepatol*, 2005). Data on adefovir indicate rates of resistance of 3% in year 2 of treatment, 11% in year 3, 18% in year 4, and 29% in year 5 among mainly HBeAg-negative patients without HIV infection. Resistance has not been observed in patients continuing lamivudine despite lamivudine resistance and was not observed in any of 29 coinfecting patients over 144 weeks of monitoring. Resistance to entecavir was observed in 9% of patients at 2 years and occurs mainly in the setting of lamivudine-resistant virus. Entecavir resistance is infrequent in the setting of wild-type HBV. Case reports from Australia now confirm several cases of entecavir resistance in lamivudine-naive, monoinfected patients (Colonno et al, *Hepatology*, 2006). Entecavir shares 2 of its 4 identified HBV resistance mutations with lamivudine. Table 2 shows cross-resistance among lamivudine, entecavir, adefovir, telbivudine, and the investigational L-nucleoside analogue, clevudine. Resistance to lamivudine is associated with resistance to other L-nucleoside analogues, raising the issue of losing class activity in the presence of lamivudine resistance. Data such as these indicate that the entecavir dose should be increased from 0.5 mg to 1 mg when lamivudine-resistant virus is present. Adefovir-resistant virus also appears to reduce susceptibility to most of the L-nucleoside analogues.

Given the above considerations, a

likely option for the patient is to replace zidovudine with tenofovir to maintain anti-HIV efficacy and provide anti-HBV activity. The addition of entecavir might also be considered, but the likelihood of lamivudine resistance in the patient suggests risk for entecavir resistance as well.

Treatment Strategies

Treatment of HBV alone

If HBV infection is to be treated without concurrent antiretroviral therapy (eg, in patients who have not yet started antiretroviral therapy), drugs that are not active against HIV should be used to prevent development of drug-resistant HIV. Peginterferon alfa is an option; it may be most useful in patients who are HBeAg-positive, have HBV genotype A, and have elevated ALT. Adefovir is another option. Published data do not show activity of entecavir against HIV, so that is another option.

Treatment of HBV and HIV

In patients receiving antiretroviral therapy, treatment for HBV infection should occur only with maximally suppressive antiretroviral therapy. In lamivudine-naive patients, the first-line therapy consists of tenofovir plus either lamivudine or emtricitabine with preference given to emtricitabine since it is coformulated with tenofovir into 1 pill. Other approaches that may be considered include entecavir with or without tenofovir or peginterferon alfa treatment. In

Table 2. Cross-resistance in Hepatitis B Virus (HBV) by Drug

HBV Strain	Fold-resistance				
	Lamivudine ¹	Adefovir ²	Clevudine ³	Telbivudine ⁴	Entecavir ^{4,5}
Wild-type	1	1	1	1	1
Lamivudine-resistant	1.7	0.5	>120	12	1
	>106	0.7	>120	236	30
	>105	0.2	>120	133	30
Adefovir-resistant	2-6	1-5	NA	NA	NA
	3-8	7-10	4.7	2.4	0.67
Entecavir-resistant	>1000	1.0	NA	>100	>1000
	>1000	2.0	NA	>1000	>1000

¹Adapted from Chin et al, *AAC*, 2001.; ²Angus et al, *Gastroenterology*, 2003.; ³Ono-Nita et al, *AAC*, 2002.; ⁴Levine et al, *AAC*, 2002.; ⁵Tenney et al, *AAC*, 2004. NA indicates not available.

lamivudine-experienced patients, the preferred option is the addition of tenofovir to ongoing lamivudine. If this is not possible, other options might include use of entecavir at the 1-mg dose (to compensate for likelihood of reduced susceptibility due to lamivudine resistance) or, in some instances, the addition of adefovir (if sparing of tenofovir is desired), although there is concern regarding efficacy and toxicity with this option.

Monitoring and Duration of Treatment

In patients starting treatment for HBV infection, HBV DNA and liver function tests should be performed every 3 months for the first year and every 3 to 6 months thereafter, provided resistance is not suspected. Patients who are HBeAg-positive should be monitored for HBeAg status and anti-HBe antibody status on the same schedule. Treatment is lifelong in patients who are HBeAg-positive. Those HBeAg-positive patients who seroconvert to HBeAg-negative and anti-HBe positive should continue treatment for at least 6 months to determine if seroconversion is stable. Duration of treatment with nucleoside or nucleotide analogues in patients who begin therapy with HbsAg-negative status is probably lifelong. The optimal duration of

treatment with peginterferon alfa in HBeAg-negative patients remains unclear. Treatment should continue for more than 12 months since relapse is virtually universal in patients treated for less than 12 months. The recommended duration of treatment in HBeAg-positive patients is 12 months.

Summary

Treatment of HBV infection should be considered in HIV-infected persons. HBV resistance occurs to single-agent therapy, but resistance rates appear to vary; cross-resistance may also occur. The treatment plan should be individualized based on the need for treatment of HIV infection and prior lamivudine therapy, with a primary objective of preventing emergence of drug-resistant HBV and HIV. More potent agents are needed, and combination therapy needs further investigation.

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Suggested Reading

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The IAS-USA would like to thank Larry Wolheim, Kevin Eddleman, and the staff of Giant Creative Strategy, LLC in San Francisco for donating their time and creative energy to developing the new look. Thank you!